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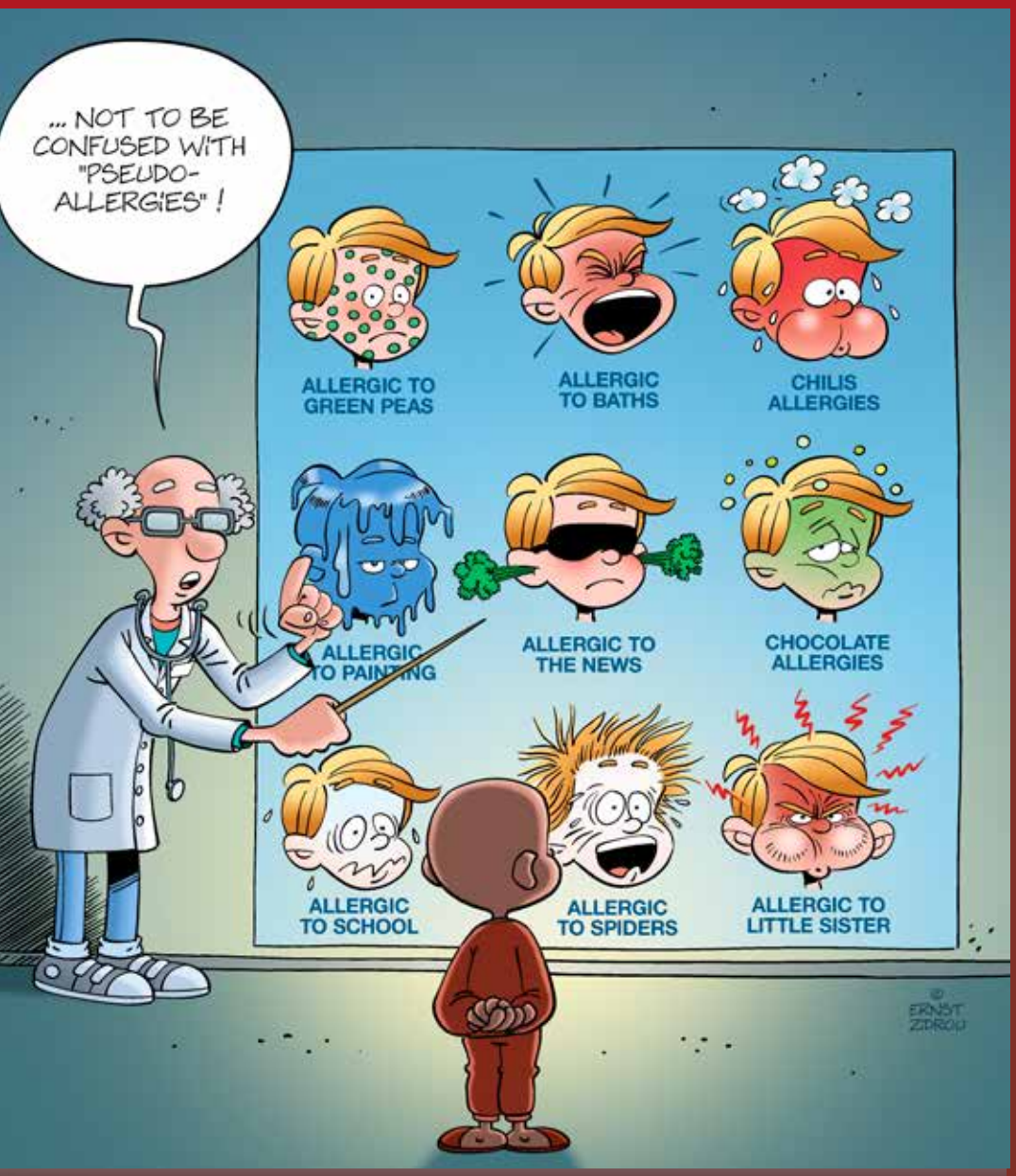


## Theme: Allergy




Belgische Vereniging voor Kindergeneeskunde
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# Contents

Publiekprijs **€ 86,52**

# If you don't recommend MenB vaccination to your patients,

# who will?

**81% van de ouders** beschouwt hun arts als een primaire bron van informatie over vaccinatie voor hun kinderen. (n=800)[2]

BEXSERO
Meningokokken groep B-vaccin
(rDNA, component, geadsorbeerd)

**BEXSERO is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door *Neisseria meningitidis* groep B.[1]**

**VERKORTE SAMENVATTING VAN DE PRODUCTKENMERKEN:** Gelieve de Samenvatting van de Productkenmerken te raadplegen voor de volledige informatie over het gebruik van dit geneesmiddel. **NAAM VAN HET GENEESMIDDEL:** Bexsero suspensie voor injectie in voorgevulde spuit. Meningokokken groep Bvaccin (rDNA, component, geadsorbeerd), EU/1/12/812/001-EU/1/12/812/002-EU/1/12/812/003-EU/1/12/812/004. Farmacotherapeutische categorie: meningokokkenvaccins, ATCcode: J07AH09. **KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING: Een dosis (0,5 ml) bevat:** Recombinant Neisseria meningitidis groep B NHBAfusieeiwit[1,2,3]: 50 microgram • Recombinant Neisseria meningitidis groep B NadAeiwit[1,2,3]: 50 microgram • Recombinant Neisseria meningitidis groep B fHbpfusieeiwit[1,2,3]: 50 microgram • Buitenmembraanvesikels (BMV) van Neisseria meningitidis groep Bstam. NZ98/254, gemeten als hoeveelheid totaal eiwit dat PorA P1.4 bevat[2]: 25 microgram • [1] Geproduceerd in E. colicellen door recombinantDNAtechnologie - [2] Geadsorbeerd aan aluminiumhydroxide (0,5 mg $Al^{3+}$) - [3] NHBA (Neisseria heparinebindend antigeen), NadA (Neisseriaadhesine A), fHbp (factor Hbindend eiwit). Voor de volledige lijst van hulpstoffen, zie rubriek 6.1 van de volledige SPK. **FARMACEUTISCHE VORM:** Suspensie voor injectie. Melkwitte vloeibare suspensie. **KLINISCHE GEGEVENS: Therapeutische indicaties:** Bexsero is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door Neisseria meningitidis groep B. Bij het vaccineren moet rekening worden gehouden met het effect van invasieve ziekte bij verschillende leeftijdsgroepen, evenals met de variabiliteit van de epidemiologie van antigenen voor groep Bstammen in verschillende geografische gebieden. Zie rubriek 5.1 van de volledige SPK voor informatie over bescherming tegen specifieke groep Bstammen. Dit vaccin dient te worden gebruikt in overeenstemming met officiële aanbevelingen. **Dosering en wijze van toediening:** Dosering: **Tabel 1. Samenvatting van de dosering: Leeftijd bij eerste dosis:** Zuigelingen van 2 tot en met 5 maanden[a]: **Primaire immunisatie:** Drie doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis[b,c]. - **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis[b,c]. • **Leeftijd bij eerste dosis:** Zuigelingen van 6 tot en met 11 maanden: **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis in het tweede levensjaar met een interval van minimaal 2 maanden tussen de primaire serie en de boosterdosis[c]. • **Leeftijd bij eerste dosis:** Kinderen van 12 tot en met 23 maanden: **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis met een interval van 12 tot en met 23 maanden tussen de primaire serie en de boosterdosis[c]. • **Leeftijd bij eerste dosis:** Kinderen van 2 tot en met 10 jaar: **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen[d]. • **Leeftijd bij eerste dosis:** Adolescenten (11 jaar of ouder) en volwassenen*: **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen[d]. • [a] De eerste dosis moet niet worden gegeven op de leeftijd jonger dan 2 maanden. De veiligheid en werkzaamheid van Bexsero bij zuigelingen jonger dan 8 weken zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. - [b] In geval van uitstel mag de booster niet later dan op een leeftijd van 24 maanden worden gegeven. - [c] Zie rubriek 5.1 van de volledige SPK. De noodzaak voor en tijdsplanning van een boosterdosis na dit vaccinatieschema is niet vastgesteld. - [d] Zie rubriek 5.1 van de volledige SPK. - * Gegevens over volwassenen ouder dan 50 jaar ontbreken. Wijze van toediening: Het vaccin wordt toegediend via een diepe intramusculaire injectie, bij voorkeur in het anterolaterale gedeelte van de dij bij zuigelingen, of in de streek van de deltaspier van de bovenarm bij oudere personen. Als meer dan één vaccin tegelijk wordt toegediend, moeten afzonderlijke injectieplaatsen worden gebruikt. Het vaccin mag niet intraveneus, subcutaan of intradermaal worden toegediend, en mag niet worden gemengd met andere vaccins in dezelfde spuit. Voor instructies over het hanteren van het vaccin voorafgaand aan toediening, zie rubriek 6.6 van de volledige SPK. **Contraindicaties:** Overgevoeligheid voor de werkzame stof(fen) of voor een van de in rubriek 6.1 van de volledige SPK vermelde hulpstof(fen). **Bijwerkingen:** Overzicht van het veiligheidsprofiel: De veiligheid van Bexsero is geëvalueerd in 17 onderzoeken, inclusief 10 gerandomiseerde gecontroleerde klinische studies met 10.565 proefpersonen (vanaf de leeftijd van 2 maanden) die minimaal één dosis Bexsero toegediend kregen. Van de personen die Bexsero toegediend kregen, waren 6.837 zuigelingen en kinderen (jonger dan 2 jaar), 1.051 kinderen (van 2 tot 10 jaar) en 2.677 adolescenten en volwassenen. Van de proefpersonen die de primaire immunisatieserie voor zuigelingen van Bexsero toegediend kregen, kregen 3.285 een boosterdosis in het tweede levensjaar. De meest voorkomende lokale en systemische bijwerkingen bij zuigelingen en kinderen (jonger dan 2 jaar) die in klinische studies zijn waargenomen, waren gevoeligheid en erytheem op de injectieplaats, koorts en prikkelbaarheid. In klinische onderzoeken bij zuigelingen gevaccineerd op de leeftijd van 2, 4 en 6 maanden, is bij 69% tot 79% van de proefpersonen melding gemaakt van koorts (≥ 38°C) wanneer Bexsero gelijktijdig werd toegediend met standaardvaccins (die de volgende antigenen bevatten: 7valent pneumokokkenconjugaat, difterie, tetanus, acellulair pertussis, hepatitis B, geïnactiveerde poliomyelitis en *Haemophilus influenzae* type b) in vergelijking met 44% tot 59% van de proefpersonen die alleen de standaardvaccins kregen toegediend. Bij zuigelingen die Bexsero en standaardvaccins toegediend kregen, is ook vaker melding gemaakt van het gebruik van antipyretica. Wanneer alleen Bexsero werd toegediend, kwam koorts bij zuigelingen even vaak voor als bij standaardzuigelingenvaccins die tijdens klinische studies werden toegediend. Eventuele koorts volgde in het algemeen een voorspelbaar patroon, waarbij de meeste koortsgevallen de dag na de vaccinatie over waren. De meest voorkomende lokale en systemische bijwerkingen waargenomen bij adolescenten en volwassenen waren pijn op de injectieplaats, malaise en hoofdpijn. Er is geen toename waargenomen in de incidentie of ernst van bijwerkingen bij opeenvolgende doses in de vaccinatiereeks. Tabel met bijwerkingen: Bijwerkingen (na primaire immunisatie of boosterdosis) die ten minste als mogelijk gerelateerd aan de vaccinatie kunnen worden beschouwd, zijn naar frequentie ingedeeld. De frequentie is als volgt geclassificeerd: Zeer vaak: (≥ 1/10) - Vaak: (≥ 1/100, < 1/10) - Soms: (≥ 1/1.000, < 1/100) - Zelden: (≥ 1/10.000, < 1/1.000) - Zeer zelden: (< 1/10.000) - Niet bekend: (kan met de beschikbare gegevens niet worden bepaald). De bijwerkingen worden binnen elke frequentiegroep gerangschikt in aflopende volgorde van ernst. Naast de meldingen uit klinische onderzoeken, zijn ook de wereldwijd ontvangen vrijwillige meldingen over bijwerkingen van Bexsero sinds de introductie op de markt in de volgende lijst opgenomen. Aangezien deze bijwerkingen vrijwillig zijn gemeld door een populatie van onbekende omvang, is het niet altijd mogelijk om een betrouwbare schatting van de frequentie te geven en worden ze daarom hier vermeld met de frequentie Niet bekend. **Zuigelingen en kinderen (tot en met 10 jaar):** Bloed- en lymfestelselaandoeningen: Niet bekend: lymfadenopathie. Immuunsysteemaandoeningen: Niet bekend: allergische reacties (waaronder anafylactische reacties). Voedings en stofwisselingsstoornissen: Zeer vaak: eetstoornissen. Zenuwstelselaandoeningen: Zeer vaak: slaperigheid, ongewoon huilen, hoofdpijn. - Soms: insulten (inclusief febriele insulten). - Niet bekend: hypotoon-hyporesponsieve episode, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Bloedvataandoeningen: Soms: bleekheid (zelden na booster). - Zelden: ziekte van Kawasaki. Maagdarmstelselaandoeningen: Zeer vaak: diarree, braken (soms na booster). Huid en onderhuidaandoeningen: Zeer vaak: huiduitslag (kinderen van 12 tot en met 23 maanden) (soms na booster). - Vaak: huiduitslag (zuigelingen en kinderen van 2 tot en met 10 jaar). - Soms: eczeem. - Zelden: urticaria. - Skeletspierstelsel en bindweefselaandoeningen: Zeer vaak: artralgie. Algemene aandoeningen en toedieningsplaatsstoornissen: Zeer vaak: koorts (≥ 38 °C), gevoeligheid op de injectieplaats (inclusief ernstige gevoeligheid op de injectieplaats, gedefinieerd als huilen wanneer de geïnjecteerde ledemaat wordt bewogen), erytheem op de injectieplaats, zwelling op de injectieplaats, verharding op de injectieplaats, prikkelbaarheid. Soms: koorts (≥ 40 °C). - Niet bekend: injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden). **Adolescenten (van 11 jaar en ouder) en volwassenen:** Bloed- en lymfestelselaandoeningen: Niet bekend: lymfadenopathie. Immuunsysteemaandoeningen: Niet bekend: allergische reacties (waaronder anafylactische reacties). Zenuwstelselaandoeningen: Zeer vaak: hoofdpijn. - Niet bekend: syncope of vasovagale reacties op een injectie, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Maagdarmstelselaandoeningen: Zeer vaak: misselijkheid. Huid en onderhuidaandoeningen: Niet bekend: huiduitslag. Skeletspierstelsel en bindweefselaandoeningen: Zeer vaak: myalgie, artralgie. Algemene aandoeningen en toedieningsplaatsstoornissen: Zeer vaak: pijn op de injectieplaats (inclusief ernstige pijn op de injectieplaats, gedefinieerd als niet in staat normale dagelijkse activiteiten uit te voeren), zwelling op de injectieplaats, verharding op de injectieplaats, erytheem op de injectieplaats, malaise. - Niet bekend: koorts, injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden). Melding van vermoedelijke bijwerkingen: Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem: **België:** Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten - Afdeling Vigilantie - Postbus 97 - 1000 Brussel - Madou - Website: www.eenbijwerkingmelden.be - e-mail: adr@fagg.be. **Luxemburg:** Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé. Site internet : www.guichet.lu/pharmacovigilance. **HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN:** GSK Vaccines S.r.l, Via Fiorentina 1, 53100 Siena, Italië. **DATUM VAN DE GOEDKEURING VAN DE TEKST:** 26/04/2023 (v15). **AFLEVERINGSWIJZE:** Op medisch voorschrift.

**References: 1.** SmPC Bexsero. **2.** Schmitt JH, Booy R, Astron R, et al. How to optimize the coverage rate of infant and adult immunisations in Europe. BMC Med. 2007;5:11. doi:10.1186/1741-7015-5-11.

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## Happiness is when what you think, what you say, and what you do are in harmony…

We are delighted to end 2023 with the winter issue of our Belgian Journal of Paediatrics. This time, it focuses on allergies in children. Allergology is at the crossroads of many paediatric sub-specialties, and it has undergone significant development in our country. We will let the guest editors (Kamal El Abd and Marc Raes) introduce the various subjects that are covered. Once again, we want to thank all the authors who have contributed to this extremely rewarding issue.

In this last issue of the year, we also want to highlight our 'behind the scenes' contributors: all the colleagues who have reviewed a manuscript submitted this year to our journal. These people are essential to higher the quality and scientific relevance of the Belgian Journal of Paediatrics. Through their comments and suggestions, they play an important role in the training of younger pediatricians. It is a real challenge for the editorial team to find qualified persons who are willing to review manuscripts quickly. These people did it, and we would like to sincerely thank them!

The holiday season is also a time for looking back, taking stock of the past and wishing well for the future. To celebrate the 100th anniversary of the Belgian Paediatric Society in 2024, we are preparing a special section that will allow us to revisit the past in the light of the present and maybe of the future. We will come back to this in our spring issue.

On behalf of all the members of the BJP editorial committee, we would also like to wish you a happy and peaceful 2024. Our world has been shaken by many crises. War has reappeared or intensified in many parts of the globe, human rights are still being violated in many societies and the repercussions of climate change are beginning to be felt in every corner of the planet. On several occasions, we have had the impression that mankind is missing opportunities to change course, to find a right balance between individual freedoms and living together. For this new year, we would like to offer you this invitation to happiness described by Mahatma Gandhi: *"happiness is when what you think, what you say, and what you do are in harmony"*. Through the small and big events of your professional, family and personal lives, we wish you happiness and harmony.

**Happy New Year to each of you !**

**Christophe Chantrain and Marc Raes**

**We would like to express our appreciation to our colleagues who voluntary reviewed the articles that were published in 2023. It requires a lot of time and dedication. We are grateful for the valuable suggestions and constructive comments, essential for the high quality and scientific relevance of the Belgian Journal of Paediatrics.**

Barrea Christophe
Bernier Vincent
Boon Mieke
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Van Den Driessche Koen
Van De Vijver Els
Van De Walle Johan
Van Gysel Dirk
Van Hoeve Karen
Vanrykel Katrien
Verhelst Helene
Wojciechowski Mark

*Thank you !*

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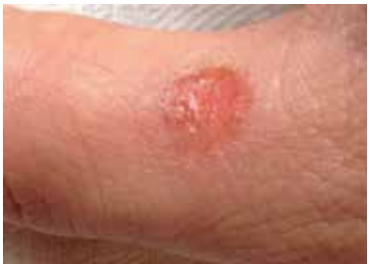
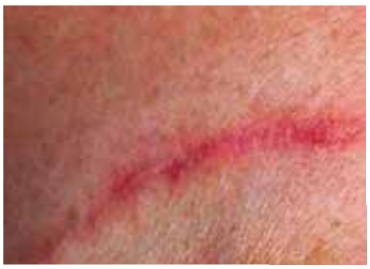


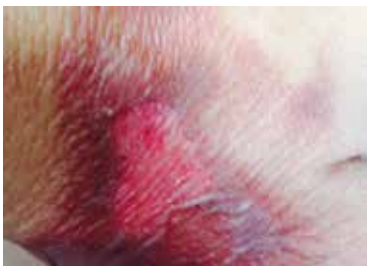
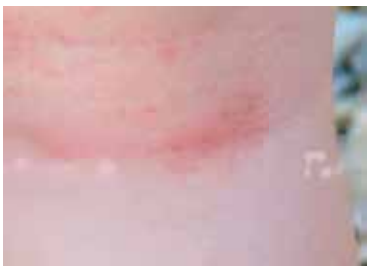

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# Editorial

## Pediatric allergies: understanding, acting, preventing

With great pleasure, we welcome you to this special edition of the Belgian Journal of Paediatrics (BJP), dedicated to pediatric allergic diseases. We are delighted to see that the field of pediatric allergy is generating increasing interest within the Belgian pediatric community. This issue aims to serve as an open window into the latest developments, current challenges, and future opportunities in the treatment of food allergies and focusses also on eczema, rhinitis, asthma, drug and hymenoptera allergy in children

Almost 10 years ago, at the same time the White Book on Allergy was published by the WorldAllergyOrganization, a theme issue of the Belgian Journal of Paediatrics was dedicated to food allergy. In both publications it was stressed that the prevalence of allergic diseases was continuously increasing worldwide over the last decades.

Current statistics cannot go unnoticed: allergies are still rising and have reached alarming pandemic proportions globally, children bearing the greatest disease burden.

Food allergies, continue to increase in number, intensity, complexity and early onset. This observation underscores an urgent need to understand, treat, and prevent these conditions that profoundly impact the quality of life for children and their families.

In place of the simplistic paradigm of non-protective avoidance, a shift to a new concept has gradually taken hold: one that focuses on the induction of tolerance. In this edition, this transformative concept and its potential to reshape the landscape of pediatric food allergy management is explored.

In the face of the rising prevalence of pediatric allergies, prevention becomes essential. The age-old adage 'prevention is better than cure' holds true not in the least in the context of food allergies. This issue explores preventive strategies, highlighting the importance of early identification of risk factors, sensitization pathways, and parental education.

Adequate management of fast evolving, complex, difficult-to-treat or unmet age-specific allergic diseases requires allergy subspecialty care, in close collaboration with primary specialists and first-line generalists.

Recently, in response to the growing need for better structured specialized care in pediatric allergology in Belgium, the Belgian Association of Pediatric Allergologists (BAPALL) was created, under the auspices of the Belgian Society of Pediatrics and the Belgian Academy of Paediatrics. In harmony with other non-pediatric allergology societies and in collaboration with other pediatric specialties, BAPALL aims to advocate for the specific needs and challenges faced by pediatric allergists, their patients and their families.

On one hand, our country, although a leader in many medical fields, remains one of the last in Europe to not recognize allergology as a separate medical specialty. On the other hand, the rapid evolution of complex diagnostic analysis and management strategies and procedures underscore the imperative need for specific training in pediatric allergology.

The current lack of well-documented, good-organized and officially recognized training programs for this constantly evolving pathogenesis-based subspecialty without clear identification of the accredited pediatric allergologist, does not only lead to patient confusion in finding the right experts but also induces a risk of over- and under-diagnoses with potential errors in the differential diagnosis and treatment.

Through the BAPALL, we aspire to contribute to the advocacy of interests and the overall improvement of pediatric allergology care in Belgium, waiting for an official recognition.

(Info: bapall.secretary@gmail.com)

In conclusion, we would like to express our great gratitude to all the authors who generously spent their time sharing us their expertise in this issue. We also want to thank Mark Wojciechowski for his professional and detailed editorial check-up of all the manuscripts

May these articles spark discussions

**We wish you a stimulating and informative read.**

**Kamal El Abd**

**Marc Raes**

**Uw vragen of commentaar**
**Vos questions ou commentaires**

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# Strategies to prevent severe Respiratory Syncytial Virus (RSV) infections in infants: the Belgian expert opinion

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## Keywords

Respiratory Syncytial Viruses ; Prevention ; Passive Immunisation ; Vaccines ; Burden ; Infant ; Child.

## Abstract

Respiratory syncytial virus (RSV) causes a significant burden of disease in children, particularly in young infants or those with comorbidities. Recently, two new effective options have been approved for the prevention of RSV-related lower respiratory tract disease in infants: a long-acting monoclonal antibody (nirsevimab, Beyfortus®) and a maternal vaccine (RSVpreF; Abrysvo®). A Belgian group of paediatric RSV experts (members of the Belgian Society of Paediatrics) recommends an immunization strategy targeting all infants aged <1 year, at the start of their first RSV season and infants with risk factors aged <2 years at the start of their second RSV season. The choice of one or a combination of these two complementary preventive options will depend on maternal and infant factors, taking into account the advantages and disadvantages of potential strategies, as well as costs and reimbursement. The expert group recommends a low cost to parents and rapid reimbursement to avoid health inequalities. Adequate supply should also be ensured. Implementation should include data collection to conduct a real-world observational survey of effectiveness over the first 5 years of use. Awareness campaigns need to be organised for all stakeholders.

## Introduction

Respiratory syncytial virus (RSV) infections are important in paediatrics and one of the main causes of infant hospitalisation and mortality (1-3). By the age of 2 years, 95% of all the infants worldwide will have been infected (4). The vast majority (75% up to 90 %) of infants hospitalised for severe RSV infection were previously healthy infants (5, 6). Most cases of hospital admissions occur in infants less than 1 year of age (2, 3, 6). The Belgian RSV expert group was formed on the basis of an analysis by the Belgian Society of Paediatrics, taking into account expertise in paediatric pulmonology, infectiology or neonatology. All have been involved in the evaluation of the burden and surveillance of RSV disease in young infants in Belgium (7). As new prevention strategies are now available, RSV prevention is being reviewed in several countries. In this context, this group of Belgian experts took the opportunity to give their opinion on the subject.

## Burden of disease

The Belgian Knowledge Centre for Health Care (KCE) recently published a report on the organisation of paediatric hospital care in Belgium (8). Hospital admissions of patients with RSV infection were defined by one of four diagnostic codes: 1) RSV as the cause of diseases classified elsewhere, 2) RSV pneumonia, 3) acute RSV bronchiolitis, or 4) bronchitis, mentioned either as a primary or secondary diagnosis in an upper or lower limit definition.

In 2018, there were 9,047 to 10,675 (depending on the definition) RSV hospitalisations of children in paediatric services. There were 260 to 313 (depending on the definition) stays of children in non-paediatric services for whom an RSV diagnosis was identified.

Depending on the definition used, 75.6% to 77.8% of children hospitalised in paediatric units with a diagnosis of RSV were aged < 1 year. A diagnosis of RSV was made in 452 (10.0%) to 533 (11.8%) hospitalisations of children in a paediatric intensive care unit (PICU) (8). RSV-related hospitalisations cause a peak in bed occupancy rates. During the seasonal peak, RSV-related hospitalisations account for 30% to 40% of bed occupancy in paediatric wards. In 2018, the national average bed occupancy rate exceeded 80% during the peak period. Without RSV, the rate would not have exceeded 70% (8). The annual incidence of RSV-associated hospitalisations was 68.3 per 1,000 children younger than 1 year and 5.0 per 1,000 children aged 1-4 years (9). Admission to the PICU is very stressful for the patient and demanding for the health care system and society. According to a Belgian PICU registry, which included 2,364 admissions of various aetiologies (age group: 0-15 years) in 2018, the main reason for PICU admission was severe and/or life-threatening lung or airway pathology (27.92%); 5.46% of PICU admissions were RSV-associated (10).

## Societal and financial burden

RSV has a significant impact on the health-related quality of life (HRQoL) of children and their parents and caregivers, and imposes a substantial economic burden on families, healthcare systems, governments and society (7). Forty-one studies reporting data from 1987 to 2017 were included in a systematic review and meta-analysis evaluating the global inpatient and outpatient costs of RSV healthcare management

in middle- and high-income countries. The average cost of RSV acute lower respiratory infection (ALRI) management was €3,452 (95% CI 3,265-3,639) and €299 (95% CI 295-303) per episode for inpatient and outpatient management without follow-up, respectively, and increased to €8,591 (95% CI 8,489-8,692) and €2,191 (95% CI 2,190-2,192) with follow-up to 2 years after the initial event (11). The global cost of RSV ALRI management in young children in 2017 was estimated to be approximately €4.82 billion (95% CI 3.47-7.93) (11).

A multi-country prospective cohort study conducted in Finland, the Netherlands, Spain and the United Kingdom (UK) prospectively measured costs and HRQoL of RSV in previously healthy term infants and their caregivers during the first RSV season in a community setting (12).The cohort of 1,041 infants experienced 265 RSV episodes with a mean symptom duration of 12.5 days. The mean costs per RSV episode were €399.5 (95 % CI 242.3-584.2) and €494.3 (95 % CI 317.7-696.1) from the perspective of healthcare payers (direct costs) and society (direct + indirect costs), respectively. The mean cost per hospitalised RSV episode was €4,587.9 (95% CI 3,085-6,229) from the perspective of the health care payer. The mean quality-adjusted life-day (QALD) loss per RSV episode of 1.9 (95 % CI 1.7-2.1) was independent of medical care. Caregivers' and children's HRQoL showed similar trends and correlated well (12).

## Seasonality

In Belgium, based on a 13-year survey, the RSV season starts around week 41 (second week of October) and peaks between week 47 and 52 (13). After the emergence of COVID-19, a dramatic reduction in RSV activity was observed, coinciding with the implementation of public health and social measures (PHSMs). After the PHSMs were gradually lifted, a shift in seasonality and a delayed RSV outbreak with a higher number of infected patients were observed in many countries (14). In Belgium, an atypical seasonality was observed in 2021, with a reappearance of the epidemic pattern in 2022-2023 and 2023-2024 (15).

## RSV prevention

### *Non-pharmaceutical interventions (NPI)*

GENERAL MEASURES

Transmission of RSV occurs mainly by inoculation of the nasopharyngeal or ocular mucosa after direct contact with secretions containing the virus (16). General measures to prevent RSV infection focus on reducing inoculation and include hand washing, cough hygiene, avoiding exposure to tobacco and other smoke, restricting childcare attendance during the RSV season for high-risk infants, and possibly reducing air pollution (16). The types of infection control precautions in the healthcare setting depend on the setting and include appropriate use of gloves, surgical masks and disposable gowns, isolation or cohorting of RSV patients, and continuing education of staff (16).

### *Passive and active immunization*

MONOCLONAL ANTIBODIES

*Palivizumab (Synagis®)*

Palivizumab is a recombinant humanised monoclonal antibody (mAb) indicated for the prevention of severe lower respiratory tract infection (LRTI) requiring hospitalisation due to RSV in children at high risk of RSV disease (17).

In a meta-analysis of three pre-licensure randomised trials comparing palivizumab prophylaxis with placebo in 2,831 high-risk infants with bronchopulmonary dysplasia (BPD) or other high-risk conditions, palivizumab reduced RSV hospitalisations from 101 to 50 per 1000 (relative risk [RR] 0. 49, 95% CI 0.37-0.64) and intensive care unit admissions from 34 to 17 per 1000 (RR 0.5, 95% CI 0.3-0.81) without increasing the risk of adverse events (16, 18). Palivizumab has a short half-life and requires monthly intramuscular administration during anticipated RSV risk periods (17).

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*Nirsevimab (Beyfortus®)*

Nirsevimab is a recombinant, long-acting human G1-kappa neutralising monoclonal antibody approved by the European Medicines Agency (EMA) for the prevention of RSV LRTI in neonates and infants during their first RSV season (19).

Unlike palivizumab, nirsevimab is administered as a single intramuscular dose. According to the label, the use of nirsevimab is not restricted to high-risk children, although it should be administered according to official local recommendations (19).

The efficacy and safety of nirsevimab for the prevention of medically attended (MA) RSV LRTI in term and preterm infants entering their first RSV season was evaluated in two randomised, double-blind, placebo-controlled, multicentre trials (D5290C00003 [phase IIb] and MELODY [phase III]) (14). The results of these trials are summarised in Table 1.

D5290C00003 randomised a total of 1,453 very and moderately preterm infants (gestational age [GA] ≥ 29 to < 35 weeks; median age 3.3 months) (2:1) to receive a single intramuscular dose of nirsevimab or placebo.

MELODY (primary cohort) randomised a total of 1,490 term and late preterm infants (GA ≥ 35 weeks; mean age 2.6 months) (2:1) to receive a single intramuscular dose of nirsevimab or placebo (19).

The primary endpoint for D5290C00003 and MELODY was the incidence of MA LRTI (including hospitalisation) caused by reverse transcription polymerase chain reaction (RT-PCR)-confirmed RSV up to 150 days after dosing (19). Hospitalisation for RSV-associated LRTI up to 150 days was a secondary endpoint. Very severe MA RSV LRTI (MA RSV LRTI with hospitalisation and need for supplemental oxygen or intravenous fluids) was also evaluated.

The primary endpoint was statistically significant in both studies. The relative risk reduction for MA RSV LRTI was 70.1% (95% CI 52.3-81.2; $p < 0.001$; incidence 2.6% with nirsevimab vs. 9.5% with placebo) in D5290C00003 and 74.5% (95% CI 49.6-87.1; $p < 0.001$; incidence 1.2% with nirsevimab vs. 4.1% with placebo) in MELODY (19, 20).

In D5290C00003, the incidence of hospitalisation for RSV LRTI was 0.8% with nirsevimab and 4.1% with placebo (efficacy 78.4%; 95% CI 51.9-90.3; $p < 0.001$) (21). Very severe MA RSV LRTI occurred in 0.4% and 3.3% of infants with nirsevimab and placebo, respectively (efficacy 87.5%; 95% CI 62.9-95.8) (19, 21).

In MELODY, hospitalisation for RSV LRTI occurred in 0.6% and 1.6% of infants in the nirsevimab and placebo groups, respectively (efficacy 62.1%; 95% CI -8.6-86.8; $p = 0.07$) (20). Very severe MA RSV LRTI up to 150 days post-dose occurred in 0.5% and 1.4% of infants in the nirsevimab and placebo groups, respectively (efficacy 64.2%; 95% CI -12.1-88.6) (19, 20).

Due to the COVID-19 pandemic, enrolment in the MELODY study was stopped early. Due to the very low number of RSV cases in both groups, the initial analysis of the study was underpowered to determine the

efficacy of nirsevimab against hospitalisation for RSV LRTI. After the pandemic, full enrolment was achieved (3012 infants) and efficacy against hospitalisation for RSV LRTI up to 150 days after injection was 76.8% (95% CI 49.4-89.4) and efficacy against very severe MA RSV LRTI was 78.6% (95% CI 48.8-91.0). Efficacy against MA RSV LRTI (primary endpoint) (76.4%; 95% CI 62.3-85.2) was consistent with that seen in the primary cohort of the study (22).

Safety was the primary endpoint in the phase II/III MEDLEY trial, in which 925 infants at higher risk of severe RSV disease and preterm infants (GA < 35 weeks) entering their first RSV season were randomised (2:1) to receive either a single intramuscular dose of nirsevimab and 4 placebo injections or 5 monthly intramuscular doses of palivizumab (19, 23). The primary endpoint was met as the incidence of adverse events was similar between treatment groups and cohorts. The incidence of MA RSV LRTI up to 150 days post-dose was 0.6% with nirsevimab and 1.0% with palivizumab (19, 22).

Nirsevimab has a favourable safety profile. The most common adverse reaction was rash (0.7%) occurring within 14 days of treatment. The majority of cases were mild to moderate. In addition, pyrexia and non-serious injection site reactions were reported at a rate of 0.5% and 0.3% within 7 days post dose, respectively (19).

Finally, HARMONIE is a real-world phase 3b study in which 8058 infants (>29 weeks GA and ineligible for palivizumab) were randomised (1:1) to receive nirsevimab or standard of care (SOC) before or during their first RSV season (24). The efficacy of nirsevimab against RSV LRTI hospitalisation (primary endpoint) and very severe RSV LRTI (secondary endpoint) was 83.21% (95% CI 67.77- 92.04) and 75.71% (32.75-92.91), respectively (24).

## VACCINES

### *Respiratory syncytial virus vaccine (bivalent, recombinant) (RSVpreF; Abrysvo®)*

RSVpreF contains two recombinant, stabilised RSV prefusion F antigens representing the RSV-A and RSV-B subgroups. RSVpreF is licensed by the EMA from July 2023 for (a) passive protection against RSV LTRI in infants from birth to 6 months of age following maternal immunisation during pregnancy and (b) active immunisation of persons > 60 years of age for prevention of RSV LTRI (25). The latter indication is beyond the scope of this paper. For infant protection, RSVpreF should be given as a single dose between 24 and 36 weeks of gestation (25).

The approval for passive protection against RSV LTRD (lower respiratory tract disease) in infants was based on the results of the MATISSE study, a phase 3, multicentre, randomised (1:1), double-blind, placebo-controlled trial in which 7,392 pregnant women with uncomplicated singleton pregnancies were randomised to receive either RSVpreF or placebo (25). Co-primary endpoints assessed in parallel were severe MA RSV LRTD and PCR-RT confirmed RSV LRTD in infants at 90, 120, 150 and 180 days of age. Vaccine efficacy (VE) was defined as the relative risk reduction of the endpoint in the RSVpreF group compared with the placebo group (20, 21). A lower limit of the CI for VE (99.5% CI at 90 days; 97.58% CI at later intervals) > 20% was considered to meet the success criterion for vaccine efficacy with respect to the primary endpoints (25, 26).

At the time of the prespecified interim analysis, the VE success criterion for the severe MA RSV LRTD endpoint was met with a VE of 81.8% (99.5% CI 40.6% to 96.3%) at 90 days and 69.4% (97.58% CI 44.3% to 84.1%) at 180 days after birth. The VE of 57.1% (99.5% CI 14.7%

**Table 1:** Efficacy of nirsevimab in term and preterm infants entering their first RSV season.

| Group | Treatment | N participants | Incidence N (%) | Efficacy [a] (95% CI) NNT |
|---|---|---|---|---|
| **Efficacy in infants against MA RSV LRTI through 150 days post dose** | | | | |
| Very and moderately preterm GA ≥29 to <35 weeks (D5290C00003) [b] | Nirsevimab | 969 | 25 (2.6) | 70.1% (52.3, 81.2) c p <0.001 |
| | Placebo | 484 | 46 (9.5) | NNT= 14.5 |
| Term and late preterm GA ≥35 weeks (MELODY Primary cohort) | Nirsevimab | 994 | 12 (1.2) | 74.5% (49.6, 87.1) c p <0.001 |
| | Placebo | 496 | 25 (5.0) | NNT=26.3 |
| MELODY full cohort | Nirsevimab | 2009 | 24 (1.2) | 76.4% (62.3, 85.2) p <0.001 |
| | Placebo | 1003 | 54 (5.4) | NNT=23.8 |
| **Efficacy in infants against MA RSV LRTI with hospitalization through 150 days post dose** | | | | |
| Very and moderately preterm GA ≥29 to <35 weeks (D5290C00003) [b] | Nirsevimab | 969 | 8 (0.8) | 78.4% (51.9, 90.3) c p <0.001 |
| | Placebo | 484 | 20 (4.1) | NNT=30.3 |
| Term and late preterm GA ≥35 weeks (MELODY Primary cohort) | Nirsevimab | 994 | 6 (0.6) | 62.1% (-8.6, 86.8) p = 0,07 |
| | Placebo | 496 | 8 (1.6) | NNT=100 |
| MELODY full cohort | Nirsevimab | 2009 | 9 (0.4) | 76.8% (49.4, 89.4) p < 0.001 |
| | Placebo | 1003 | 20 (2.0) | NNT=62.5 |
| **Efficacy in infants against very severe MA RSV LRTI through 150 days post dose** | | | | |
| Very and moderately preterm GA ≥29 to <35 weeks (D5290C00003) [b] | Nirsevimab | 969 | 4 (0.4) | 87.5% (62.9, 95.8) [d] |
| | Placebo | 484 | 16 (3.3) | |
| Term and late preterm GA ≥35 weeks (MELODY Primary cohort) | Nirsevimab | 994 | 5 (0.5) | 64.2% (-12.1, 88.6) [d] |
| | Placebo | 496 | 7 (1.4) | |
| MELODY full cohort | Nirsevimab | 2009 | 7 (0.3) | 78.6% (48.8, 91.0) |
| | Placebo | 1003 | 17 (1.7) | |

a: based on relative risk reduction versus placebo. / b: All subjects who received 50 mg irres

**Table 2:** Efficacy of RSVpreF against RSV LRTI in infants.

| Time period | Abrysvo® (N subjects =3 495) | Placebo (N subjects =3480) | VE% (CI) [a] |
|---|---|---|---|
| **Severe MA LRTI due to RSV in infants from birth to 6 months of age (N (%))** | | | |
| 90 days | 6 (0.2) | 33 (0.9) | 81.8 (40.6, 96.3) |
| 120 days | 12 (0.3) | 46 (1.3) | 73.9 (45.6, 88.8) |
| 150 days | 16 (0.5) | 55 (1.6) | 70.9 (44.5, 85.9) |
| 180 days | 19 (0.5) | 62 (1.8) | 69.4 (44.3, 84.1) |
| **MA LRTI due to RSV in infants from birth through 6 months of age (N (%))** | | | |
| 90 days | 24 (0.7) | 56 (1.6) | 57.1 (14.7, 79.8) |
| 120 days | 35 (1) | 81 (2.3) | 56.8 (31.2, 73.5) |
| 150 days | 47 (1.3) | 99 (2.8) | 52.5 (28.7, 68.9 |
| 180 days | 57 (1.6) | 117 (3.4) | 51.3 (29.4, 66.8) |

a= 99.5% CI at 90 days; 97.58% CI at later intervals.

to 79.8%) at 90 days and 51.3% (97.58% CI 29.4% to 66.8%) at 180 days after birth did not meet the success criterion for the endpoint MA RSV LRTD (25, 26).

Vaccine efficacy (VE) is shown in Table 2.

In MATISSE, maternal adverse events reported within 1 month after vaccination were similar in the RSVpreF group (14%) and the placebo group (13%). In pregnant women at 24-36 weeks of gestation the most frequently reported adverse reactions were vaccination site pain (41%), headache (31%) and myalgia (27%). The majority of local and systemic reactions in maternal participants were mild to moderate in severity and resolved within 2-3 days of onset (27). No safety signals were observed in infants up to 24 months of age. The incidence of adverse events reported in infants within 1 month after birth was similar in the RSVpreF group (37%) and the placebo group (35%). Major birth outcomes assessed in the RSVpreF group compared to placebo included premature birth (6% and 5%, respectively), low birth weight (5% and 4%, respectively) and congenital anomalies (5% and 6%, respectively) (25). In a subgroup analysis, a difference in the rate of preterm birth was found between vaccine recipients (8.3%) and placebo recipients (4.0%) in South Africa and Brazil (upper middle income economies) (27). This difference was not observed in cohorts from high-income countries.

The Food and Drug Administration (FDA) prescribing information for RSVpreF includes a warning to inform that there was a numerical imbalance in preterm births in those receiving RSVpreF (5.7%) compared with those who received placebo (4.7%). Therefore, the FDA restricts administration of RSVpreF to pregnant women between 32 and 36 weeks of gestation (28). According to the Medicines and Healthcare Products Regulatory Agency (UK), RSVpreF should not be used in pregnant women at less than 28 weeks of gestation (29). In contrast, according to the EMA, RSVpreF can be administered between weeks 24 and 36 of gestation (25). The Superior Health Council (SHC) is relatively reassured that there is no clear signal of an increase in preterm births in high-income countries following administration of Abrysvo in pregnancy. According to the SHC, vaccination later in pregnancy may reduce the potential risk of preterm birth. In addition, an interval of at least two weeks is recommended between the administration of RSVpreF and the administration of tetanus, diphtheria and acellular pertussis vaccine (Tdap), which is recommended in Belgium for all pregnant women between 24 and 32 weeks. Therefore the SHC favours administration during weeks 28-36 of pregnancy) (30).

## IMPLEMENTATION STRATEGIES

There are no head-to-head comparisons between passive infant immunisation with nirsevimab and maternal immunisation with RSVpreF. Therefore, the RSV subcommittee of the Joint Committee on Vaccination and Immunisation (JVCI) (UK) sought expert opinion on the comparison of the endpoints of the MELODY (nirsevimab) and MATISSE (RSVpreF) trials (31). The Committee noted that the background attack rates in the control groups for RSV MA LRTI and RSV hospitalisations were higher in MELODY than in MATISSE. Seasonal recruitment in MELODY versus year-round recruitment in MATISSE, interruptions in RSV transmission during the pandemic, and the different populations included may all have contributed to the difference in background rates. The median age at passive immunisation of infants in MELODY was 2.6 months (range 0.03-11). In the maternal vaccine trial, babies were born with maternal antibody and therefore protected from birth (26). The primary endpoints for RSV MA LRTI were considered similar between the trials. However, the definitions for severe or very severe LRTI and the secondary endpoints of hospitalisation were considered to be very different (31).

Modellers at the London School of Hygiene & Tropical Medicine (LSHTM) simulated 2 options for RSVpreF:

- a seasonal programme between July and the end of December and
- a year-round programme.

Coverage was estimated to be 60% based on pertussis vaccination uptake data (31).

Three scenarios were modelled for nirsevimab with a 90% uptake:

- seasonal from September to February;
- seasonal with catch-up for children aged < 6 months at the beginning of the season; and
- a year-round birth dose offer from March to February.

The impact of each programme was compared in terms of QALYs and costs averted, and the number needed to vaccinate (NNV) for

- a seasonal and a year-round maternal programme, and
- a seasonal, a seasonal with catch-up, and a year-round monoclonal programme.

The greatest impact was seen with the seasonal catch-up and year-round monoclonal programmes, while the most efficient in terms of NNV was the seasonal programme, both maternal vaccination and monoclonal antibodies (without catch-up). For both products, estimates for weaning immunity beyond the published data are highly uncertain and could have major impacts on their cost effectiveness (31).

The most cost-effective programme was seasonal for either product, followed by seasonal with catch-up for nirsevimab, followed by the year-round programme for either product. When the products were similarly priced, it was difficult to differentiate between the 2 on the basis of cost-effectiveness.

Following modelling of the impact and cost-effectiveness of potential immunisation strategies undertaken by the London School of Hygiene and Tropical Medicine (LSHTM), the Joint Committee on Vaccination and Immunisation (JVCI, UK) requested the University of Antwerp (UA) to conduct a second opinion modelling using a model developed for the REspiratory Syncytial virus Consortium EUrope (RESCEU) project. Overall, despite the different approaches used, the cost-effectiveness results were similar between the two models, ensuring that the

**Table 3:** Published RSV prevention Guidelines.

| Country | Nirsevimab | RSVpreF | |
|---|---|---|---|
| Spain | For the 2023-24 season:<br>In order of priority:<br>1. Child populations at high risk of severe RSV disease, including:<br>(a) premature infants with a GA<35 weeks (1 dose before 12 months of age);<br>(b) patients with CHD with significant haemodynamic involvement; (c) with BPD and (d) with other underlying pathologies who are at a high risk of developing severe RSV bronchiolitis. In risk conditions b, c and d, administration prior to each RSV season up to 24 months of age<br>2. Children < 6 months of age at the beginning or during the RSV season: For the 2023-2024 season, the administration is recommended to children under 6 months of age born from April 1, 2023 to March 31, 2024. Immunisation of those born during the season will be prioritized and those born earlier will be immunised as soon as possible. | Not included. | Comité Asesor de Vacunas. Asociación Española de Pediatría. July 2023 (35, 36). |
| France | For 2023-2024 season:<br>All infants < 6 months at the start of the RSV epidemic period.<br>Vulnerable infants (GA < 32 weeks, chronic lung disease, CHD):<br>extension to infants < 12 months at the start of the epidemic period.<br>Nirsevimab could also be used during the second epidemic season for the most vulnerable infants currently affected by the second season of palivizumab. | The place of the maternal vaccine should also be considered in a combined strategy with nirsevimab | Société Française de Néonatologie (SFN) et du Groupe de Pathologie Infectieuse Pédiatrique (GPIP). June 5, 2023 (37).<br>Avis des Sociétés Savantes Françaises de Pédiatrie (38). |
| Sweden | The Läkemedelsverket, with the support of the expert group, recommends the following order of priority:<br>Prophylaxis up to 12 months of age (first RSV season)<br>• Risk group level 1: nirsevimab, or palivizumab if nirsevimab is not available. Priority group for winter season 2023/2024.<br>• Risk group level 2: nirsevimab, if available, in which case priority group for winter season 2023/2024.<br>• Risk group level 3 and 4: nirsevimab, provided that the drug is available to all children in these risk groups and that an equitable national implementation can be achieved | Not included | Läkemedelsverket Swedish Medical Products Agency.<br>September 22, 2023 (39). |
| Luxembourg | Nirsevimab is recommended for:<br>• All newborns born during a period of high circulation of the RSV virus (from October 1 to March 30) preferably before the leaving the maternity ward.<br>• As a catch-up in 2023, non-immunised children born after January 1, 2023 at the beginning of the season of high circulation of the RSV virus (from October 2023).<br>• From 2024, all infants under 6 months of age, born outside the period of high circulation of RSV (April to September), at the start of the season of high circulation of the RSV virus.<br>• Children aged over 12 months of age with underlying conditions that increase the risk of severe RSV infection, annual injection/year, up to 2 years of age | Not included | Conseil Supérieur des Maladies Infectieuses (CSMI).<br>July 14, 2023 (40). |
| Italy | We should consider organising universal administration of nirsevimab before discharge from the maternity ward, for all children born during the October-March epidemic period.<br>Children born between April and September should be passively immunised in October of the year of birth by the local services and their paediatrician of their choice. | Not included | Position Paper. Board del Calendario Vaccinale per la Vita e della Società Italiana di Neonatologia (41). |
| United Kingdom | Preference for year-round immunisation programme to ensure high uptake and for reasons of operational effectiveness, as it would be less complex and resource-intensive to deliver than running seasonal campaigns.<br>No preference for either product. | | Joint Committee on Vaccination and Immunisation (JCVI).<br>September 11, 2023 (31). |
| United States | Maternal RSV vaccination or RSV mAb in infants. Most infants will not need both.<br>Vaccination for pregnant women:<br>• 1 dose of maternal RSV vaccine during weeks 32- 36 of pregnancy, immediately before or during the RSV season.<br>Immunisation of infants and young children:<br>• 1 dose of nirsevimab for all infants aged < 8 months born during or entering their first RSV season.<br>• 1 dose of nirsevimab for infants and children aged 8-19 months who are at increased risk of severe RSV disease and entering their second RSV season. | | Centers for Disease Control and Prevention (CDC) (42). |
| Belgium | Either maternal vaccine for women expected to give birth between early September and the end of March, preferably during weeks 28-36 of pregnancy;<br>or nirsevimab (Beyfortus®) for all babies born to unvaccinated mothers or born prematurely (< 30 w) or within the two weeks following the vaccine administration.<br>Nirsevimab could be offered:<br>- At birth (maternity ward) for babies born during the RSV season (October to March) with a single dose of 50 mg (as < 5 kg)<br>- During the regular immunisation programme (catch-up) for those aged ≤ 6 months at the start of the RSV season, using the dose of 50 mg if < 5 kg; and 100 mg if > 5 kg.<br>- Nirsevimab could be administered with other vaccines.<br>Administration of nirsevimab to infants born to vaccinated mothers could be considered for<br>• infants with a sufficiently increased risk of severe RSV disease and born to mothers vaccinated at the end of the season (between January and March)<br>• infants born to women expected to have an inadequate immune response to vaccination (immunocompromised status) or reduced transplacental antibody transfer<br>• infants who have undergone cardiopulmonary bypass or neonatal blood exchange resulting in loss of maternal antibodies.<br>In premature babies, nirsevimab should be administered 48 hours before discharge home (during the RSV season or during the month before).<br>Nirsevimab is recommended for children at increased risk of severe disease nirsevimab during their first RSV season until age of 11 months at start of the season and if the mother has not been vaccinated or has been vaccinated at the end of the season (January - March) and during their second RSV season (regardless of the vaccination status of the mother). | | Superior Health Council. December 2023. |

Some of these recommendations are outside the EMA label (prevention of RSV LRTI in neonates and infants during their first RSV season)(14)

modelling was robust (31).

The JVCI Committee raised the question whether existing and future maternal vaccines for other diseases might make maternal vaccination a crowded space (26).

The JVCI Committee agreed that, based on current data, no product can be preferred over the other and that at present there is a preference for a year-round programme of either maternal vaccine or mAb, but that a seasonal programme is also an option.

The JCVI had previously recommended that palivizumab should be replaced by nirsevimab for the currently eligible cohort (31).

## Recommendations

Strategies for implementing preventive measures should be based on epidemiological and socioeconomic data (32). Recommendations will depend on the organisation of health care systems in different countries and settings. Issues for discussion include the optimal choice between available agents and their respective target population (i.e., only infants with risk factors or all infants in the first 6 or 12 months of life) and schedule (i.e., pre-seasonal, seasonal with catch-up, all year-round). Because all infants are at risk of developing MA RSV LRTI during their first year of life and more than 85 to 90 % of infants hospitalised for RSV infection are previously healthy, experts support universal pre-seasonal immunisation against RSV (33, 34).

Published recommendations about RSV prevention in children are summarised in Table 3 (30, 31, 35-42). Some of these recommendations are outside the EMA label (prevention of RSV LRTI in neonates and infants during their first RSV season).

## The Belgian Paediatric RSV Experts Group opinion

Based on the literature review, available epidemiological data, guidelines from other countries and taking into account:

- the accumulating epidemiological data on the severe health burden
- the major social and economic impact of RSV infection, with high direct and indirect costs
- that virtually all infants are infected before the age of 2 years
- that most MA cases, including hospitalisations, occur in otherwise healthy term infants
- that most RSV-associated hospitalisations occur before the age of 1 year, with almost 25 % occurring between 6 and 12 months of age (2, 3, 6)
- the seasonality of RSV infections in infants
- the availability of a safe and effective long-acting mAb (nirsevimab) and an effective maternal vaccine (RSVpreF) for the prevention of MA RSV LRTD in newborns and infants from birth through their first RSV season,
- the recommendations and advice of many European paediatric societies, JVCI, CSMI, and CDC

<u>The Belgian Paediatric RSV Experts Group recommends:</u>

- an immunisation strategy for:
  - all infants aged < I year, at the start of their first RSV season
  - infants with risk factors aged < 2 years, also at the start of their second RSV season
- implementation both in and out of-hospital
- either
- passive immunisation with nirsevimab (Beyfortus®):
  - for neonates at the maternity/neonatal unit before discharge or at the paediatric outpatient come-back visit at one week of age during the epidemic season from October to March.
  - at the beginning of the season (October) for infants born outside epidemic seasons of:
    - all infants under one year of age,
    - infants with risk factors in the second year of life,
  - OR passive immunisation of the newborn with the maternal RSVpreF vaccine (Abrysvo®):
- strategy and implementation to be discussed and agreed with obstetricians, gynaecologists and experts on maternal immunisation. The Superior Health Council (SHC) recommends vaccination, preferably between 28 and 36 weeks of gestation, for mothers suspected to deliver between early September and the end of March (30).
- Administration of nirsevimab (Beyfortus®):to infants born from vaccinated mothers could be considered (30):
  - For infants at sufficiently increased risk of severe RSV disease and born from mothers vaccinated at the end of the season (between January and March)
  - For all babies born within 2 weeks following maternal RSVpreF vaccine administration
  - For infants who have undergone cardiopulmonary bypass or neonatal blood exchange, resulting in loss of maternal antibodies.
  - When pregnant woman is expected to have an inadequate immune response to vaccination or a reduced transplacental antibody transfer.
- a low cost to parents and quick refund, in order to avoid health inequalities
- a sufficient supply
- a well-coordinated referral system with clear communication channels to optimise interdisciplinary collaboration
- a practical, easily accessible online registration procedure to collect immunisation data in a national immunisation/vaccination database
- a real-world observational survey of efficacy during the first 5 years of use
- awareness campaigns with tailored messages addressed to health care professionals, parents, lay public and caregivers.

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## Conflict of interest

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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BIOCODEX

ESSENTIELE GEGEVENS. NAAM VAN HET GENEESMIDDEL Enterol 250 mg poeder voor orale suspensie. Enterol 250 mg harde capsules. *Saccharomyces boulardii* CNCM I-745. KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING Enterol 250 mg poeder voor orale suspensie: Elk zakje poeder voor orale suspensie bevat 250 mg gelyofiliseerde *Saccharomyces boulardii* CNCM I-745 (hetzij minstens 6 x $10^9$ levensvatbare cellen op het ogenblik van de fabricage en 1 x $10^9$ gelyofiliseerde levensvatbare cellen op de vervaldatum). Enterol 250 mg harde capsules: Elke harde capsule bevat 250 mg gelyofiliseerde *Saccharomyces boulardii* CNCM I-745 (hetzij minstens 6 x $10^9$ levensvatbare cellen op het ogenblik van de fabricage en 1 x $10^9$ gelyofiliseerde levensvatbare cellen op de vervaldatum). Hulpstof(fen) met bekend effect (zie rubriek 4.4 van de SKP): Enterol 250 mg poeder voor orale suspensie: fructose, lactosemonohydraat, sorbitol. Enterol 250 mg harde capsules: lactosemonohydraat. Voor de volledige lijst van hulpstoffen, zie rubriek 6.1 van de SKP. FARMACEUTISCHE VORM Enterol 250 mg poeder voor orale suspensie: Poeder voor orale suspensie. Enterol 250 mg harde capsules: Harde capsule. KLINISCHE GEGEVENS Therapeutische indicaties • Preventie van diarree bij behandeling met breedspectrumantibiotica van patiënten voorbeschikt tot het ontwikkelen van diarree door *Clostridium difficile* of hervallen in een diarree veroorzaakt door *Clostridium difficile*. • Adjuverende behandeling naast orale rehydratie van acute diarree bij kinderen tot 12 jaar. Dosering en wijze van toediening Dosering: Volwassenen: 2 tot 4 harde capsules of 2 tot 4 zakjes per dag, in 2 innames. Pediatrische patiënten Kinderen: 2 harde capsules of 2 zakjes per dag, in 2 innames. Wijze van toediening: • Harde capsules: de harde capsules met wat water inslikken. • Zakjes: het poeder mengen in een glas water. Te nemen voorzorgen voorafgaand aan gebruik of toediening van het geneesmiddel Vanwege een risico op besmetting via de lucht, mogen zakjes of capsules nooit worden opengemaakt in patiëntenkamers. Beroepsbeoefenaren in de gezondheidszorg moeten tijdens het hanteren en het toedienen van probiotica handschoenen dragen, waarna de handschoenen onmiddellijk moeten worden weggegooid en de handen moeten worden gewassen (zie rubriek 4.4 van de SKP). Duur van de behandeling Preventie van een nieuwe episode of recidief van diarree door *Clostridium difficile*: 4 weken. Behandeling van diarree als aanvulling op orale rehydratie bij het kind: 1 week. Contra-indicaties • Overgevoeligheid voor de werkzame stof of voor één van de in rubriek 6.1 van de SKP vermelde hulpstoffen. • Patiënten met een centrale veneuze katheter, patiënten in kritieke toestand of immuungecompromitteerde patiënten, vanwege een risico op fungemie (zie rubriek 4.4 van de SKP). • Allergie voor gisten, vooral *Saccharomyces boulardii* CNCM I-745. Bijwerkingen De bijwerkingen worden hieronder geklasseerd per orgaansysteem en volgens de frequentie. Die laatste wordt als volgt gedefinieerd: zeer vaak (≥ 1/10), vaak (≥ 1/100, < 1/10), soms (≥1/1.000, < 1/100), zelden (≥ 1/10.000, < 1/1.000), zeer zelden (< 1/10.000), niet bekend (kan met de beschikbare gegevens niet worden bepaald). Systeemorgaanklasse Frequentie Infecties en parasitaire aandoeningen Zeer zelden: fungemie in patiënten met een centraal veneuze katheter en in patiënten in kritieke toestand of immuungecompromitteerde patiënten (zie rubriek 4.4 van de SKP), mycose door *Saccharomyces boulardii* CNCM I-745. Frequentie niet bekend: sepsis bij patiënten in kritieke toestand of immuungecompromitteerde patiënten (zie rubriek 4.4 van de SKP) Immuunsysteemaandoeningen Zeer zelden: anafylactische shock Bloedvataandoeningen Zeer zelden: anafylactische shock Ademhalingsstelsel-, borstkas- en mediastinumaandoeningen Zeer zelden: dyspneu Maagdarmstelselaandoeningen Zeer zelden: verstopping, epigastralgie, abdominaal meteorisme (epigastralgie en abdominaal meteorisme werden waargenomen in klinische studies) Huid- en onderhuidaandoeningen Zeer zelden: jeuk, exantheem, Quincke-oedeem Algemene aandoeningen en toedieningsplaatsstoornissen Zeer zelden: dorst Melding van vermoedelijke bijwerkingen Het is belangrijk om na toelating van het geneesmiddel vermoedelijk bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem (Website: www.eenbijwerkingmelden.be, e-mail: adr@fagg.be). HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN BIOCODEX Benelux NV/SA - Marie Curiesquare 20 - 1070 Brussel - België Tel: 0032(0)23704790. NUMMERS VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN Enterol 250 mg poeder voor orale suspensie: BE 269026. Enterol 250 mg harde capsules in glazen flesje: BE 269035. Enterol 250 mg harde capsules in blisterverpakking: BE 397896. AFLEVERINGSWIJZE Vrije aflevering DATUM VAN HERZIENING VAN DE TEKST Herziening: 01/2023. Goedkeuring: 03/2023.

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# Gut colonising microbiota in early life as a crucial step in the acquisition of tolerance to food antigen in the first months of life

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## Keywords

Milk human ; Breast Feeding ; Infant ; Newborn ; Intestine ; Mucous Membrane ; Microbiota ; Epigenesis.

## Abstract

Perinatal bacterial colonisation of the newborn's intestine is an essential key stage in the development of local immunity. The quality of its initiation on a still immature digestive mucosa and submucosa will eventually enable the acquisition of an immune balance between defence mechanisms and tolerance to antigenic epitopes of all kinds, firstly locally and then in the whole body. Failure to acquire this immune balance, favoured by complex epigenetic reactions linked to inadequate environmental modifications, can have a lasting impact on the development of subsequent general immunity. Exclusive and prolonged breastfeeding as stated by the World Health Organization (WHO) remains the only way of ensuring not only the quality of the colonising microbiota in the first few months of the infant's life, but also the quality of the development of this immune balance. This is linked to the completeness of human milk, rich in perfectly bioavailable constituents and complex, multiple immunomodulatory factors, which together enable it to be described as a functional food par excellence.

## Introduction

Our understanding of the immune mechanisms governing the acquisition of tolerance to food antigens, firstly in the digestive epithelium, with secondary effects on other epithelia, has made enormous progress in recent years (1-13). Thanks to the various experimental studies carried out in this field, in which the similarities between intestinal immune responses in humans are becoming increasingly apparent, it is now clear that the perinatal microbiota that colonises the newborn's intestine plays a key role (14, 15). This colonising microbiota of a mucosa that is still immature enables both the initiation of immune defence mechanisms against invading bacteria and those that are set up in parallel and govern the tolerance of a progressively selected commensal microbiota (16). This balanced immune response will also provide the means to ensure good memory tolerance to environmental antigens, including food. This immune initiation takes place within the intestinal mucosa and submucosa. Without this colonising microbiota in the newborn, none of these defence and tolerance immune responses can be properly established (8, 12). Although these responses are at first sight opposites, they complement each other to achieve a balance that must be maintained throughout life (Figure). Failure to establish this all-important balance correctly at an early age can then have repercussions both locally and throughout the body, increasing the risk of immune deviations of all kinds. Preventing these problems involves firstly finding the best way of ensuring the quality of this colonising microbiota, and secondly improving the way in which food antigens are administered at a very young age.

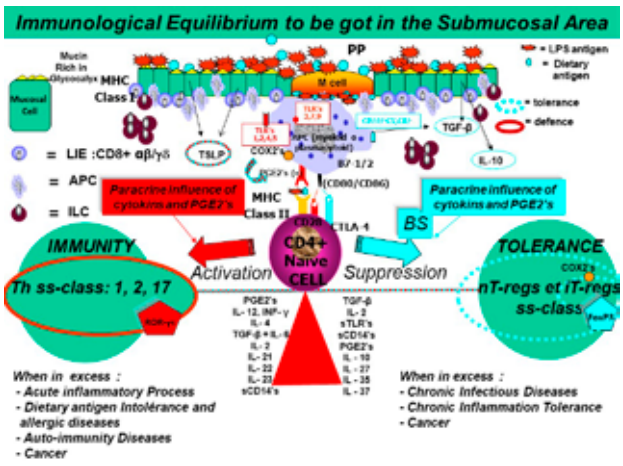
The neonatal enterocyte appears to be particularly well prepared for the initial establishment of a reciprocal biochemical dialogue with invading bacteria (17, 18). The colonising microbiota enables gene modulation of this mucosal cell and the creation of specific niches through specific glycosylation of the glycocalyx under the action of bacterial enzymes. It is this interaction between the host and the invading microbes that will gradually lead to the establishment of this all-important interface between the cells of innate immunity and the cells of adaptive immunity, the essential cellular organs of this digestive immunity and of essentially paracrine expression (from the Greek (παρα = beside) and (κρίηο = to secrete). This is done through various cytokines, i.e., the small proteins secreted by the cells of innate and adaptive immunity (Figure), with either pro-inflammatory or suppressive anti-inflammatory cascade actions.

There can be no doubt that exclusive and prolonged breastfeeding in early childhood is the only way not only to ensure the quality of the intestinal microbiota gradually tolerated by the child, but also to optimise this interface between the host and its microbiota, enabling locally induced immune defence mechanisms and long-term mechanisms for tolerance of environmental antigens, including food. The WHO is constantly reminding us of this, as it is responsible for ensuring the ideal nutritional recommendations for young children throughout the world (19). However, the human milk microbiome is largely influenced by perinatal maternal environmental factors (20).

## Critical period: immune priming of the antigenic epitope on an immature digestive mucosa, de facto immaturity during the first year of life.

At this stage in the general debate on how to help prevent all these immune deviances, which could be linked to the type of food given at

Figure:




Legends : PP: Peyer's patches; ILL: intraepithelial lymphocyte; APC: antigen-presenting cell or dendritic cell; CD: Cluster of differentiation; TLR: Toll Like Receptor; LPS: Lipopolysaccharide; MHC: Major Histo-compatibility Complex; IL: Interleukin (or cytokine); TSLP: Thymic stromal lymphopoietin; ILC: Innate Lymphocytic Cell; PGE2: Prostaglandin E2; COX: Cyclooxygenase; TGF : Transforming Growth Factor; CTLA: Cytotoxic-T-Lymphocyte- Antigen 4 protein ; nTreg: Native regulatory lymphocyte (thymic origin (n for native)); iTreg: Induced regulatory lymphocyte (peripheral origin (p) or induced (i)); INF : Interferon; BS: Bystander Suppression; MHC: Major Histocompatibility Complex; ROR-γτ: retinoic acid-related orphan receptor-γt transcription factor; FoxP3: forkhead box P3 transcription factor.

an early age, the problem that some people do not seem to understand sufficiently is the risk of sub-optimal *priming*, i.e. the risk of an inadequate imprint left on the intestinal immune system by the dietary antigenic epitope when it is administered inadequately for the first time. This is particularly true when the exogenous environmental antigenic load is too rapidly excessive, and not reproduced in a progressive increase. This notion of the importance of repetition of the antigenic epitope to mark the immune acceptability of tolerance had previously been highlighted in experimental models, and subsequently confirmed (3). Although these data are mainly based on experimental animal studies, it has become clear in recent years that the same principles of response by the innate and adaptive immune cells of these digestive mucous membranes and submucosa apply to all vertebrates and specifically to humans (14). However, the nomenclature of the immune cell receptors involved may sometimes be slightly different (15).

At an early age, this sub-optimal *priming* of the environmental antigen protein on the digestive mucosa may in fact be the source of induced immune deviations which will only manifest themselves when the antigenic epitope in question is reintroduced at a later stage. The risks of intolerance to this epitopic antigenic food imprint on the immature digestive immune system in infancy are all the greater now that there has been a change in the birth paradigm in recent years, which clearly impacts on the quality of the colonising microbiota of the newborn's intestine (16). Indeed, there has been a marked increase in the hyper-medicalisation of the birth process, as well as an increase in antibiotic therapy, but also a repetitive increase in the administration of certain xenobiotics at an early age, an increase in Caesarean section births, and an excessively marked decrease in prolonged exclusive breastfeeding (21, 22, 23).

We now know that this excessive and unique antigenic load in infancy, i.e. not repeated, on a mucosa that is still partially immature and not stabilised at the level of its interface with a colonising microbiota that is often disturbed by our modern perinatal medicine, creates tolerance essentially by stimulation of innate immunity, with apoptotic cell deletion and/or anergy of innate immunity cells, but without optimal solicitation of adaptive immunity (3). Only by stimulating the adaptive immune system can this tolerance be permanently memorised and acquired centrally.

## Basic mechanisms involved: complex optimal interface at the digestive level between innate and adaptive immunity.

This immune tolerance to environmental antigens in the broadest sense, acquired locally at first and then memorised throughout the body, can only be achieved through the intervention of innate immunity cells which correctly control the development of adaptive immunity cells, first locally and then more generally (10,11,13,24). This local innate immunity is, first and foremost, represented by the mucosal cell itself, and the M cells which overlie Peyer's patches, submucosal lymphoid organs extremely rich in naive T and B lymphocyte cells (7). This submucosal region also contains many other innate cells, and particularly $CD8^{+}\gamma\delta$ intraepithelial lymphocytes (IELs), innate lymphocytic cells (ILCs) in submucosal clusters and their respective main specific cytokines (IL's-2,22) (24). These cells express type I histocompatibility factor (MCH-I), which expresses their limitations. The relay of information within the submucosal chorion on the nature of the antigenic epitope is then essentially conveyed by a wide variety of other multifunctional and highly specific innate cells, present in very large numbers at this level from an early age. They play a truly crucial role. Through direct contact and co-stimulation, these key cellular organs enable the immune orientation of naive $CD4^{+}$ effector lymphocyte cells, which are the linchpins of adaptive immunity: these cells driving all immune signals to the $CD4^{+}$ naïve lymphocyte are the dendritic cells, also known as antigen-presenting cells (10, 13, 25). These dendritic cells, still classically classified in the broad category of macrophages and therefore part of innate immunity, express histocompatibility factor type II (MHC-II), which makes their multiple respective functions clearly visible, depending on the information received via some of their specific receptors (Figure) (26). This cellular pluripotentiality of immune function will contribute, through their different receptors expressed on their surface, to the optimal analysis of the nature of the antigenic epitope presented to them by the intestinal mucosa (mucosal enterocytic cells, goblet cells and M cells) but also by these other innate immune cells (7).

## Proper initiation of innate cellular immunity in the chorion-submucosa optimises the messages it transmits to the local adaptive immune system.

These dendritic cells will therefore transmit this information about the nature of the antigenic epitope to the naive lymphocyte cells of the adaptive immunity, which is composed primarily of naïve $CD4^{+}$ (effector) and CD8+ αβ (suppressor) lymphocytes present in large numbers in lymphoid nodules and Peyer's patches. This transmission occurs by direct contact, giving rise to a paracrine secretion of cytokines of corresponding quality and number, in response to the type of co-stimulation recorded. For bacterial and/or fungal and/or parasitic antigens of all kinds, as well as for environmental antigens, this transmission of information takes place in parallel via co-stimulation of their respective cell receptor (between dendritic cell and naive $CD4^{+}$ lymphocyte cell) (Figure). This optimisation of the immune information transmitted to the naïve $CD4^{+}$ lymphocyte by parallel co-stimulation in close cell contact, via one of its receptors (the CD28 receptor), followed by the specific paracrine secretion of these immunomodulating proteins, the cytokines, will initially enable an adaptive immune defence response. This will be balanced between naïve $CD4^{+}$ lymphocytes (Th1 and/or Th2 and/or Th17 type effector response, and their respective essential cytokines (IL-12, IL-4, Il-17). This will be followed, on the one hand, by the mature $CD4^{+}$ Th1 lymphocyte (cytokine INF-gamma, Il-2), and the appropriate initiation of the CD8+ αβ lymphocyte (killer), allowing this latter immune pathway to control delayed hypersensitivity (DHS), and, on the other hand, the parallel maturation of the naïve $CD4^{+}$ lymphocyte into a Th2 lymphocyte, under the impetus of the Il-4 cytokine, which immune pathway will promote, by subsequent direct contact, the transformation of the naïve B lymphocyte into a plasmocyte cell. After maturation in the lymphoid organs, this plasmocyte cell can synthesise the IgGs for which it has been programmed. The recolonisation of the submucosal chorion by IgA's-secreting plasmocyte cells, and even more so by secretory IgA's (sIgA's), i.e. IgA's which include the joining chain and secretory component (SC), plays a vital role. These sIgA's are found not only in the intestinal lumen

but also in exocrine glands, in this case and in adulthood the mammary gland in breast-feeding women. Of outstanding interest, the mother thus distributes not only her own microbiota to her child from birth, but also, through her milk, these corresponding sIgA's. In other words, sIgA's do represent the best immune means for the newborn to protect himself from the perinatal invading microbiota, as he is not yet capable of synthesising them correctly.

Following this defensive immune stimulation, in a recurrent situation of bacterial receptor saturation, marked in particular by their consequent partial paracrine extrusion, in the form of soluble glycoproteins (sTLR's (*Toll Like Receptors*) and sCD14's for the essential ones, ....), the newly generated local paracrine immune climate will enable a paradigm shift in the immune response of dendritic cells, via some of their specific receptors ($CD103^+$, for the most part). This will promote the adaptive transformation of the same naive $CD4^+$ lymphocyte, but this time, through another type of co-stimulation of one of its receptors (the CTLA-4 receptor), into an iTreg induced regulatory suppressive lymphocyte ($CD4^+$ $CD25^+$ $FoxP3^+$), capable of continuing to secrete the tolerance suppressing cytokine TGF-β) and, by bystander suppression (or direct proximity suppression), into a peripherally induced suppressor lymphocyte iTreg Tr1, with secretion of the tolerance suppressor cytokine, (IL-10) and Th3 $FoxP3^-$, with secretion of the tolerance suppressor cytokine, (TGF-β).

Our general immune health will in fact depend on the balance shown in the Figure, progressively acquired at local level and then maintained at the level of all the other mucous membranes, between, on the one hand, the effector response of adaptive immunity, capable of providing this defence against foreign micro-organisms, and, on the other hand, the tolerance suppressive response of adaptive immunity, capable of providing tolerance of the commensal microbiota as well as tolerance of the environmental antigen, including the food antigen.

Although this process is still immature at an early age, it is now clear from current experimental models that the inadequacy of this intestinal mucosal response at an early age, through complex epigenetic mechanisms is likely to have a negative impact on the quality of general immunity to this same environmental antigen, including in other mucous membranes (particularly respiratory) (27, 28). This can lead to subsequent severe immune deviations, which may be more marked if a genetic background conducive to their development is also present.

## In practice, what attitudes should be recommended for all nutritionist clinicians working in maternity wards: their role in preventing subsequent immune deviations is crucial.

In practical terms and based on a general principle, it is essential to avoid at all costs giving the newborn single supplements of formula milk, i.e., with large quantities of foreign protein epitopes, at least when the mother's intention is to breastfeed over the long term (29). Human milk given exclusively is Nature's way of repeatedly distilling all the mother's environmental antigenic epitopes, including all the food antigens present in her own milk in small quantities (30,31). Furthermore, human milk contains large quantities of soluble immunomodulatory factors described in the digestive submucosal chorion, which help the newborn to acquire immune tolerance within its digestive tract (Table). The microbiome content of human milk is also largely dependent of maternal perinatal factors (20).

Whatever the nature of a milk formula supplement given to a baby whose mother is planning to breastfeed completely, this food supplement runs the risk of negatively modifying the beneficial protective action exerted on her child's digestive tract thanks to the perfect completeness of human milk. Only this completeness makes it a unique functional food par excellence, capable of promoting the establishment of an ideal digestive microbiota. Midwives in maternity wards have understood this well when, on the contrary, they favour the manual extraction of colostrum from breastfeeding mothers. This is particularly the case when spontaneous breastfeeding is less well initiated by the newborn itself and/or when its medical situation requires a very temporary nutritional supplement. Where there is a risk of hypoglycaemia and/or proven hypoglycaemia, for example, the use of dextrose gels should be recommended as a priority, based on the results of recent well-conducted studies (32). It also appears that it does not alter the quality of the neonatal colonising intestinal microbiota. In fact, in addition to the risk of an incorrect immune imprint on the newborn's digestive tract when given inadequately in a single dose with a high epitopic load, any milk formula supplement - which is therefore not of human origin - interferes negatively with the benefits provided by the famous bifidogenic triad in breast milk. This complementary triad of three specific constituents, enabling the establishment of a beneficial acidophilic microbiota, is recalled here: 1) the high lactose content; 2) the low protein content of human milk but with a high bioavailability value; 3) the low phosphorus content of human milk with an optimal calcium/phosphorus ratio for at term neonate. Together, with the interesting acidophilic bacteria's nutritional support of human

| Nutrients | Amount | Function |
|---|---|---|
| **Protein** | | |
| - sIgA (IgG, IgM) | 50 – 100 mg/dL | Specific immune protection |
| - Lactoferrin | 100 – 300 mg/dL | Bacteriostasis and bactericidy; iron carrier |
| - Lysozyme | 5 - 25 mg/dL | Bactericidy |
| - α-Lactalbumin | 100 - 300 mg/dL | Part of lactose synthase; anti-infective |
| - Hamlet Component | - | Anti-infective; bactericidy, tumoricidy |
| - sTLR2,4,5; sCD14, TGFβ | Variable | Anti-inflammatory action – specific receptors |
| - Lactadherin | Variable | Bacteriostasis – immune modulator |
| - β-defensin 2 | Col ± 8.5; Mat ± 1;0 µG/ml | Bactericidy – negative modulation on TLR7 |
| - Caseins | 200 - 300 mg/dl | κ-Casein; bifidogen; inhibition bacterial adherence |
| **Carbohydrates** | | |
| - Lactose | 6.5 – 7.3 g/dL | Energy source |
| - Oligosaccharides | 1.0 – 1.5 g/dL | Microbial ligands; 3'GL neg modulation on TLR3 |
| - Glycoconjugates | - | Microbial and viral ligands |
| **Fat** | | |
| - Triglyceride | 3.0 - .4.5 g/dL | Energy source |
| - LC-PUFA | Variable | Essential for brain and retinal development |
| - FFA | Variable | Anti-infective as bacterial detergents |

The essential immunomodulatory components of human milk. LC-PUFA: long chain polyunsaturated fatty acids; FFA: Free Fatty Acids; sTLR: soluble Toll Like Receptors; TGF-β: Transforming Growth Factor.

milk oligosaccharides (HMO's), because of their quantity and structural diversity, they maintain this low buffering capacity in the intestinal lumen and encourage the growth of this beneficial fermenting microbiota. This low buffering capacity, which is conducive to the establishment of an acidophilic microbiota composed essentially of bifidobacteria and acid-lactic bacteria (*Lactobacilli, Akkermansiae,...*), is only present when human milk intake is complete. In fact, it is the low buffering capacity of human milk that generates and maintains a fermenting microbiota. This microbiota, thanks to the local anaerobic metabolism it induces, is uniquely able to maintain a low pH in the intestinal lumen of exclusively breastfed newborn infants, thereby reducing the risk of intestinal invasion by more pathogenic germs (33). This maintained fermenting microbiota is also able to favour this ideal interface with the colonised host at the level of its digestive mucosa, for a high-quality local immune response.

The only indication to give the neonate, very temporarily and preferably, an advanced casein hydrolysate, or even an amino acid complex, could prevail when there is an absolute and well-considered (and therefore rare) need to give a single supplement - or one that is very rarely repeated. It does matter if the mother has a clear plan for prolonged breastfeeding. This may be understandable only because her breastfeeding does not start immediately and perfectly and there is not enough hand-extracted colostrum available. Only advanced casein hydrolysate - and better still, the complex elementary formula made up solely of amino acids - has shown some prevention of this inadequate priming in the case of the former - and therefore some preventive efficacy, but the level of evidence remains low (34). In fact, no hydrolysed milk given at an early age, whether partially or completely, is currently capable of preventing the development of long-term immune deficiencies, whatever their nature (allergic and/or autoimmune deficiencies) (35, 36). Only in well-conducted studies (and only in those studies) has prolonged exclusive breastfeeding shown to some limited extent a tendency to prevent immune deviations (37,38). The relative disappointment observed in the absence of long-term prevention of these immune deviations by prolonged breastfeeding, as also demonstrated in the PROBIT study, is linked to the existence of the early epigenetic reactions on the genome already mentioned which interfere with local digestive immunity, factors not yet sufficiently identified - and therefore not controlled - but probably linked to these inadequate repetitive environmental factors (27, 28, 39).

In other situations, particularly those where mixed breastfeeding by choice of the mother is used for a longer period from the outset, and/or of course if the mother does not wish to breastfeed, it does not really matter which milk is given as a supplement, if it is not given all at once in large quantities, but rather repeated over several days, gradually increasing the antigenic load. This basic principle should also be borne in mind when improving antigen *priming* during the dietary diversification phase, which should ideally be initiated at around 6 months, as the WHO continues to recommend (19). Any introduction of food antigens during the first year should therefore ideally be initiated according to the same principle of gradually increasing epitopic load repetitions, in the same way between 6 and 12 months, on a digestive mucosa and submucosa that are still immature in terms of the immune response induced. This should happen for all newly introduced foods, ideally as a complement in addition to breastfeeding, which should be preferred for as long as possible. In fact, during this period, breastfeeding should be maintained as the essential milk intake. According to new concepts, this defined period of optimal diversification represents an ideal immune window to try to reduce the subsequent risks of allergy (40). It is therefore desirable to take greater responsibility for the immune *priming* of any food newly introduced during the first year, which is far from being the current approach. This new form of dietary diversification must (should) therefore also consist of a gradual and repeated increase in the antigenic load of this new food, whatever it may be, and whatever the possible genetic susceptibility of the atopic family.

This new way of proceeding would promote memorised immune tolerance to these newly introduced environmental antigens. This will allow the appropriate immune *priming* of the submucosal intestinal chorion, which is so important for the lifelong acquisition of the necessary memorised immune tolerance, which should make it possible to control any inadequate reaction to the introduced environmental antigen. This locally acquired tolerance is then transmitted to the other epithelia through the colonisation of all the lymphoid organs by immune cells with tolerance memory for this antigen. Experimental studies show that a fortnight's repetition, every day, of the dietary antigen is enough to obtain tolerance that is permanently anchored in the immune memory, but this remains to be proven in humans.

However, the latest studies show that, when this initial priming of the food antigen is inadequate, it is difficult to recover the tolerance induced by the oral route, even though certain recent trials using the same principles of repetition of a small stabilising daily dose with a progressive increase in load are beginning to give interesting results, i.e., a certain degree of recovery of the immune tolerance response. This highlights the lifelong impact of the inadequacy of the initial *priming*, which has led to a memorised immune intolerance response. It is precisely this inadequacy of *priming* at an early age, on this still immature mucosa ,that must be avoided in the first place to enable the induced tolerance to the antigenic food epitope to be initiated for life and not, on the contrary, to induce a memorised intolerance that is difficult to recover later on (16).

## What are we to make of the recommendations recently published by French paediatric allergists?

French paediatric allergists now seem to have understood the importance of primary prevention of food allergy by improving the immune *priming* of the food antigen at a very early age in the mucosal and submucosal intestinal system, a *priming* that is optimally obtained as described briefly above in terms of the complex immune mechanisms involved (41). They understand the importance of this form of introduction of food antigens, a form of introduction which was raised long before their observation as requiring well-conducted studies to try to improve this memorised optimal acquisition of tolerance to the food antigen and, consequently, to try to prevent immune deviations of intolerance (42).

However, what these paediatric allergists are currently tending to do, and what poses a major ethical concern in the way they are progressing, is to recommend the introduction of small quantities of formula milk at a very early age, in case of familial atopic diseases, even in newborns who are perfectly and completely breastfed by their own mothers. What's more, this is being done without any validation support in the form of prospective, randomised scientific research that has demonstrated the merits of this practice. The European *Academy of Allergy and Clinical Immunology* (EAACI) had suggested that further in-depth studies should be carried out (43). In addition, the *American Academy of Pediatrics* (AAP) has also taken a position on two occasions (2008 and 2019), concluding that there was insufficient evidence to suggest changing the timing and type of dietary diversification. It invited stakeholders to carry out further randomised prospective studies (44). This debate in Europe on the very early introduction of food antigens during the breastfeeding phase is not new (45). It was vehemently opposed in the past, when it was first recommended for children exclusively breastfed by their mothers (46). In so doing, French paediatric allergists are ignoring what Nature itself spontaneously ensures by repeated distillation of all the mother's environmental antigens present in her own milk (30, 31). Even if these data still need to be clarified, as they are essentially based on experimental models, this 'neglect' of what Nature seems to do in all mammals to promote food tolerance in their offspring is also being done with the 'benevolence' of the firms that manufacture milk formulas and infant products. On the other hand, they have found here an opportunity to promote their product in the very early administration of milk supplements to mothers who wish to breastfeed their babies completely.

How can it be imagined that a mother could be involved in this 'sorcerer's apprentice' approach when each of them considers that her milk, given exclusively and over a long period of time to her newborn baby, is reputed - quite rightly - to be the best food for him at an early age. This subliminal "benevolence" on the part of milk companies was virulently denounced in a recent special issue of the Lancet (https://www.thelancet.com/series/Breastfeeding-2023) (47). By acting in this way, these French paediatric allergists are bypassing the essential research stages required to confirm the validity of these practices in humans and are playing the sorcerer's

apprentice. Worse still, they are ignoring WHO recommendations, which stress the importance of exclusive breastfeeding for 6 months and, if possible, breastfeeding in addition to dietary complements thereafter (19). Let's not forget that the WHO publishes recommendations and provides the impetus for optimal public health research for the world's children, first and foremost. It is not a question of giving small quantities of formula milk to babies breastfed by their own mothers, in countries where food safety is more precarious, with the possibility of reconstituting the formula milk with contaminated water. Just imagine the damage this could cause, as we have seen in the past! What is just as serious mistake in this article recently published by French paediatric allergists is that they recommend repeating ultra-processed foods from the age of 4 months, which is precisely what needs to be combated in terms of obesity prevention (48).

Whatever the atopic familial status, the point here is therefore to reiterate the importance of not giving milk formula supplements in maternity wards, and as a single administration, an importance that must be asserted vigorously, giving preference to all other known means, including manual extraction of colostrum to get through any difficult stage at the start of breastfeeding. As explained above, these one-off supplements, with their high antigenic load from the outset, are precisely the source of possible subsequent immune deficiencies when cow's milk protein is reintroduced. The one and only indication for repeating small doses of formula milk would be when the paediatrician and/or clinical nutritionist is confronted with newborns who have had to receive a single supplement of formula milk for medical reasons, and where natural supplements following colostrum extraction from the mother could not be provided.

It may be possible to discuss with French paediatric allergists the merits of introducing diversification at around 4 to 5 months of age, which is often the case in our so-called civilised countries, if possible, also in addition to breast milk. However, there can be no question at this stage of systematically giving formula milk supplements to mothers who full breast feeders are! This is quite simply nonsense at this stage, nonsense that runs counter to *Evidence Based Medicine* (EBM) and risks having serious consequences for infants the world over!

## In conclusion

At this point, it is important to reiterate in the strongest terms the importance of prolonged and exclusive breastfeeding during the first 6 months of life: this is the only way to ensure an optimal colonising microbiota in the newborn's intestine and, consequently, an immune response initiated, and defined as optimal, in the intestinal mucosa and submucosa. This is Nature's way of ensuring a good balance in the immune response, between defence and tolerance, to counteract as best as possible any inadequacy in the *priming* of the environmental antigen on the neonatal digestive tract. While this new concept of repeating the antigenic load of a food given for the first time is perfectly acceptable, if the doses are increased gradually and in in addition to breastfeeding, it will first be important to demonstrate its value through well-conducted randomised trials from 6 months of age up to 12 months, which seems to be the ideal immunity window. However, the WHO recommendations on exclusive breastfeeding for up to 6 months should be respected.

In absolute terms, and in keeping with the scientific rigour that must be maintained, we should avoid recommending practices that have not yet been tried and tested, and we should not act like sorcerer's apprentices. Above all, it is important for all doctors and others involved in perinatal health to think of the interests of all the world's newborns, some of whom are born in conditions that are sometimes more difficult in terms of their health care. Nature provides them with protection through well-managed, exclusive, and prolonged breastfeeding, a natural protection that should not be disrupted.

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LABORATOIRE

# Food allergy in children in 2023

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## Keywords

Food hypersensitivity ; allergens ; anaphylaxis ; allergic dysmotility disorder ; proctocolitis ; enterocolitis ; atopic dermatitis ; child.

## Abstract

The aim of this article is to describe the most common clinical presentations of non-IgE-mediated, IgE-mediated and mixed forms of food allergy.

Four clinical groups of non-IgE-mediated food allergy can be distinguished: food protein-induced dysmotility, food protein-induced allergic proctocolitis (FPIAP), food protein-induced enterocolitis syndrome (FPIES) and food protein-induced enteropathy (FPE). In non-IgE mediated food allergy, cow's milk and soy are the 2 most common offenders, but other food allergens may be involved. Diagnosis is based on clinical criteria, elimination of the suspected food and, if necessary, oral food challenge.

IgE-mediated food allergy has a wide spectrum of clinical manifestations which can involve several organ systems. The most severe manifestation is anaphylaxis. Eight food allergens are responsible for 90% of allergic reactions in children: cow's milk, hen's egg, hazelnut, peanut, soy, wheat, fish and shellfish. Diagnosis is based on a thorough medical history, skin prick testing and serum IgE testing.

Food allergy can also occur as a mixed IgE and non-IgE mechanism, with atopic dermatitis and eosinophilic oesophagitis being the most common clinical manifestations.

Strict avoidance of the offending foods is the main goal in the management of food allergy. This is best achieved in multidisciplinary collaboration with dieticians experienced in food allergy.

## Introduction

When talking about food allergy terms as “allergy”, “intolerance” and “sensitisation” are often inadequately and inappropriately used, causing confusion about which underlying mechanism or diagnosis is exactly meant. In 2001 a taskforce of the European Association of Allergy and Clinical Immunology (EAACI) introduced a revised nomenclature for allergy (1). They proposed the term “hypersensitivity” to be used as an umbrella term for all unexpected reactions (Figure 1). Since then, the term “allergy” is used to describe a hypersensitivity reaction initiated by immunologic mechanisms, which can be antibody- or cell-mediated. In the non-allergic hypersensitivity reactions, an immunologic mechanism cannot be proven. The antibodies typically involved in allergic reaction belong to the IgE-isotype, so we refer to this mechanism as an IgE-mediated allergy. The non-IgE-mediated allergic reactions are often T-cell mediated reactions.

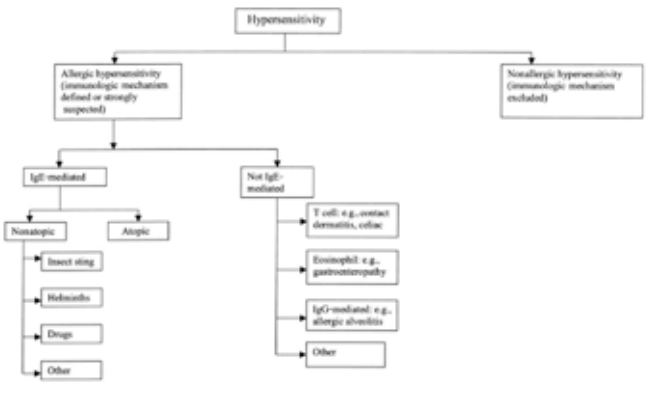



**Figure 1:** A revised nomenclature for allergy: An EAACI position statement from the EAACI nomenclature task force (Johansson SGO et al. Allergy. 2008;56(9):813-24).

This article describes the most common clinical presentations of food allergy in children; non-allergic non-immunologic food hypersensitivity reactions, such as lactose intolerance, are not included in this review.

In IgE-mediated food allergy symptoms arise shortly after ingestion of the culprit food, within minutes to two hours. A thorough anamnesis is the first key to a correct diagnosis of IgE-mediated allergy, i.e. reconstructing the food and contact history in detail, taking into account the time frame, detailed list of the ingredients, previous exposures and reactions, family history, history of eczema, asthma etc. An anamnestically suspected allergy can be confirmed by skin prick tests (with commercial extracts or fresh food allergens) or by measuring specific IgE-levels in a blood sample (CAP-tests). Spontaneous tolerance is rarely seen before two years of age. In 90% of the cases of IgE-mediated food allergy in children, the trigger can be found in the “big 8” group, i.e. cow’s milk, egg, nuts, peanuts, soy, wheat, fish and crustacea.

In non-IgE-mediated allergies, symptoms can develop over a period of one hour to several days, making it more difficult to establish a link between ingestion of the allergen and the onset of symptoms. The diagnosis is suspected after a thorough anamnesis and needs to be confirmed with an elimination diet and possible provocation; other diagnostic tests are not available for this type of food allergy. Cow’s milk and soy are the two most common culprits. In most cases non-IgE-mediated food allergy is infantile pathology; 90-95% of the children are tolerant by the age of one year (2).

Mixed forms of these two types of allergy may also occur, for example in eosinophilic oesophagitis and eczema. And in some patients, we see a switch from the non-IgE to the IgE-mediated form.

## Non-IgE mediated food allergy

Non-IgE-mediated food allergies can be divided into 4 clinical groups: Food protein-induced allergic dysmotility disorders, food protein-induced allergic proctocolitis (FPIAP), food protein-induced enterocolitis syndrome (FPIES) and food protein enteropathy (FPE).

A child suffering from multiple digestive problems, such as gastro-oesophageal reflux disease (GERD), irritability, food refusal/aversion, abdominal discomfort, abnormal bowel frequency and consistency, sometimes in combination with persistent atopic dermatitis, is a frequent reason for parents to seek help from a paediatrician. These symptoms heavily impact the families' quality of life. Non-IgE-mediated allergy is often the cause, with cow's milk protein being the most common trigger. The diagnosis of non-IgE-mediated food allergy is challenging, because of the variable onset of symptoms after ingestion, intervals ranging from 2 hours to several days. The spectrum of symptoms of non-IgE-mediated allergy is also broad, ranging in severity from GERD or mild rectal bleeding to severe vomiting and collapse or failure to thrive (3).

### *A. Food protein-induced allergic dysmotility disorders*

All infants with multiple digestive/abdominal symptoms in the first months of life such as gastro-oesophageal reflux, vomiting, diarrhoea and severe constipation, should be suspected of having cow's milk allergy. Food proteins are detectable in breast milk for many hours or days after the mother's meal, so breastfed infants are also prone to food allergy. These children often cry for several hours a day, leaving their parents desperate for help. They are categorised as "food protein-induced allergic dysmotility disorders" (4).

The 2009 joint ESPGHAN-North American Society for Paediatric Gastroenterology Hepatology and Nutrition guidelines on GERD already recognised the possible role of non-IgE mediated cow's milk allergy (CMA), and the 2018 updated guidelines this have further increased its importance in the treatment pathway by considering a cow's milk elimination diet prior to the use of medications in infants <1 year of age (5,6). In 2009, Cavataio et al. suggested a role for cow's milk allergy in up to 40% of infants with GERD, but dysmotility disorders can also occur with other food allergens such as soy, egg and wheat (4,7).

A strict cow's milk elimination diet for at least 2 weeks is the first-choice treatment, ideally implemented with the support of an allergy dietitian. If symptoms persist, other allergens such as egg, soy and wheat have to be eliminated from the diet of the infant and, if breastfeeding, the mother. Allergens have to be eliminated sequentially, and non-responsible allergens have to be reintroduced (8).

Most children with food protein-induced allergic dysmotility disorders develop tolerance around the age of one year. Reintroduction of the allergen is best done gradually. The milk scale is an easy and effective recent tool for safe home reintroduction in children with non-IgE-mediated cow's milk allergy. The Flemish milk ladder provides several recognisable products, making it easy for the parents to reintroduce cow's milk into their child's diet step by step, giving larger amounts and less heated milk the higher up the ladder (Figure 2a) (9). The French scale works on the same principle and was inspired by the Flemish scale (Figure 2b).

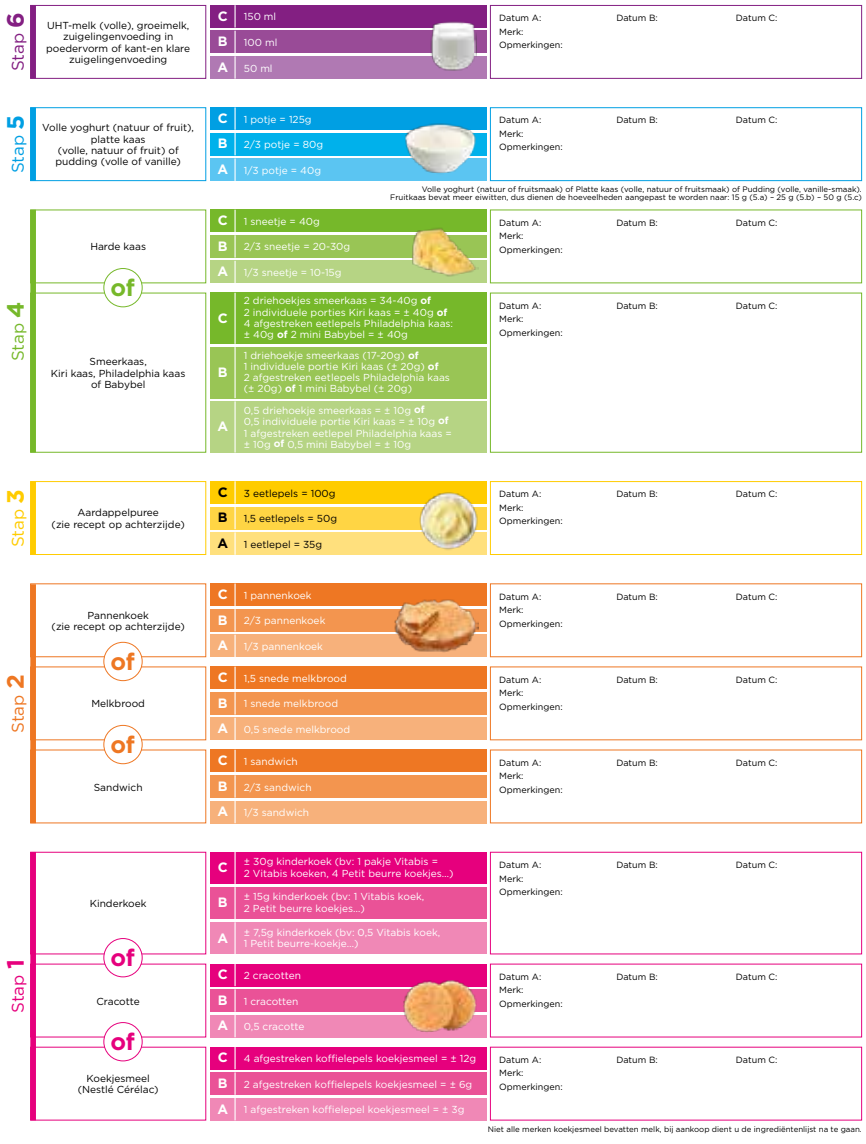
### *B. Food protein-induced allergic proctocolitis (FPIAP)*

Food protein-induced allergic proctocolitis (FPIAP) is an eosinophilic colitis that causes blood-streaked and mucous stools in otherwise well-appearing and well-growing infants. Symptoms typically begin in the first weeks of life. Onset is rarely after six months of age, with a later onset in breastfed infants compared with formula-fed children. Up to 60% of cases of FPIAP develop during exclusive breastfeeding. Cow's milk is the most frequently involved allergen, but soy, egg and wheat can also trigger FPIAP. FPIAP is estimated to account for up to 60% of healthy infants with rectal bleeding. Sometimes increased gas and bowel movements, colic and intermittent emesis can be present (2). A strict cow's milk elimination diet often results in the disappearance of visible blood in the stool within a few days, and a minimum trial period of 2 weeks is recommended. Better results are seen if the mother receives dietary advice from a dietician. As in children with food protein-induced allergic dysmotility disorder, tolerance can be expected around 12 months of age, and the milk ladder can be used for gradual introduction for most of the children. Tolerance in FPIAP is often seen in some children even sooner, between 6 and 8 months.

### *C. Food protein-induced enterocolitis syndrome (FPIES)*

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy typically diagnosed in infancy and childhood. It was first described in the 1970s. Diagnosis is based on clinical

**Figure 2a:** 2a: The Flemish milk ladder ; **2b**: The French échelle du lait.



criteria and there are no diagnostic laboratory tests for this type of allergy. Many cases of FPIES go unrecognized and therefore FPIES is still under-reported. However, in the last several years more and more epidemiologic studies were published, estimating incidence rates of 0.015% to 0.7% worldwide (10,11). The incidence of milk FPIES is close to that of IgE-mediated cow's milk allergy (12). FPIES typically presents within the first year of life, although the age of onset varies depending on the triggering food and the timing of solid food introduction. Often cow's milk or soy is the first culprit, causing FPIES within 1 to 4 weeks after birth, in most cases before the age of six months. Cow's milk is the most common trigger of FPIES in infants, followed by soy in countries where infant soy formula is also used. Approximately 60% of the infants with cow's milk or soy FPIES will also develop solid food FPIES, this type of FPIES develops later because solid foods are usually not introduced before six months of age. Multiple solid food allergens can cause FPIES and the trigger foods vary geographically. In our regions the most frequent culprits are cow's milk, followed by egg and fish.

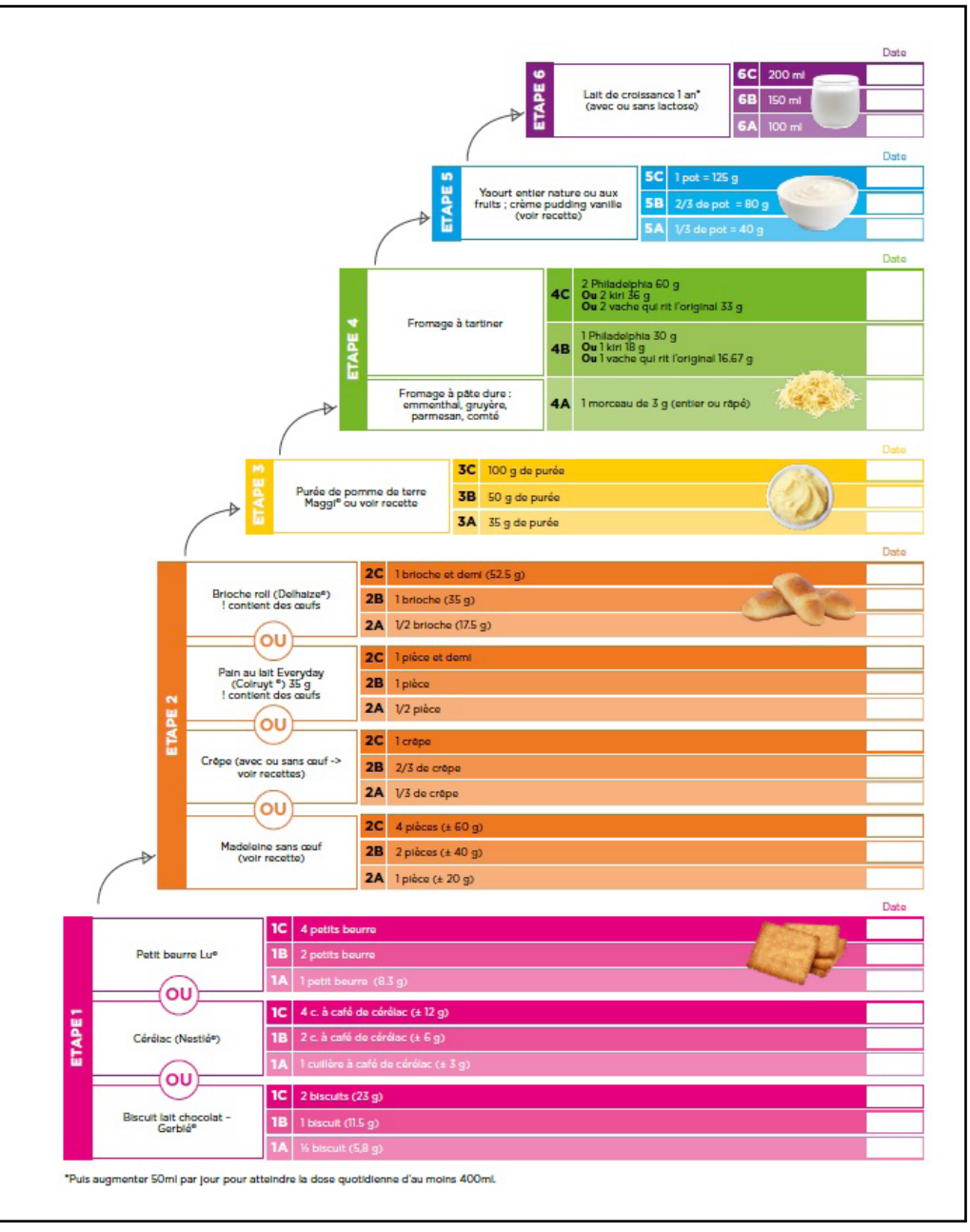
Worldwide the most commonly reported solid triggers are oats and rice, but also egg, seafood, wheat, tree nuts, peanuts, vegetables (sweet potato, carrot) and fruits (avocado, banana, apple) and several others have been described as triggers (10). One third of the patients have problems with different food allergens. A recent large French multicentre study examined 179 cases of FPIES and showed that cow's milk (60,3%), hen's egg (16,2%) and fish (11,7%) were the most frequent triggers (11). Patients with solid food FPIES tend to have more severe reactions and a longer time to tolerance (10).

FPIES is a clinical diagnosis, develop in two forms: acute and chronic FPIES, the acute form being the most common. Chronic FPIES is more difficult to diagnose and is often associated with cow's milk and soy. Transition from one form to the other is possible. The international consensus guidelines for the diagnosis of FPIES, published in 2017 by Nowak-Wegrzyn et al., were updated in 2022. FPIES is diagnosed when one major criterion (vomiting 1 to 4 hours after ingestion of the suspected food trigger and absence of skin or respiratory symptoms) and at least 3 minor criteria are present as shown in Table 1.

Acute reactions can be classified as mild-to-moderate and severe, depending on the severity of dehydration and lethargy and the therapeutic interventions needed. In a mild to moderate reaction sometimes leucocytosis with a neutrophilic predominance, thrombocytosis and faecal leukocytes or eosinophils can be found. Children with severe acute episodes can develop metabolic acidosis and methaemoglobinaemia. The most important diagnostic criterion for chronic FPIES is resolution of the symptoms within days of eliminating the trigger food and acute relapse on reintroduction. Laboratory findings may include anaemia and hypoalbuminemia (10).

If the clinical history is not clear enough sometimes a supervised oral food challenge (OFC) is needed to diagnose FPIES, this is the gold standard for diagnosis (13). The OFC is considered diagnostic when the major criterion and 2 or more minor criteria are present (Table 2). OFC in FPIES patients is also used to determine whether the child has developed tolerance to a specific food and is best performed 12 to 18 months after the last documented reaction (10). Lemoine et a.l found that performing an OFC earlier increased the risk of failing the test (11). The age of resolution is strongly influenced by food, country, and study design, but overall most patients develop tolerance by school age.

Serum sIgE and/or skin prick testing should be performed prior to OFC as a small number of FPIES patients may develop IgE-mediated allergic reactions (10).




### *D. Food protein enteropathy (FPE)*

Food protein enteropathy is a less frequent but severe form of non-IgE mediated food allergy. Patients generally present before the age of 9 months, with chronic symptoms of diarrhoea, anorexia, vomiting, abdominal distension and malabsorption. 50% progress to failure to thrive, sometimes with hypoalbuminemia. Cow's milk is the most frequent causative agent, but soy, cereals and hen's egg can also trigger this type of allergy. An atopic predisposition is found in 50 % of patients. Endoscopy shows villous atrophy with lymphocyte infiltration, mimicking celiac disease (14).

## Mixed IgE-Non IgE mediated food allergy

Food allergy can also present as a mixed IgE and non-IgE mechanism with atopic dermatitis (AD) and eosinophilic oesophagitis being the major clinical presentations. Eosinophilic oesophagitis will not be discussed in this review.

**Table 1:** criteria for the diagnosis of FPIES (adapted from (22).

| Diagnosis requires meeting the major criterion and more than 3 minor criteria | |
|---|---|
| **Major criterion** | Vomiting 1 to 4 hours after ingestion of the suspected food trigger and absence of skin or respiratory symptoms |
| **Minor criteria** | More than 2 repetitive episodes of vomiting after ingestion of a suspected food trigger |
| | Repetitive vomiting 1 tot 4 hours after eating a different food |
| | Diarrhoea within 24 hours (typically within 5-10 hours) |
| | Hypotension |
| | Hypothermia |
| | Extreme lethargy with any kind of suspected reaction |
| | Any suspected reaction requiring emergency care |
| | Any suspected reaction requiring intravenous fluid support |

**Table 2:** criteria for diagnosis of FPIES by oral food challenge (adapted from (22).

| Diagnosis requires meeting the major criterion and more than 2minor criteria | |
|---|---|
| **Major criterion** | Vomiting 1 to 4 hours after ingestion of the suspected food trigger and absence of skin or respiratory symptoms |
| **Minor criteria** | Lethargy |
| | Pallor |
| | Diarrhoea within 5 to 10 hours |
| | Hypotension |
| | Hypothermia |
| | Increased neutrophil count |

In the allergic march of IgE-mediated allergy, AD is the first presenting atopic disease. Food sensitisation is much higher in the first 3 months of life in these children with AD compared to controls. Even in non-IgE-mediated allergy, AD is present early, often within the first three months of life, and often in combination with gastrointestinal symptoms (15). In children with moderate to severe AD, food allergy is a frequent cause of eczema flares. However, prior to allergy testing, eczema exacerbations need to be treated with topical steroids and daily moisturising creams to make the skin less vulnerable (16). In infants from atopic families with moderate-to-severe eczema that frequently relapses and requires corticotherapy, despite correct daily hydration and avoidance of classic triggers (perfumes etc.), food allergy has to be excluded. The most frequent food triggers in infancy are cow's milk, soy, egg and peanut (17).

## IgE-mediated allergy

IgE-mediated food allergy has a wide spectrum of clinical manifestations, presenting as cutaneous, gastrointestinal, respiratory, cardiovascular or neurological symptoms, in an isolated or concomitant manner, in acute, recurrent and/or chronic episodes, ranging from mild local to fatal or near-fatal reactions. Classic symptoms include AD, erythema, urticaria, angio-oedema, failure to thrive, food refusal, oral allergy syndrome, rhinoconjunctivitis, asthma and anaphylaxis, with anaphylaxis being the most severe manifestation. The severity of the reactions depends on the type and amount of allergen ingested, the preparation of the food and whether or not cofactors are involved (e.g. exercise, stress, infection, non-steroidal anti-inflammatory drugs and alcohol), which can aggravate the reaction.

In 2021, the European Academy of Allergy and Clinical Immunology Anaphylaxis Multidisciplinary Task Force updated the 2014 guideline. It suggested the use of clinical criteria to identify anaphylaxis (Figure 3), supplemented by serum tryptase measurement 30 minutes to 2 hours after the onset of symptom if blood sampling does not delay the treatment (18).

Diagnosis of IgE-mediated food allergy begins with a thorough anamnesis, mapping all acute reactions, chronic symptoms such as AD, duration of breastfeeding, age of introduction of formula and solid foods, family history etc. Skin prick testing (SPT) with commercial extracts or fresh foods and measurement of specific IgE in the blood (Cap-testing) can confirm the diagnosis. The advantages of SPTs over in vitro measurement of specific IgE antibodies are the short duration of the test (15-20 minutes), the minimally invasive nature and the low cost. The measurement of specific IgE's in serum is an important complementary tool, especially in children who cannot undergo SPTs because of severe eczema, dermographism, urticaria or the use of antihistamines (19). Often a combination of the two tests is necessary for a complete diagnostic work-up.

Component resolved diagnostics (CRD) uses purified native or recombinant allergens to detect the sIgE antibody response to the individual allergenic molecules. CRD can discriminate between genuine sensitisation and sensitisation due to cross-reactivity. It can be useful in estimating the clinical risk associated with a sensitisation pattern and in predicting the outcome of an oral food challenge (OFC) (20). The OFC remains the gold standard for diagnosis but is a time-consuming test and must be performed under controlled conditions. In 2012 the PRACTALL guidelines for provocation were written, a collaboration between the European Academy of Allergy and Clinical Immunology (EAACI) and the American Academy of Asthma, Allergy & Immunology (AAAAI) (21). It is a useful tool to organize and compare provocation test in different centres.

In Europe, 8 food allergens are responsible for 90% of the food allergic reactions in children: cow's milk, hen's egg, hazelnut, peanut, soy, wheat, fish and shellfish. But also, less common allergens such as cashew nuts, pine nuts, lentils and sesame seed are increasingly being identified as triggers of severe IgE-mediated food allergic reactions in children.

In the management of FA, strict avoidance of the trigger foods is the main goal. Referral to an allergy dietician is recommended to learn how to read food allergen labelling, prevent deficiencies and provide a varied and palatable diet for the child and his parents. As accidental ingestion

**Figure 3:** Clinical criteria for diagnosing anaphylaxis.

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g., generalized hives, pruritus or flushing, swollen lips–tongue–uvula)
AND AT LEAST ONE OF THE FOLLOWING
a. Respiratory compromise (e.g., dyspnoea, wheeze–bronchospasm, stridor, reduced PEF and hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to
several hours):
a. Involvement of the skin–mucosal tissue (e.g., generalized hives, itch-flush, swollen lips–tongue–uvula
b. Respiratory compromise (e.g., dyspnoea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced BP or associated symptoms (e.g., hypotonia, [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
a. Infants and children: low systolic BP (age specific) or >30% decrease in systolic BP*
b. Adults: systolic BP of <90 mmHg or >30% decrease from that person's baseline PEF, peak expiratory flow; BP, blood pressure.
*Low systolic blood pressure for children is defined as <70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 × age]) from 1 to 10 years and <90 mmHg from 11 to 17 years.

can always occur, every food allergic patient needs a detailed action plan must attend a training session to learn how to recognise anaphylaxis symptoms and how to use the epinephrine autoinjector (18).

## Conclusion

IgE and non-IgE mediated food allergies are a growing medical problem. A detailed anamnesis and clinical examination, supplemented with skin prick tests and measurement of sIgE's, can lead to the diagnosis of IgE-mediated allergies, but provocation tests remain the gold standard when in doubt. Elimination and reintroduction diets are the only way to confirm clinically suspected non-IgE mediated allergy. The milk ladder can be used to reintroduce milk in mild to moderate non-IgE-mediated cow's milk allergy. Oral immunotherapy, gradually increasing the daily amount of protein ingested, is a promising treatment for IgE-mediated food allergy.

## Conflicts of interest

The author has no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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# How can component- resolved diagnostics help in diagnosing food allergies, such as peanut and/or tree nut allergy in children and adolescents?

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## Keywords

Food allergy ; anaphylaxis ; hazelnut allergy ; peanut allergy ; child ; allergens ; immunoglobulin E ; component-resolved diagnostics.

## Abstract

Food allergy is the most common cause of anaphylaxis in children. In pre-schoolers under 3 years old, cow's milk and hen's egg are the most common elicitors and most children outgrow this allergy. Tree nuts and peanuts are the next most common triggers of anaphylaxis in both children and adolescents and tend to persist from a very young age into adolescence/adulthood. In this article we will focus on the diagnostic tools for hazelnut and peanut allergy. Skin prick tests and specific IgE antibody titres to allergen extracts alone are generally not sufficient to determine whether an acute reaction can be explained by a specific food allergen. Component resolved diagnostics clearly has added value for the diagnosis of clinically relevant food allergy in children and adolescents.

Allergic diseases are characterized by the occurrence of symptoms upon contact after ingestion, inhalation or skin contact with innocent products, being protein structures, called 'allergens' that cause an immunological reaction. We here only consider type I or IgE mediated allergies. Mechanistically an allergen will be presented to naïve T-cells by allergen-presenting cells that will drive naïve T cells towards T helper 2 cells, instructing B cells to produce IgE antibodies towards those allergens. Circulating IgE antibodies can bind to their receptors on mast cells and/or basophils and upon renewed contact, those cells can degranulate with symptoms as a result (figure 1) (1). However, the presence of circulating specific IgE (sIgE) antibodies on itself is called 'sensitization' and is not necessarily associated with clinical symptoms or symptomatic allergy, neither are positive skin prick tests (2). It is crucial for clinicians to understand the differentiation between allergic sensitization and clinical allergy (in case of symptoms) and to consider both in test interpretation and diagnostic decision making. In clinical practice, IgE mediated allergy can be diagnosed in the first place by a detailed clinical history, followed by skin prick tests and/or blood analysis: sIgE antibody titres to an allergen extract (mixture

**Figure 1:** "Immunological mechanisms of allergic sensitization. Epithelial cells produce alarmins such as IL-25, IL-33, and TSLP in response to external insults. These cytokines are central regulators of type 2 immunity, as they act on dendritic cells to induce TH2 responses and activate ILC2 cells leading to production of IL-13 and IL-5. Allergens and pathogens that pass skin or mucosal epithelial barriers are captured and processed by dendritic cells (DCs), which in turn migrate to draining lymph nodes, where they present allergen-derived peptides on MHC class II molecules to naïve T cells, which in turn (depending on co-stimulatory and cytokine signals) can differentiate to TH2 cells or TFH cells. TH2 cells produce type 2 cytokines such as IL-4, IL-13, IL-5, and IL-9, and function as effector cells that drive many aspects of allergic inflammatory responses. TFH cells produce IL-21, IL-4, and IL-13 and induce IgE class switch recombination in B cells, plasma cell differentiation and allergen-specific IgE production. Plasma cell produce allergen-specific IgE antibodies that are released into circulation and can bind to FcεRI molecules on mast cells and basophils. Subsequent exposure to allergen can result in mast cell and basophil degranulation".



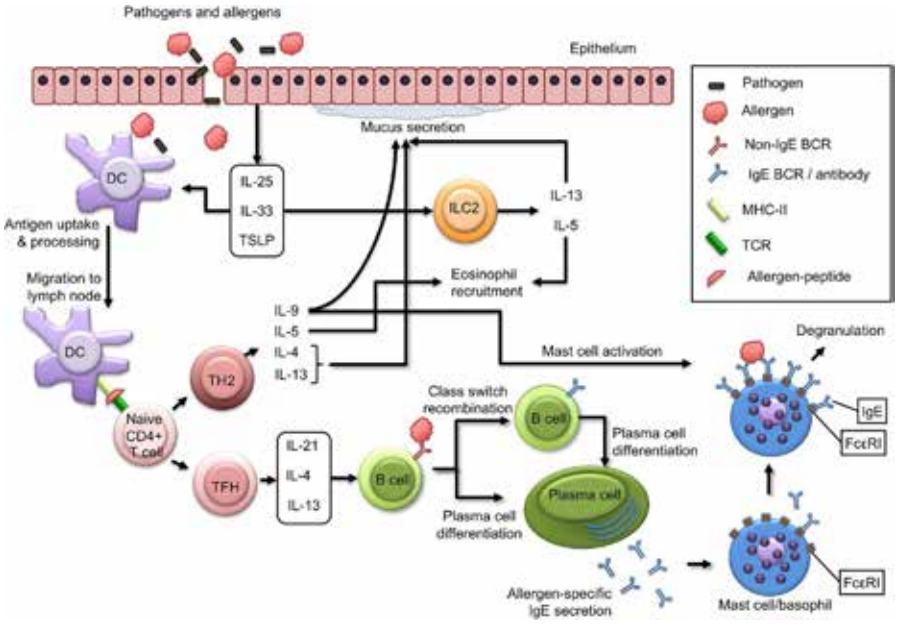
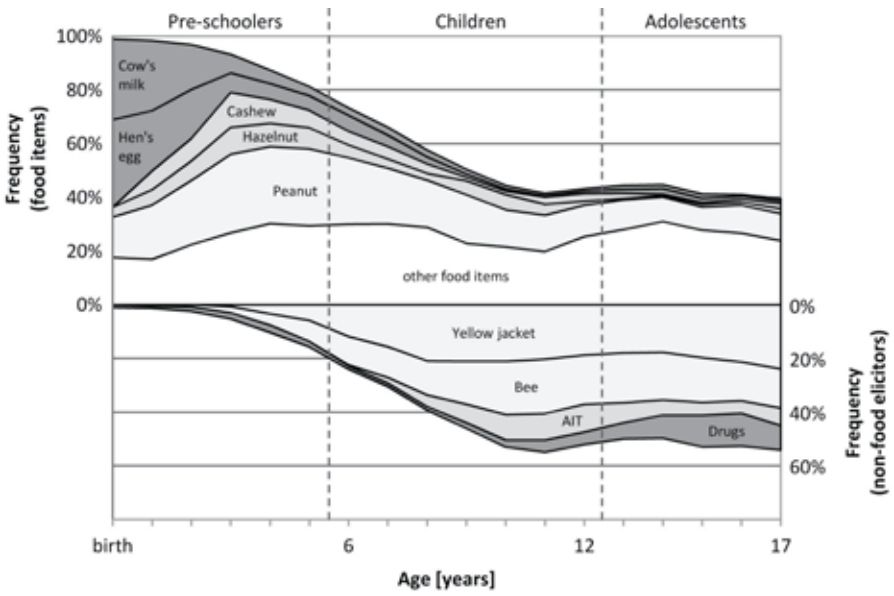


**Figure 2:** The elicitors of anaphylaxis by age according to the European anaphylaxis registry (7).




of proteins from the allergen) and sIgE antibody titres to specific proteins in an allergen, called allergen components. Multiplex tests such as ISAC® (Immuno Solic-phase Allergen Chip), a multiplex test available since 2008, analyses at the same time sIgE tests against 112 allergen components from 48 different allergen extracts. ALEX® (Allergy Xplorer) tests simultaneously sIgE against 120 allergen extracts and 170 allergen components and is available since 2019 (3). If based on a detailed history no culprit of the allergic reaction can be found, the multiplex test is available, but currently not reimbursed. In research settings the Basophil Activation Test (BAT) and Mast Cell Activation test (MAT) are being developed (4). We define three types of allergens: environmental allergens that can be inhaled, allergens that can be injected (insect venom allergens or drug allergens) and food allergens that can be ingested.

We here will discuss more in detail specific diagnosis of food allergy, as food is globally the most common trigger for anaphylaxis admissions to hospital in children and adolescents (5). According to the food anaphylaxis registry, the most frequent elicitors for an anaphylactic reaction in pre-schoolers under 3 years are cow's milk and hen's egg and most children will outgrow this allergy before the age of 8 and 12 years respectively, provided that they do not present with very high sIgE levels for these food products at diagnosis (6,7). Tree nuts (such as hazelnut) and peanut are the following most frequent elicitors of anaphylaxis in both children and adolescents and they generally persist from a very young age until adolescent/adulthood (fig 2) (7). As these are frequent triggers of anaphylaxis, we have chosen to specifically highlight the diagnostic tools for hazelnut and peanut allergy. To determine if an acute reaction can be explained by a specific food after eating e.g. a complex meal, skin prick tests and sIgE antibody titres to (an) allergen extract(s) are generally not satisfying. Component-resolved diagnostics can further unravel the history and differentiate between primary and secondary food allergy, being an IgE mediated allergy for food and IgE mediated allergy for aeroallergens with secondary cross-allergy to food respectively. We know that primary food allergy can strongly be associated with severe reactions such as anaphylaxis. The most clinical relevant components for a primary hazelnut and peanut allergy are respectively seed storage proteins Cor a 9, Cor a 14 and Ara h 2, Ara h 6 (8,9). Other known major proteins of peanut are Ara h 1, Ara h 3 and Ara h 9 (10). If the child reports mild local oral or throat pruritus without systemic symptoms, when ingesting the food it can be caused by a pollen-food allergy syndrome or oral allergy syndrome (2). Rarely, in 1,7% of the cases, a pollen-food allergy syndrome might even cause an anaphylactic shock (11). Allergen components Cor a 1 and Ara h 8 (PR-10 components) are Bet v 1 structural homologues allergens from respectively hazelnut and peanut (table 1), which can cause a cross-reactivity with the birch tree causing a pollen-food allergy syndrome then called secondary or 'cross-allergy' (10). Therefore, the measurement of allergen components is useful to make the distinction between a primary food allergy and a pollen-food allergy syndrome. If the patient has a positive sIgE antibody titre for hazelnut or peanut extract, birch extract and Cor a 1 or Ara h 8 respectively, in the absence of symptoms after ingestion of hazelnut or peanut, this might be considered as pollen-food cross-reactivity causing cross-sensitization, without cross-allergy. In that case, children should not stop their hazelnut or peanut intake. On the contrary, regarding new guidelines they should be encouraged to further ingest these food proteins (12). New allergies may arise from strict avoidance of all nuts, there are consequences on nutrition and growth, especially in children with other food allergies (13). On the other hand, it is nowadays hypothesized that tolerance induction towards other treenut families might be induced by regular consummation of tolerated treenuts and/or peanuts. Results of a clinical trial designed to prove this hypothesis, are awaiting (14). In case the clinical history is suggestive for a primary IgE mediated allergy to hazelnut or peanut and the clinically relevant antibody titres to the components are negative, we can still not rule out a primary hazelnut or peanut allergy, because not yet all tests towards clinically relevant allergen components are routinely available or certain responsible allergen components within the food proteins might even not yet be defined. An oral food challenge (OFC) remains the gold standard to diagnose food allergies in children. An OFC is labour intensive, the child can be traumatized afterwards and it can lead to anaphylaxis which rarely might be fatal. Enabling an OFC requires a specialized service in a hospital with a highly skilled clinical team and the ability to transfer quickly to intensive care units if needed. On the

**Table 1 :** Hazelnut and peanut allergen components (10).

| Family | Biochemical name | Hazelnut | Peanut |
|---|---|---|---|
| Family | PR10 | Cor a 1 | Ara h 8 |
| Bet v 1 homologues (PR10) | 2S albumin | Cor a 14 | Ara h 2, Ara h 6 |
| Prolamin | Non-specific lipid-transfer protein (LTP) (PR14) | Cor a 8 | Ara h 9 |
| Prolamin | Legumin | Cor a 9 | Ara h 3 |
| Cupin | Vicilin | Cor a 11* | Ara h 1 |
| Cupin | 13.01 - 17 | 4 | 13.01 - 17 |
| | 17.01 - 21 | 5 | 17.01 - 21 |

*Cor a 11 is only available in a multiplex test.

other hand, an OFC can reduce anxiety and improve health-related quality of life, therefore allergy work-up today still relies on OFCs (15). Potential alternatives to an OFC are newer diagnostic tests such as component-resolved diagnostics which were highlighted above but also BAT and MAT are more and more used to diminish the frequency of OFC and to come to a final diagnosis before renewed introduction of the suspected food (4).

We are convinced that a diagnostic work-up for food allergy by component- resolved diagnostics has an added value in clinical practice of specialists of paediatric allergy along with a detailed clinical history, sIgE antibody titres to allergen extracts and/or skin prick tests for diagnosing a clinically relevant food allergy. Since the differentiation of a pollen-food allergy syndrome versus primary food allergy needs component-resolved diagnostics, the limited reimbursement in Belgium of 6 sIgE antibody titres in total should be reconsidered. For example, if sIgE antibody titre for peanut extract is positive, it is our conviction that the available sIgE tests towards all components of peanut should be reimbursed (Ara h 1,2,3,6,8 and 9).

## Conflict of interest

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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# Cashew nut allergy

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## Keywords

Nut allergy ; Anacardium ; Anaphylaxis ; Child.

## Abstract

Cashew allergy is one of the most common tree nut allergies, and its prevalence appears to be increasing. Furthermore, ingestion of low doses of cashew is associated with a high rate of severe anaphylactic reactions in allergic children. Over the past decades, the world production of cashew nut has significantly grown, thereby increasing the risk of exposure.

The goal of this topic is to review clinical aspects of allergy to cashew nut, allergic components, cross-reactivity, diagnosis and management.

## Introduction

The cashew nut (Anacardium occidentale) belongs to the Anacardiaceae family (figure). It is usually considered as a nut, but is actually a seed and not a nut. The seed is surrounded by a shell and by a layer of toxic oil, the cashew nut shell liquid (CNSL). So cashew nuts must be roasted to be safe to eat. CNSL is a resin, made up of 80% anacardic acid and the rest of cardol and cardanol. Its applications to green chemistry and polymer chemistry are wide. CNSL is not edible, so its use as a chemical feedstock does not compete with the food supply chain. It is used in the manufacture of inks, varnishes, friction elements (brakes and clutches), and can cause contact dermatitis (1).

Half of the cashew nuts is consumed as a snack, whether salted or spiced, alone or in combination with other nuts. The other half is processed as sweets, chocolates, bakery, ice creams, butters, pesto's, etc.

In less than 30 years, world production has grown significantly, from 1 million tons in 1993 to over 5 million tons in 2021. The leading producer is Côte d'Ivoire, in addition to Benin, Nigeria, India and Vietnam.

The average weight of a cashew nut is 1.4 gr. The protein concentration of the roasted cashew nut is 18.8 %. One cashew nut thus contains an average of 260 mg of proteins.

## Prevalence

Cashew nut allergy is a common and increasing tree nut allergy. Whilst this may be a real increase, increased cashew nut consumption may be revealing more cases, and more cases may be noticed and declared because of increased awareness of patients and doctors.

There are significant geographical disparities. In the USA, cashew nuts are the main foodstuff involved in allergic reactions to nuts since many years; in Europe, however, hazelnuts were the most frequently involved nut. More recent data from the RAV (Réseau d'Allergo-Vigilance), however, place cashew nuts as the leading nut causing anaphylaxis (2).

In Europe, cashew nuts are the fourth leading cause of anaphylaxis amongst food allergens, after peanuts, milk and egg. We found only a few studies on its prevalence : 41 % of the nut allergic patients in France, 0.08% of children under 4 in the UK (3). Cashew nut allergy is more prevalent in the Asian population, due to earlier exposure in its dietary practices.

Despite a natural history of spontaneous non-healing, recent works have showed that an allergy to cashew nut, even severe, can progress towards spontaneous acquisition of tolerance in 9 to 30% of patients.

## Allergens

The major cashew allergens belong to the family of storage proteins. Ana o 1 is a vicilin-like protein, Ana o 2 is a legume-like protein and Ana o 3 is a 2S albumin. These proteins are resistant to heat and gastric proteolysis. Most of patients (> 80%) allergic to cashew nut are sensitized to Ana o 3.

In current practice, only cashew and Ana o 3 specific IgE assays are available. Ana o 2 is included in the 112 allergens of the ISAAC microarray (4).

## Cross-reactivity

Both pistachio (Pistacia vera) and mango (Mangifera Indica) belong to the Anacardiaceae family, and are thus botanically related to cashew nut. In vitro reactivity between cashew nut and pistachio has been established by sIgE inhibition tests. Willison et al., 2008, demonstrated that Ana o 1 and Pis v 3 (specific pistachio protein) had large structural homologies (5). Moreover, Uotila et al., 2016, reported that pistachio and cashew nut had the strongest co-sensitization linkages among edible nuts (6). The clinical cross-reactivity has also been proven : the PRONUTS study in 2019 showed that cashew nut and pistachio were the most highly

correlated nut allergies, as almost 80% of children allergic to cashew nuts are also allergic to pistachio (7). This prevalence is similar to that reported in previous studies (IDEAL study, 2016, or NUT CRACKER study, 2018) or by Saba et al., 2020, but higher than the prevalence described by Van der Valk et al. in 2017 (31%) (8-11). Saba et al. demonstrated that in multivariate analysis, low threshold dose to cashew nut is the only significant factor associated with allergy to pistachio in children allergic to cashew nut (8).

There is also a cross-reactivity in vitro between pistachio nut and mango seed (not mango fruit). Mango juice may contain traces of mango pits due to contamination during the industrial process.

Other allergens include a high degree of homology with cashew nut in their allergenic proteins : walnut (Ana o 3/Jug r 1 or Ana o 2/Jug r 4), peanut (Ana o 2/ Ara h 3), soybean (Ana o 2/Gly m 6).

Finally, a study of Savvatianos et al., 2016, established a cross-reactivity between cashew nuts and the seeds of fruits of the Rutaceae family (orange and lemon) (12). Several cases of allergic reactions or anaphylaxis have been reported after consumption of lemon seeds in patients allergic to cashew nuts. Fruit pulp can be eaten without triggering a reaction, as with mango.

## Clinical features

Cashew nut allergy often has an early onset, with an average age of 3 years at diagnosis. New dietary habits (early consumption of nut pastes) are likely to lower this average age further.

Allergic reactions to cashew are the same as other food allergies : skin lesions followed by respiratory and gastro-intestinal symptoms. 30% of the anaphylactic cases to cashew have no cutaneous reaction, delaying the diagnosis of anaphylaxis. Cashew nut allergy causes more digestive symptoms than peanut allergy.

Cashew nuts allergens are obviously highly potent and can cause relatively severe reactions. Anaphylactic reactions seem to be more frequent for cashew nut than for peanut (50% and 30%, respectively). Clinical observations reveal that significant reactions may happen for minimal levels of exposure. Studies determining the eliciting doses by double-blind placebo-controlled food challenge test (DBPCFC) show that the ED50 (protein dose at which 50% of the allergic population is likely to react), is 25.4 mg (for any type of symptoms) (13). This corresponds to the protein content of one tenth of a cashew nut. This ED50 is comparable to peanut or hazelnut, but clearly lower than that of egg or milk (>80 mg). The ED05, which is likely to trigger a reaction in 5% of cashew-allergic children, is estimated at 0.32 mg of proteins, or 1.7 mg of cashew.

## Diagnosis

As with other foods, cashew nut allergy is diagnosed by history, combined with in vitro specific IgE tests and skin prick tests. These tests do not distinguish between sensitization and clinical allergy. For the diagnosis of allergy, the gold standard remains the oral challenge test. However, as in most cases children have a clear-cut history of anaphylaxis after consumption of cashew nuts, oral food challenges should not be used.

Skin prick tests seem to be superior to sIgE to cashew nut in predicting challenge tests outcome : Corderoy et al., 2011, showed that patients with positive or negative cashew nut challenge tests do not differ in median cashew nut sIgE; in contrast, the SPT was significantly larger in patients with positive challenge tests (14). A cut-off value of ≥ 8 mm gave a 95% positive predictive value for a positive challenge test outcome (15).

Sensitization to cashew nut 2S albumin, Ana o 3, is highly predictive of cashew and pistachio allergy: using 0.16 kU/L as the optimal threshold, they showed that Ana o 3 had a sensitivity of 98% and a specificity of 94% (12).

In addition, Van der Valk et al., 2017, demonstrated that the components Ana o 1,2 and 3 discriminated better between cashew nut allergic and tolerant children sensitized to cashew nut than the skin prick tests (9).

So there are 3 indications for oral challenge tests in cashew nut allergy :
- confirm the allergy to cashew nuts;
- investigate spontaneous acquisition of tolerance, which is possible and probably less rare than previously thought;
- establish a reactive threshold for the implementation of oral immunotherapy.

Bourcier et al. carried out an oral food challenge (OFC) on 36 patients with cashew nut allergy confirmed by skin and biological tests, without an accidental episode over a period of at least 3 years, or with clinical and biological sensitization of fortuitous discovery (allergic skin tests performed in the case of a reaction to another nut or in the context of atopic dermatitis) (16). The average age at the time of the first allergy tests was 3 years and at the time of OFC was 8 years. 15 children tolerated the maximum cumulative dose of 4441 mg and were able to reintroduce cashew nuts immediately into their diet. 15 patients had to continue with a strict avoidance regime. 6 children received oral immunotherapy (OIT).

Oral food challenges are not without risk; they are time-consuming, labor-intensive, stressful and possibly costly. So, Van der Valk et al., 2017, developed a prediction model for cashew nut allergy (9). The Van der Valk score is a predictive score, combining the determination of specific IgE antibodies to Ana o 3, the diameter of the papule in skin tests and the sex of the patients (table). The OFC could thus be refuted in patients with a score ≥ 8 (highly probable clinical reactivity), while children with a low score < 4 would be the preferred target population for an OFC (probability of asymptomatic sensitization or tolerance acquisition).

**Table :** van der Valk score (6).

| Predictor | Value | Score |
|---|---|---|
| Gender(girl) | | 1 |
| Ana o 3(kU/l) | 00 - 0.1 | 0 |
| | 0.11 - 0.5 | 1 |
| | 0.51 - 1.5 | 2 |
| | 1.51 - 5 | 3 |
| | 5.01 - 19 | 4 |
| | 19.01 - 60 | 5 |
| | 60.01 - 100 | 6 |
| SPT(meandiameter(mm)) | 0 - 2 | 0 |
| | 2.01 - 5.5 | 1 |
| | 5.51 - 9.5 | 2 |
| | 9.51 - 13 | 3 |
| | 13.01 - 17 | 4 |
| | 17.01 - 21 | 5 |
| | 21.01 - 23 | 6 |
| | 24+ | 7 |
| **Total sum score** | | ... |

## Management

Based on the LEAP study, infant feeding guidelines now recommend introducing peanuts as part of complementary feeding, in order to prevent peanut allergy prevalence. These food allergy prevention guidelines do not include tree nuts, nor cashew nuts in particular. Palmer et al. showed that regular consumption of cashew nuts from 6 months of age was feasible and safe, but they did not determine whether this strategy could reduce the prevalence of cashew nut allergy (17).

The mainstay of therapy in food allergic patients is avoidance of the culprit food. Avoidance of cashew nut is increasingly difficult to achieve, because of the presence of cashew nuts in more and more food products. Furthermore, avoidance of botanically related foods such as pistachio must be advised.

In 2006, Ferdman et al., demonstrated that 27% of children with peanut or nut allergy were unable to recognize the target food (18). Only 25% of the children in this study correctly identified the cashew nut. Therapeutic education therefore has an important place in the management of cashew allergy.

As for other food allergies, a written action plan is essential, including details of evictions and an emergency protocol with instructions for treatment in case of reaction. In the school environment, the entire teaching team should be aware of the evictions, the emergency action plan, the location of the emergency kit with adrenaline and its proper use.

Since a few years oral immunotherapy (OIT) plays a role in the treatment for cashew nut allergy. Several teams have published their protocols and results of oral cashew (and/or pistachio) immunotherapy (19, 20). These protocols appear secure and allow children at high anaphylactic risk to tolerate a high dose of cashew nuts, thus protecting them from anaphylaxis.

In 2022, the NUT CRACKER study demonstrated that cashew OIT is effective in desensitizing most cashew allergic patients; it cross-desensitizes all pistachio and some walnut allergic patients (20). The safety of cashew OIT is similar to OIT for other foods. Low cashew dose consumption is sufficient to maintain full desensitization.

## Conflict of interest

The author has no conflicts of interest to declare in relation to the subject matter of this manuscript.

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# SPA® REINE

## Développement du microbiote, eau et santé infantile

**Le microbiote intestinal se développe dès le début de la vie du bébé, pendant la grossesse, et plusieurs facteurs influencent la colonisation microbienne de l'intestin. L'alimentation et la bonne hydratation du bébé jouent un rôle majeur dans le bon développement des communautés microbiennes, avec un impact considérable sur la santé de l'enfant.[1,2]**

Le microbiote intestinal constitue une communauté complexe de micro-organismes qui vivent dans le tractus gastro-intestinal, avec plus de 1.500 espèces. Les 1000 premiers jours de la vie sont essentiels pour l'établissement du microbiote interne du nourrisson et de son système immunitaire, et le développement du microbiote intestinal au cours de cette période aura une incidence sur la santé du nourrisson tout au long de sa vie. La communauté microbienne du tractus intestinal des nourrissons joue de nombreux rôles importants au début de la vie et affecte directement la santé des nourrissons. Par exemple, les nourrissons dépourvus de certains types de bactéries (*Faecalibacterium, Lachnospira, Rothia* ou *Veillonella*) présentent risque accru d'asthme à l'âge de 1 à 3 ans.[1,3]

### *Alimentation et microbiote du bébé[3]*

Le lait maternel est considéré comme la meilleure source d'alimentation pour les nouveau-nés, car il peut fournir tous les nutriments nécessaires et contient de nombreuses substances biologiquement actives. Il constitue une source de bactéries symbiotiques qui empêchent la fixation d'agents pathogènes et stimulent la colonisation du tractus intestinal par des micro-organismes bénéfiques. Les nourrissons allaités ont un microbiote intestinal plus dynamique et l'incidence de certaines maladies, telles que l'asthme, est diminuée. Parallèlement, les oligosaccharides présents dans le lait maternel pourraient favoriser la croissance de micro-organismes bénéfiques dans l'intestin du nourrisson.

### *L'eau, le nutriment oublié du microbiote intestinal ?[4-6]*

Consommée quotidiennement en grandes quantités, **l'eau est une source potentielle de diversité microbienne intestinale.** Cependant, son effet sur le microbiome intestinal est mal connu.

Quelques études ont exploré la composition du microbiote après l'ingestion de différents types d'eau potable et ont observé que le type d'eau entraînait des différences dans la composition du microbiome intestinal. Au cours du développement du microbiome infantile, la consommation d'eau (de différentes origines) est en corrélation avec les signatures du microbiote intestinal, ce qui indique que l'eau peut être un facteur déterminant de l'acquisition du microbiome. Chez les adultes, des données limitées suggèrent que la source d'eau potable consommée est associée à la composition du microbiote intestinal.

Une vaste étude de cohorte, réalisée auprès de plus de 3 000 participants, a montré que la consommation de différents types d'eau entraînait des différences dans la composition du microbiote intestinal. Notamment, les personnes buvant peu d'eau présentaient des différences de microbiote intestinal par rapport aux personnes buvant beaucoup d'eau ($p < 0,05$) ainsi qu'une plus grande abondance de *Campylobacter* - connus pour provoquer des infections gastro-intestinales. Selon les auteurs, les mécanismes par lesquels l'eau potable peut interagir avec les communautés microbiennes pourraient impliquer le pH de l'eau, la composition en solutés et en minéraux, les communautés microbiennes naturelles intrinsèques ou le chlore résiduel et les sous-produits de désinfection qui subsistent dans la plupart des eaux du robinet.

Très récemment, une autre étude, réalisée sur des souriceaux, a montré que la quantité d'eau consommée, indépendamment de sa minéralisation, était un élément clé du bon développement du microbiome. D'autres travaux sont nécessaires, mais ces données suggèrent qu'une bonne hydratation, avec une eau faiblement minéralisée, recommandée chez les nourrissons, est une bonne pratique pour optimiser le bon développement du microbiote.

**Le microbiote intestinal est un facteur essentiel pour la santé, la croissance et le développement, avant même la naissance**. De nombreux facteurs viennent moduler l'instauration du microbiote du bébé, et de bonnes démarches, peuvent l'aider à créer un microbiote intestinal idéal et sain. Toutefois, de nombreuses recherches sont encore nécessaires dans ce domaine, notamment pour mieux comprendre des facteurs tels que la consommation d'eau par la mère et le jeune enfant.


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# Oral Immunotherapy for Ig-E mediated Food allergy: in practice

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## Keywords

Food hypersensitivity ; food allergen ; immunotherapy ; quality of life ; child.

## Abstract

Oral immunotherapy (OIT) is a treatment that can be proposed to food allergic patients with very favorable results, especially in the short-term. OIT consists of administering the food allergen in progressively increasing amounts attempting to reach a normal dose. Guidelines vary from country to country. EAACI recommends OIT for children over five years of age with a persistent allergy to cow's milk, egg and peanut. In Spain and Canada, it is proposed for any age and any food. Since adverse events are always possible, the patient and his family must be well trained to manage these allergic reactions. The aim of OIT is to improve the quality of life of these patients by increasing the reactogenic threshold or in the best cases, by attempting to achieve a state of desensitization or tolerance to the allergen.

## Introduction

Food allergy concerns recently 4-8% of the children of the United States and Europe, and the prevalence of anaphylaxis in Europe is around 0.3% (1-4). We observe an increase of severe anaphylaxis in the last years in the western countries, especially in children under 5 years old, without an increase of mortality (2). Severe anaphylaxis appears essentially with allergies to cow's milk (CM) and eggs under 2 years old, cashews nuts and hazelnuts under 6 years old and peanut for all ages (2, 4). Approximately 80% of CM and egg' allergies outgrow naturally as children grow, while only 15 to 20% of nut and peanut allergies outgrow naturally. This motivates allergists to find a way to help those patients who do not naturally become tolerant (3-5). Accidental exposure is also not so rare: in the USA, the annual incidence rate of accidental peanut ingestion is between 12 to 23% while in Japan, 17-36% of CM allergic patients and egg allergic patients have been exposed accidentally (4). The standard care to treat allergy is, for the moment, allergen avoidance and rescue treatment (antihistaminic and epinephrine) (3).

Oral immunotherapy (OIT) seems to be an interesting solution. It consists of giving daily a dose of allergen to an allergic patient, starting with a very small and tolerated dose, which is increased monthly, until attempting a normal dose for that allergen (for example, a cup of 200ml of CM). The goal of OIT is for the patient to become tolerant to the allergen, but most of the time this state is not achieved and patients become desensitized. Tolerance and desensitization (or "sustained unresponsiveness") are two different concepts that are important to understand. Tolerance means that the patient is able to eat the allergen without symptoms, even if he does not eat it regularly. Desensitization is a step below tolerance: the patient needs to consume the allergen without discontinuation to maintain a non-allergic response to that allergen. Desensitization is most often the state achieved at the end of OIT (1, 4). By achieving desensitization or tolerance, OIT reduces the risk of allergic reactions, especially anaphylaxis, in the event of accidental exposure. For example, in peanut allergy, it reduces the risk of mild allergic reaction by 12% per year and the risk of anaphylaxis by 7% per year (3).

The roles of the allergologist before OIT were to diagnose the allergy, to explain the avoidance regime, to educate the patient to notice the allergic reaction symptoms and to treat them. Avoidance regime may cause stress to the patient and his entourage, accidental reaction, nutritional deficiency and so on. With OIT, the allergologist is able to cure his patient and allow him to avoid the above mentioned embarrassments.

## Oral immunotherapy (OIT)

### *A. OIT: Which patients are concerned?*

In 2018, the EEACI recommends OIT only for patients from 4 or 5 years of age with persistent Ig-E mediated allergy to egg, CM and peanut (1). They do not recommend it for other food because it has been not enough studied for now. As more studies on OIT for other foods are found, these recommendations might change in the future.

In Canada and Spain, OIT can be offered to any patient with a food allergy, for any food, even in the context of multiple food allergies and for adults (4).

Patients and their families must be correctly selected. Indeed, patients must have a clear history of allergy with an acute reaction, have a positive skin prick test and/or specific Ig-E for the allergen and pass an oral food challenge (OFC) to confirm the allergy and to evaluate the reactive dose (1). The family should be well informed about the type of protocol, the type of side effects that may occur during treatment, the rigor and length of time that this type of processing may take. Only very motivated and awarded families should start these protocols (1, 4).

Patients who have great chances to outgrow their allergy naturally (allergy for CM and egg in particular) should not be treated with OIT (1).

Some contraindications are summarized in Table 1, some of them are absolute and others more disputable (1, 4, 6).

**Table 1:** Contraindications to oral immunotherapy.

| Absolute Contraindication |
|---|
| Uncontrolled asthma |
| Low family compliance |
| Neoplasia or autoimmune disorders |
| Eosinophilic esophagitis |
| Non Ig-E allergy |
| **Relative Contraindications** |
| Pregnancy |
| Chronic urticaria, severe eczema |
| Beta-blockers or ACE inhibitors use |
| Active mastocytosis |

**Figure 1**: Classic protocol of OIT.


### *B. OIT: Classic protocols and practical recommendations for the patients*

As shown in Figure 1, a classic OIT protocol would begin with an OFC to prove the allergy. This OFC also allows the reactive dose to be determined. The first OIT dose will correspond to 1/10th of the reactive dose to make sure no reaction would occur at home. The next doses are generally increased every 2 to 4 weeks until the final dose is reached. Every first increased dose is given in the hospital under medical supervision (4, 7). Then the dose is consumed every day at home for 2 to 4 weeks according to the protocols. When the final dose is reached, the patient enters the maintenance phase (7).

The daily dose consumed at home must be taken according to certain rules: it must be taken at a regular time, under parental supervision (not before nap time or night time), with food (snack or meal), without exercise 1 hour before and 2 hours after (1, 7).

Some situations may increase the risk of allergic reactions during OIT, such as fever, exercise, stress, NSAID or alcohol use, uncontrolled asthma. In these cases, OIT should be suspended until the patient is in a normal state. The protocol may change if the break is too long: the allergist may suggest restarting it at a lower dose for a while (1, 7).

Parents and family should be well trained and equipped to manage the potential reactions during OIT (7).

To prove that the patient has become tolerant to the allergen, the patient should pass another OFC after an eviction period at the end of the maintenance phase. The duration of the eviction phase is not well defined in studies and can vary between 4 weeks to several months. If the OFC is positive at that time, the patient has become desensitized but not tolerant (6).

### *C. OIT: Side effects*

Allergic reactions are extremely frequent during OIT (about 80% of the patients), which is even more than with the eviction diet. Most of the side effects occur during the build-up phase or in association with cofactors (fever, sport, pollen season…) (7, 8). Most of them are mild or moderate reactions, such as perioral rash, urticaria, rhinitis or mild gastrointestinal reaction. Most of them resolve with antihistamine treatment or even by themselves (8). Anaphylactic reactions can also occur, affecting approximately 25% of patients in the studies (3, 7). Kansen et al. followed patients under avoidance in real life for 3 years and concluded to an annual risk of anaphylaxis of 9.8%. None of these patients used epinephrine as it was proposed to do in such situations. Chu et al. found a lower rate of severe reactions in avoidance patients (2.7%) but this was in a clinical trial population that was more strictly followed medically (3, 9, 10). Eosinophilic esophagitis is also a side effect in 0.5% to 5% of the cases and requires discontinuation of OIT treatment. Hopefully, the situation is reversible when the contact with the allergen is discontinued (7, 8).

Given the possibility of developing anaphylaxis during OIT, the whole procedure must be supervised by a center with a high food allergy expertise and full resuscitation equipment (1).

On the long term, the mild side effects can be a barrier to the treatment of patients who eventually end OIT due to the discomfort of these side effects (7, 8). The discontinuation rate of OIT can be as high as 14% according some studies (8). Fatigue and aversion to food may also reasons for treatment discontinuation (7).

A meta-analysis on peanut allergy, published in The Lancet in 2019, confirmed these prerogatives of side effects. They included 12 RCTs with a total of 1041 patients (medium age 8 years, 39% girls and 61% boys). The control group were patients with placebo OIT (8 studies), patients under avoidance (3 studies) or patients ongoing sublingual immunotherapy for a food allergy (SLIT) (1 study). The median final dose was 2000 mg of peanut. There was no OFC at the beginning of each study. The OIT groups showed an increased risk of anaphylaxis with a RR of 3.12 (95% IC 1.76-5.55) and an increased epinephrine use with a RR of 2.21 (95% IC 1.27-3.83), both in the build-up and the maintenance phase. Non-anaphylactic reactions were also increased in the OIT groups: vomiting (RR 1.79 with 95% IC 1.35-2.38), angioedema (RR 2,25 with 95% IC 1.13-4.47), upper respiratory tract reactions (RR 1.36 with 95% IC 1.02-1.81), lower respiratory tract reactions (RR 1.55 with 95% IC 0.96-2.5). Trials, which had not done an OFC at study entry, had a 2.68-times lower risk of anaphylaxis during OIT than the other studies. No patients died in any of the studies. Only 3 cases of eosinophilic esophagitis were reported (3). The biggest difference between side effects that would occur during an eviction diet and during an OIT protocol is that, in the second situation, side effects can be expected: the patient is under parental supervision, medication is available and the parents have been well trained to react. In the eviction diet situation, the accidental exposure occurs mainly when patient is not at home, with absence of rescue medication, or under the supervision of a non-well-trained adult (10).

### *D. OIT: Does it work?*

EAACI has conducted the largest review on the efficacy of OIT in 2021. They reviewed 18 randomized and controlled trials (RCT) and 5 controlled clinical trials (CCT) with a total of 982 patients allergic to egg, cow's milk or peanut. They excluded other foods because they have not been sufficiently studied at that moment. The authors concluded that OIT gives good results. A majority of patients (76.9%) tolerated the expected dose of food at the end of the protocol, regardless of the type of protocol (e.g. dose escalation which can vary from one study to another) or the type of food, compared with 8.1% in the control group. Four of these studies (25 patients allergic to CM and 169 to eggs) statue on the medium-term efficacy of tolerance by testing patients with an OFC after a period of avoiding the food. The period of avoidance

was quite short: between 1 and 3 months, which does not allow us to conclude to a real tolerance in the long term. This is nevertheless a recurrent problem in most studies: the tolerance status is often unknown. The conclusion of this review did not really change from the one of 2018: OIT is indicated for children from 4 or 5 years of age with persistent allergy to CM, eggs or peanuts and OIT is effective. EAACI does not currently recommend OIT for other food or for adults due to lack of evidence (1).

Two Cochrane meta-analyses showed almost identical results. The first one is on 10 controlled trials (3 with placebo, with a total of 249 patients) on egg's allergy where desensitization was obtained in 82% of patients, versus 10% in the control group. The second meta-analysis included 196 children from 5 randomized trials on cow's milk allergy: 62% became desensitized in the OIT group versus 8% in the control group (4).

But, according to certain trials, OIT might be more effective in younger children (under 5 years of age) than in older children. This has been lately illustrated in 2 studies.

The first one is a real-life study published in 2020, without any control groups or randomization, on peanut allergy, in a cohort of preschoolers (9-70 months old). Children were required to have a positive OFC for peanut or a clear history of peanut allergic reaction and a positive skin prick test or positive level of specific Ig-E for peanut. The build-up phase was short (16 to 22 weeks) to achieve the maintenance dose of 300 mg. Eventually, after a maintenance phase of 12 months, 117 patients (mean age = 25 months, 59.8% boys) completed the protocols and passed the final OFC. Ninety-two of 117 patients (78.6%) succeeded this test and tolerated cumulative dose of 4000 mg peanut protein and 115 of 117 (98.3%) were able to tolerate a cumulative dose of 1000 mg peanut protein. The skin prick test decreased significantly more in the successful OFC group than in the group that still had a positive OFC (43.5% vs 20.2%, $p<0.05$). They didn't find a significant difference in the decrease of Ig-E in these 2 groups. This study shows that nearly all patients can achieve the protective dose of 1000mg, which according to other studies provides protection against accidental exposure. Side effects were also very low: 9.5% had an allergic reaction (grade 1 and 2) and 1.6% received epinephrine during the maintenance phase (10).

The second study in a young population is a multicenter RCT in children aged 1 to 3 years. The 146 enrolled children passed at first a double blind, placebo-controlled OFC and had to have a reaction to 500mg of peanut or less to participate to the study. 96 patients received peanut OIT (2000 mg peanut protein per day) and 50 patients received placebo for 134 weeks; then they all achieved a period of peanut avoidance for 26 weeks. In the per-protocol analysis, at week 134, a first OFC showed that 84% (68/81 patients; 15 patients dropped-out) of the peanut group passed the challenge (with a median dose of 5005 mg of peanut protein) and only 3% (1/35 patients; 15 patients dropped-out) of the placebo group (risk difference 69%, 95% CI 59-79; $p<0.0001$). After the avoidance period (week 160), in the per-protocol analysis, 29% (20/70 patients; 11 patients dropped-out) of the peanut group succeeded the challenge compared to 4% (1/23 patients; 12 patients dropped-out) in the placebo group (RD 19%, 95% CI 10-28; $p=0.0021$). This time, the median dose of peanut protein in the non-placebo group was 755mg. However, 57% of these children (40/70 patients) were able to consume 1755-3755 mg of peanut, which is a safe level for accidental ingestion. Another surprising result is that the chance of tolerance success is higher when the patient is young: in fact, 71% became tolerant in the group younger than 24 months (although this group was quite small, 12% of the population), 35% between 25 and 34 months and 19% between 36 and 48 months. Most participants in both groups experienced side effects during the study (98% in the peanut group and 80% in the placebo group). The reactions were mild to moderate and 35 moderate reactions were treated with epinephrine (only in the peanut group) (11).

Compared to study on peanut allergy in older children, the results of the study in young children are slightly better. Effectively, the POISED study shows that 20% of the patients (median age 11 years) were able to consume 4000 mg of peanut after an avoidance period of 26 weeks (11).

### *E. OIT: impact on quality of live*

Some studies have investigated the impact of OIT on the quality of live (QoL) of patients undergoing OIT. Goldberg et al. showed a significant improvement in QoL in the OIT-treated group (56 patients) compared to the placebo group (47 patients) ($p<0.001$) (12). Levy et al. have studied a population of 191 patients between 4 and 12 years undergoing OIT and have shown an improvement in QoL in terms of emotional and social impact and a reduction in stress related to food consummation. Some of them reported a decrease in QoL during OIT, but an improvement of it at the end of an OIT protocol (13). So far, studies about QoL on the long term are missing.

These studies remind us of the importance of correct selection of patients and their families for such a protocol. The patient should be aware of his wishes regarding the evolution of his allergy and should be well informed about the impact of these protocols on his life.

### *F. OIT: Open questions*

A lot of questions concerning OIT are still without any answer for the moment. Therefore we need more studies. What is the long-term efficacy of OIT? When can we consider a patient to be tolerant? Is it possible to establish a standardized protocol or do we need an individual protocol for each patient? What is the impact of OIT on long-term QoL? Can we find safe biological markers of OIT efficacy? Can we use other drugs to improve OIT response (omalizumab, probiotics,…)? What is the ideal age to start OIT?

## Conclusion

We can conclude that OIT can be proposed to selected patients with a permanent food allergy. The patient and his family should be well informed and motivated. Side effects are more frequent than in an eviction diet, but parents are well-equipped and well-trained to react to them. The short-term efficacy of OIT has been proven. We still have a lot to learn about this topic and we hope to have more answers to the remaining questions in the future.

## Conflicts of interest

The author has no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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# Current trends in pediatric food oral immunotherapy - early start, low dose and long maintenance, multi-food protocols

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## Keywords

Food allergy ; oral immunotherapy ; oral multi-food immunotherapy ; early protocol ; low maintenance dose.

## Abstract

***Background:*** Oral immunotherapy (OIT) has been the best studied therapeutic approach for the treatment of food allergy over the past decade, with clinical trials evaluating its efficacy, safety and ability to improve participants' quality of life.

***Methods:*** In this article we review trends in the evolution of treatment regimens, beneficial and side effects of current OIT protocols for single or multi food allergy. We report the conclusions drawn from the publication of some studies and a meta-analysis that highlighted the drawbacks of OIT, as well as studies concerning multi-food oral immunotherapy.

***Results:*** OIT protocol with a low maintenance dose, slow progression, early onset even at preschool age and tailored to the severity phenotype has shown significant feasibility, efficacy and safety, offering a promising option for the management of patients with severe food allergy. Studies have also shown that a short course of omalizumab can safely accelerate the OIT schedule for multiple allergens simultaneously. Therapeutic education and informed shared decision-making between patients and the medical team are essential.

***Conclusions:*** According to literature data and for reasons of safety, cost-effectiveness and logistics, OIT protocols are mainly aimed at single food allergy cases. This approach is becoming increasingly complex, as multiple food allergies (30% of cases) are generally more severe, have a greater impact on quality of life, and are less likely to resolve spontaneously over time. Future research should evaluate the short- and long-term effectiveness of this therapy in the real world, predictors of efficacy, and the use of adjunctive therapies that may mitigate adverse events.

## Introduction

Due to the challenging evolution of food allergy in the last decade – oral immunotherapy (OIT) protocols have brought real benefit with relatively easy acquisition of desensitization. A recent systematic review showed that this approach is effective and to be associated with an 80% improvement in quality of life (1). In addition to the increase in prevalence, more and more severe phenotypes are being reported as food poly-allergy, polysensitization. Up to 30% of food allergic patients react to more than one food allergen. This estimate rises to 70% in highly atopic patients. These severe phenotypes appear very early in life, and their quality of life is severely compromised due to multiple and recurrent adverse reactions (AR). As a significant finding, the results of the Immune Tolerance Network IMPACT trial have suggested that early intervention with OIT can induce clinical remission (2). Many studies have also shown that it is possible to perform OIT to several foods simultaneously at preschool age. The main goal of OIT is to raise the threshold of reactivity in order to prevent severe anaphylaxis due to accidental ingestion of the allergen. Currently protocols are heterogeneous and vary, according to the type of food used (e.g., fresh or cooked, single or multi-food), the progression of doses, the amount of protein/maintenance dose, the duration of each stage and the adaptation of the protocol according to the phenotype.

The clinical efficacy of OIT is assessed by the increase in the threshold of reactivity to a specific food, consumption without ARs or clinical remission. In the past the high maintenance doses were considered effective in achieving clinical remission (3). This practice has been abandoned over time in the face of serious adverse reactions (SAR) at higher rates than with elimination diets. The development of remission is directly linked with immunological biomarkers. On the other hand, sublingual immunotherapy and epicutaneous immunotherapy have been reported to have acceptable safety and efficacy profiles, to be applied especially in severe phenotypes of interest as a transition to the OIT.

According to current studies, OIT with early onset (even before preschool age) adapted to the severity phenotype (slow progression, low maintenance dose), has shown significant efficacy and safety. Although OIT-related ARs are common during treatment, SARs are rare (1-3).

## OIT protocols: maintenance doses, efficacy, adverse effects, MFOIT according to recent studies

To date, only the guidelines of the Canadian Society of Allergy and Clinical Immunology recommend OIT multi foods, while other scientific bodies recommend OIT only for peanuts, eggs and cow's milk. In the literature, the foods involved in OIT in small doses are milk, eggs, peanuts, wheat, nuts and a multi-food mix (up to 15). Therapeutic education, detailed information and informed shared decision making, between patient and the medical team, are essential. An early start is desirable for several reasons: better immunological plasticity, easily controllable co-morbidities, good acceptance given few food phobias (neophobias) and better protocol compliance due to parental support. Regarding timing and dosage: a lower allergen delivery dose and a slow, delayed escalation rate in OIT treatment seem approachable in the near future. Multifood oral immunotherapy (MFOIT) versus OIT has shown a real benefit in terms of protocol duration for polyallergic patients. In older children, it is essential to respect the patient's personal objectives: some may wish to be able to consume large amounts of allergens, while others may simply want protection against anaphylaxis in the event of accidental ingestion. Small maintenance doses vary from 125 mg to 300 mg of protein for peanuts and tree nuts. In other studies, the

doses were 3 ml of milk, 1/32 of a whole egg, 2 g of boiled noodles (4-6). Studies have also shown that a short course of omalizumab can safely accelerate the multi-food OIT schedule. There are still many unanswered questions regarding the optimal dosage, duration of treatment and evolution of OIT after omalizumab discontinuation.

Regarding the monitoring of OIT, some studies have shown that small skin test diameters and serum IgE (sIgE) at the beginning and end of the maintenance phase, in addition to reduced basophil reactivity, can predict the achievement of sustained unresponsiveness (SU), whereas IgG4 is not predictive of SU (7). Regulatory markers, in particular FOXP3 + and Tregs, appear to play a key role in the induction of long-term tolerance in therapeutically successful patients (8). The current hypothesis is that immune memory is allergen-specific; however, synergistic effects cannot be ruled out.

## *Lessons from different studies: arguments for early, low dose, long, multifood protocols*

### PEANUTS AND TREE NUTS

**An Atlanta research** team in 2017 demonstrated the efficacy of small maintenance doses after comparing 3000 mg vs. 300 mg of food protein (FP) in children aged 9-36 months. Thus, 78% of subjects achieved desensitization (300 mg arm, 17/20 [85%] vs. 3000 mg, 12/17 [71%], p=0.43) over an mean period of 29 months. Peanut IgE levels decreased significantly in the active group (AG) versus placebo group (PG) (p<0.001). Early OIT was safe and well tolerated with predominantly mild symptoms, a single home reaction requiring epinephrine and 2 withdrawals due to persistent gastrointestinal ARs (3). According to Kulis et al. no differences in T-cell or basophil responses were found between subjects on low-dose or high-dose maintenance peanut OIT. The risk of ARs and study withdrawal was higher in the high-dose group. These results suggest that lower maintenance doses are preferable in the long term (3, 9).

**The PALISADE study, 2018** included patients (aged 4-55 years) with a history of severe anaphylaxis and a maximum cumulative reactogenic dose (CRD) of 100 mg FP. The induction phase, lasting around 6 months, aimed at a maintenance dose of 300mg FP. This was followed by a 6-month maintenance phase. OIT was effective in 496 patients aged 4-17 years (not in adults), with 67.2% of the AG tolerating a 600 mg dose after 6 months of maintenance compared to 4% of the PG. After 1 year of treatment, 50% tolerated 1000 mg FP. However, SARs occurred in 6% of the AG participants and less than 2% of the PG participants. Overall, systemic allergic reactions occurred in 53 patients (14.2%) in the AG and 4 (3.2%) in the PG. One patient developed an eosinophilic esophagitis (EoE) and 4.3% of the AG participants withdrew due to chronic gastrointestinal symptoms. [10]. The randomized, controlled PALISADE trial demonstrated the benefit of daily oral immunotherapy with peanut (Arachis Hypogaea) allergen powder (AR101) at a low maintenance dose in peanut-allergic children and adolescents (10).

**German researchers in 2019** confirmed the efficacy of OIT (children aged 3 to 17 years, 31 in each group (AG/PG)) with a better safety profile due to a slower progression pattern and lower maintenance doses than in the PALISADE study. Dose escalation took place over a maximum of 14 months, followed by a 16-month maintenance period (30 mg FP). As a result, 74.2% of the AG tolerated at least 300 mg FP vs. 16.1% in the PG ($p < 0.001$). Mild to moderate ARs occurred in 90% of AG patients versus 77% of PG patients,2.17% of AG patients received epinephrine. The study found no differences between the groups in dropout rates (6.7% of ARs due to OIT), symptom severity and treatment, or worsening of pre-existing atopic diseases. In conclusion low-dose OIT to nuts at preschool age is safe and effective in the real world (11).

**Canadian preschool peanut oral immunotherapy (CPPOIT) in 2020**: this is the first group to describe OIT (mono- and multifood) in preschool age, a real-life multicenter study whose aim was to design a protective OIT with minimal risk. Among 270 children (aged 9 to 71 months), 90% achieved maintenance of 300-320 mg FP with an mean induction duration of 16-22 weeks. 36.3% of patients reported mild symptoms and 31.1% moderate symptoms (grade 2). There were 11 epinephrine administrations, or 4.10% of patients, 6 in the clinic and 6 at home. The limitations of this publication are related to the fact that this is a real-life study, with a lack of adherence to the protocol (no diary, so missed doses were not assessed). This lack of adherence induces a risk of ARs during OIT, hence the need for close education in the use of adrenaline (in this study, all 11 adrenaline injections were given for moderate reactions). There was no correlation between increased IgE antibodies and exit from the study. SARs were in the order of 0.4%, less than in the PALISADE study (4.3%), as was the use of adrenaline during induction: CPPOIT 4.07% versus PALISADE 14%. EoE was diagnosed in 1/270 patients (0.37%), similar to PALISADE. Asthma was not recorded as an AR in CPPOIT, which recruited preschoolers with mild/moderate asthma under optimal control, with the intention to minimize the risk of ARs and study exit (12).

**The Grzeskowiak et al. 2020 meta-analysis**: 27 studies (1488 subjects) of peanut OIT (large and small maintenance doses) in children under 18 years of age, charting ARs, ability to reach the target maintenance dose and success of OFC after OIT. They show that the risk of protocol interruption due to ARs is lower when co-treatment (AH, probiotics, omalizumab) is associated. After the stratified analysis the treatment with omalizumab proved to be superior to AH and probiotics. ARs were frequent and led to treatment discontinuation in 6.6% of children. ARs requiring epinephrine treatment occurred in 7.6% of participants, at a rate of 2/10,000 doses. Specific IgE levels and the presence of asthma were the main risk factors for treatment discontinuation observed in univariate meta-analysis.

The use of an initial rush phase was consistently associated with an increased risk of SARs, just as aiming for a higher target maintenance dose (above 1 g FP) was also associated with an increased risk of epinephrine use. The risk of SARs was identical during the rush, dose escalation and maintenance phases, but the frequency was higher during the rush phase. Although the risk of SARs requiring epinephrine treatment may seem high at 7.6%, this must be conveyed to the patient along with the excellent benefits of OIT in protecting against accidental allergen ingestion. According to this meta-analysis, once children have reached the long-term maintenance phase, the risk of a SAR requiring epinephrine treatment is 3.2%, while the frequency is extremely low, on the order of 9 episodes per 100,000 doses. In terms of objective analysis, failure to reach dose was more important in the high-dose protocols. The final oral food challenge (OFC) success was 68.9% in 17 studies (small and large doses), and was higher in studies that used co-treatment (probiotics or omalizumab, but not antihistamines (AH)). Only three RCTs examined the effects of different approaches to OIT. These include different target maintenance doses, the use of co-treatment (omalizumab vs. placebo) (4). These studies have provided encouraging evidence that a lower maintenance dose and the use of co-treatment may reduce the risk and frequency of ARs (4, 12).

**A French single-center retrospective study in 2020**, of 100 children (mean age five years) who received a hazelnut OIT. Maintenance was performed with 416 mg of hazelnut protein. After six months of treatment, 34% were successfully desensitized (tolerance of 1635 mg FP); patients with positive reintroduction tests were able to acquire an increased reactogenic dose. The proportion of desensitized patients increased as the maintenance phase was extended. Successful desensitization was associated with an earlier treatment initiation, a smaller hazelnut skin

test wheal diameter, lower hazelnut IgE levels, and absence of cashew nut allergy. The success of desensitization was not dependent on comorbidities (atopic dermatitis, asthma) or a higher level of Cor a 14 IgE. No SARs were associated with OIT (13, 14).

**Israeli researchers in 2019** demonstrated the efficacy of OIT to walnuts at a maintenance dose of 1200 mg walnut FP. Of the 55 patients in the AG, 49 (89%) were desensitized to walnuts, compared to none of the 18 patients in the CG ( p<0-0001). Following walnut desensitization, all patients who were co-allergic to pecan (n=46) were also desensitized to pecan. In addition, 18 (60%) of the 30 patients co-allergic to hazelnut or cashew, and 14 (93%) of the 15 patients co-allergic to hazelnut alone, were desensitized. 47 (85%) of the 55 patients had an adverse event (mainly grade 1 or 2) when the dose was increased in the clinic; eight patients required epinephrine in response to a home dose. According to this study, walnut OIT can induce desensitization to walnut as well as desensitization to pecan and hazelnut in patients co-allergic to tree nuts. The safety profile is reasonable. A low daily dose of allergen maintained desensitization (15).

### COW'S MILK, WHEAT

**In a 2016 Japanese study**, the OIT protocol included 403 subjects: 217 subjects for cow's milk (CM) (median age, 6.0 years; interquartile range, 3.8–9.3 years) and 186 subjects for wheat median age, 6.8 years; interquartile range, 3.3–9.3 years). The OFC for CM or wheat contained 3 mL heated CM (102 mg CM protein) or 2 g udon noodles ( 52 mg wheat protein), respectively. The low-dose OFC appears to be useful for confirming tolerance to low doses of causative foods and improving the prognosis after 1 year. Inclusion of low doses of causative foods in the diet of patients with a food allergy after a low-dose OFC may improve quality of life. Subjects who passed the low-dose OFC were advised to consume a food containing 3 mL of heated CM or 10 g of butter (equivalent to 2.9 mL CM) for CM allergy or 2 g of cooked udon noodles for wheat allergy at home at least once a week. Within 1 year after confirming the tolerance to the low-dose OFC, 45% (18/41) of patients were able to consume 25 mL of heated CM. With regard to wheat, within 1 year of confirming tolerance to 2 g of cooked udon noodles, 56% (18/32) of patients were able to consume 15 g of cooked udon noodles. Only a few patients had symptoms at home, 9.8% of those with CM allergy and 3.1% of those with wheat allergy, and the symptoms were not severe in any of the cases (16).

### MFOIT- A PROGRESSIVE, REAL-LIFE PROTOCOL

**A first study of MFOIT** without omalizumab pretreatment was published in 2014 by Bégin et al. including up to 5 foods simultaneously in 25 patients, with the result that 22/25 patients were able to achieve daily doses 10 times greater than the initial reactogenic cumulative doses (RCDs) for each food (17).

**In 2019, a Detroit research team** enrolled 45 patients in an MFOIT. The foods included were peanuts, nuts and seeds. Most patients (76%) received an OIT for 4 or fewer foods, although a few patients had more foods (up to 12). Thirty-five patients started OIT on the basis of positive single-food OFC results; 10 patients started treatment on the basis of a history of anaphylaxis to the food (ranging from 1 to 12 years prior to starting OIT) and still remained positive on allergy testing. Three of these 10 patients had allergic reactions when the dose was increased. The mean time to maintenance was 24 weeks (range, 9-54 weeks). Six patients (13%) discontinued OIT. According to Eapen, MFOIT is feasible and safer than multiple food avoidance. Most patients can achieve a maintenance dose that provides good protection against reactions to involuntary food ingestion. Four patients reached the end of the protocol and continue to receive the food 3 times per week to maintain long-term tolerance. The OIT diet in this study was adapted to each patient for safety, tolerance and practical reasons to match real-life conditions. The final maintenance dose was also determined individually (18).

**In a retrospective analysis (2020-2022) at CHRSM Namur** of the medical records of 31 food-allergic patients (age 2- 10 years) who had received MFOIT(egg, peanut, nut, sesame), it was found that 87% (27/31) of patients tolerated 300 mg of protein from each food at the end of the protocol, thus protecting against most accidental exposures. The protocol included 6 months of induction and 6 to 18 months of maintenance, depending on the severity of the phenotype. 51% of patients passed the final OFC at 2g PF, and all patients increased the reactogenic dose by more than 15-fold compared to the initial RCD. ARs were predominantly grade 1 and 2 (Ring and Messmer). An initial OFC was performed for each food in the MFOIT (in the absence of anaphylaxis to the food concerned in the anamnesis or other elements with high predictive value for allergy), and the maintenance dose was 300 mg protein/food/day. In 4 patients, adrenaline was used during the maintenance period, in the context of cofactors or abdominal pain whose worsening was not notified to the physician.4 patients dropped out due to relocation, family separation and worsening of pre-existing food phobias. In our experience, low-dose MFOIT with a long maintenance period is an effective treatment option. It is essential to put in place the tools to guarantee good safety, such as -practice in specialized centers, with permanent medical assistance, a therapeutic education (TE) at each visit and systematic control of understanding and rigor. It's a rigorous approach that requires a high degree of commitment from clinicians, patients and their families (2). The results of this analysis suggest that the daily consumption of small amounts of multiple allergens daily (even in those with asthma, eczema or those at high risk of atopy) may be safe and effective.

**In 2019, according to Cincinnati research** in the open-label phase of the MFOIT study (n = 70, age 5– 22 years), participants received omalizumab (weeks 1–16) and multi-OIT (2–5 allergens; 1 g each; weeks 8–30), after which they were tested by food challenge (week 30). Subsequently, 60 eligible participants (excluding 10 dropouts) were randomized 1:1:1 in a blinded manner to receive either 0 mg, 300 mg, or 1 g of food allergens (weeks 30–36). These participants were then tested again by food challenge at week 36. Success was defined as passing the 2 g food challenge to at least 2 foods at week 36. Most participants were able to reach a dose of 2 g or more of each of 2, 3, 4, and 5 food allergens (as applicable to the participant's food allergens in OIT) in the week 36 food challenges. The authors found no evidence that a 300 mg dose differed from a 1 g dose in maintaining desensitization, and both together were more effective than OIT discontinuation (0 mg dose) (85% vs 55%, P = 0.03). Fifty-five percent of the intent-to-treat participants and 69% of the per-protocol participants randomized to the 0 mg arm showed no objective reactivity after 6 weeks of discontinuation. Cross-desensitization was observed between cashew/pistachio and walnut/pecan when only one of the foods was part of the OIT. There were no statistically significant safety differences between the three arms. These results demonstrate for the first time that omalizumab-facilitated MF-OIT and induces changes in immune polarization. Multi-OIT promoted a decrease in Th2A and Th17 cell frequencies while increasing regulatory markers in blood, particularly evidenced for patients aged 10 and over for whom desensitization was successful. Such results will need to be confirmed with a larger cohort of patients in double-blind, placebo-controlled clinical trials, the limitations of this study are due to the small number of participants (19).

## Discussion

Current guidelines for OIT emphasize the importance of accurate diagnosis and shared decision making before initiating the protocol, as it is a logistically demanding, time-consuming and risky therapy.

Therefore, allergists, patients and their families need to be aware of and consider all aspects of this process. The primary goal of OIT is not to cure FA, but rather to increase tolerance to the allergen, improve quality of life, reduce the risk of serious reactions in the event of accidental ingestion, and reduce the psychological distress and anxiety associated with the disease.

The evidence is still limited and there is little data on long-term tolerance. There is a need for studies in this area to provide good quality evidence for standardized protocols. At present, many allergists (especially in France) have adopted protocols based on ongoing clinical research trials, with protocol initiation in specialized centers and cautious dose escalation at home to acquire small maintenance doses. Obviously, the optimal age range is between 4 and 7 years. Exclusion factors include patients with partially controlled allergic comorbidities, immune disorders, and neoplasia. It is important to be aware of the social context and to give priority to motivated and rigorous families.

Risks associated with OIT include SARs occurring at home, after the dose has been taken and, in the long term, severe anaphylaxis due to tolerance breakdown (after irregular or spaced dosing) or eosinophilic esophagitis. Targeted patient selection, close follow-up, telephone/email hotlines and TE sessions are essential to reduce the incidence of SAR's. Efficacy and risks must be discussed transparently with patients and their families, as written in informed consent forms and patient OIT protocols. Detailed information on the need for daily intake, dose adjustment in the context of cofactors or reactions, and rapid feedback of ARs are required. A higher frequency of ARs may be associated with specific predictors such as comorbidities (partially controlled atopic dermatitis, rhinitis, asthma), high skin test and IgE levels (20, 21). Indicators of OIT failure reported in several studies are high maintenance dose, high IgE level and low CRD on OFC. Low maintenance doses and, most importantly, matching the dose to the severity of the phenotype are considered the correct approach (4, 5, 20).

Low-dose maintenance therapy, multi-food if polyallergic, with slow dose escalation and tailored to the patient, therefore appears to be a safe and effective approach for children at risk of anaphylaxis. According to the studies cited, small doses have the same effect on efficacy as large maintenance doses, with a better safety profile and lower discontinuation rates. In this sense, in our opinion, the idea of starting MFOIT based on an accumulation of elements with a high predictive value in a child who has already experienced anaphylaxis and/or polyallergy remains an option of medical and ethical interest to be studied and proposed to the family. Although data are scarce, available analyses of quality of life suggest an improvement over time in most studies (20, 21).

## Conclusion

OIT remains a promising therapy, reserved for specialized centers. It seems important to be able to offer it early, before teen aging or even as early as pre-school age. A review of the various studies shows the importance of identifying severe phenotypes at risk of SARs and of individualizing a closely supervised MFOIT, aiming at a slow induction phase (preferably without rush), the administration of low maintenance doses or even co-treatments for maintenance periods adapted to the phenotype of allergy severity and family possibilities.

Many questions still need to be answered: to identify the clinical characteristics and biomarkers of SARs and efficacy, and to guide the protocol in terms of optimal duration, testing these therapies in other populations (i.e., ethnic and racial groups that were underrepresented in these trials) and in patients with multiple comorbidities will also be useful. Current trials are significant for the pediatric age group, but extending research to the adult population remains another major challenge. Finally, specific tools will need to be developed to assess the impact on quality of life. This still requires larger, real-life clinical studies.

## Conflict of interest

The author has no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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# Prevention of food allergies: to eat or to hydrate?

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## Keywords

Food hypersensitivity ; Prevalence ; Anaphylaxis ; Prevention.

## Abstract

In Western countries, food allergy (FA) is one of the most common chronic diseases in childhood with an increasing prevalence of food-related anaphylactic reactions. Food allergy is associated with a significant health and socioeconomic burden. It is important not only to consider the different impacts of food allergies, but also to try to mitigate this growing epidemic through primary prevention. After focusing on the epidemiology and the multifactorial etiology, this review will give an overview of the current prevention strategies, consisting of dietary recommendations during pregnancy, breastfeeding and infancy, as well as prevention by epicutaneous sensitization.

## Introduction

In 2017, 30% of the world's population suffered from allergies. Without preventive measures, the World Health Organization (WHO), predicts that 50% of the population will be affected by allergies by 2050. The atopic march is a representation of the progression of allergic disease with age in patients with a genetic predisposition to atopy and contributing environmental factors (1). Atopic dermatitis (AD) and food allergy (FA) are the first manifestations of the atopic march followed by asthma and allergic rhinitis (AR). Some of the allergic conditions, such as allergic rhinitis and asthma, showed a strong increase in incidence while in the last decade there is a worrying increase in the frequency of FA with a parallel increase in the prevalence of food-induced anaphylaxis (2-7).

Several studies show a large discrepancy between self-/parent-reported and diagnosed FA, using double-blind placebo-controlled oral food challenge (DBPCFC) (4-6). FA is a growing health concern with a high prevalence of 10% in Western countries, with the highest prevalence in infants and young children (7,8). There is also an increasing prevalence in rapidly developing countries (9). In Belgium there are few accurate data on the prevalence of FA and anaphylaxis. In 2009, the Health Council published a prevalence of FA of 6-8% in children under 3 years of age and 2-3% in adults (10). The 2018 Sciensano Health Survey reported that 9% of the population suffered from a food allergy or -intolerance but only 5,2% were diagnosed by a physician (11). The Allergo-Vigilance® network (RAV) analyzed the fatal/near-fatal anaphylaxis cases from 2002 to 2021 in France, Belgium, and Luxembourg (12). Of the 3510 anaphylaxis cases, 70 patients had grade 4 anaphylaxis of which 25 patients died. Food was the main allergen (60%) and in the group of children younger than 16 years the responsible allergens were peanut (24%), cashew nut (13,7%), milk (8,9%), hazelnut (4,3%) and hen's egg (4,1%).

In addition to the increasing prevalence, there are other important reasons to pay more attention to the primary prevention of FA. First, there is an increase in complexity, with nearly 40% of children suffering from multiple FAs (13). Second, the psychosocial burden should not be underestimated. FA can affect the individual's health and the quality of life of patients and their families. Previous studies have shown that quality of life is worse in patients with multiple FAs or allergy to an allergen that is difficult to avoid (e.g., egg/cow's milk) or a history of severe food allergic reactions (4). Third, studies in several countries have shown an increase in emergency department visits and hospitalizations due to food-induced anaphylaxis, resulting in a significant economic burden (4). In Europe, the average annual household costs are much higher in households with a food-allergic child compared to those without a food-allergic child. Finally, the current management of FA consists of allergen avoidance and treatment of acute allergic reactions, requiring patients to carry a permanent emergency kit due to the risk of reactions by accidental ingestion. Currently, there are more and more specialized centers around the world that are establishing oral food immunotherapy protocols with the main goal of increasing the reactogenic threshold, improving the child's quality of life and trying to induce tolerance. The problems of food allergen immunotherapy are that it is allergen-specific, time-consuming and associated with adverse reactions that limit tolerability (14).

Based on the above arguments, it is important that all health professionals pay attention to the primary prevention of FA. This review provides an overview of current measures for the primary prevention of FA in infants and young children.

## Overview of the underlying hypotheses of FA to make prevention measures effective.

### *Hygiene hypothesis*

In 1989, Strachan proposed the hygiene theory as possible explanation for the increasing epidemiology of eczema, asthma, and allergies (15). In this study, hay fever and eczema were less frequent in children from larger families, most likely due to a higher incidence of early childhood infections. Several studies have shown that several other factors, such as birth by cesarean section, antibiotics, anti-acids, exposure to pets, etc., can have an impact on the microbiome (16). Reduced diversity of microbial exposure or dysbiosis leads to a Th1/Th2 cell imbalance that is skewed toward a Th2 cell-mediated inflammatory response and is thus predetermined for FA.

### *Dual allergen exposure hypothesis*

For many years, it was thought that gastrointestinal exposure to allergens led to sensitization to food allergens. In contrast, the dual

allergen exposure hypothesis suggests that sensitization occurs via the non-oral route. This hypothesis is based on the observation that many patients react to the first oral exposure to peanut. Epicutaneous exposure to food allergens induces a potent type 2 immune response and can lead to systemic food allergic reactions on subsequent oral exposure (17). The article by du Toit et al. provides a good overview of the preclinical and clinical data on epicutaneous sensitization (18). It emphasizes that AD is an important risk factor for FA. In another study, du Toit et al. observed that early introduction of peanut in infancy in Israel resulted in a lower prevalence of peanut allergy compared to a similar population in the United Kingdom where peanut was avoided (19). The Learning Early About Peanut Allergy (LEAP) clinical trial showed that introducing peanut in an age-appropriate manner between 4 and 6 months of age significantly reduced the incidence of peanut allergy in high-risk children (20).

In addition, there are studies showing that the respiratory tract is an alternative route of sensitization leading to FA (21).

Therefore, oral exposure to food allergens early in life leads to tolerance as opposed to epicutaneous and inhaled allergen exposure leading to FA. Therefore, it is important to achieve oral tolerance prior to skin or airway exposure to prevent the development of FA.

### *Vitamin D hypothesis*

Vitamin D deficiency has been suggested as a contributing factor to FA. Further studies are needed to support this hypothesis because of inconclusive results due to methodological limitations (16,18).

## Overview of the recommendations to prevent FA

The goal of primary prevention of FA is to prevent the development of allergic IgE sensitization and associated symptoms, while secondary prevention focuses on interrupting the development of FA in IgE-sensitized patients. The window of opportunity for primary prevention is early infancy, as the first manifestations of FA usually occur in infancy. It is important to apply early preventive measures to all infants regardless of family history or atopy, otherwise 10-15% of children may be missed. (16)

This review will focus on the modifiable factors such as dietary and cutaneous factors. The non-modifiable factors such as genetics, race and sex will not be discussed in detail.

### *A. Dietary factors*

#### 1. MATERNAL DIET

Women, who are pregnant or breastfeeding, should eat a healthy, balanced diet without restricting the consumption of specific allergenic foods (22). There is no reduction in the prevalence of FA if women avoid potential food allergens during pregnancy or breastfeeding. In contrast, it can be harmful due to insufficient intake of vital nutrients and fibers.

#### 2. BREASTFEEDING AND INFANT FORMULA

The 2003 WHO guidelines recommend exclusive breastfeeding for the first 6 months of life based on its nutritional value and protective effects for both mother and child against a number of health outcomes (23). To date, there is no evidence that breastfeeding reduces the risk of food allergy or cow's milk protein allergy (CMPA) (22).

The EAACI Task Force proposes avoiding cow's milk supplementation in the first week of life, as this leads to a large reduction in CMPA in early childhood (21). If necessary, temporary association of donor breast milk, advanced hydrolysate cow's milk formula, rice protein formula or even amino acid formula can be used, depending on clinical, cultural and economic factors.

On the contrary, several observational studies have shown that early and persistent daily introduction of cow's milk into the infant's diet from the first days of life is associated with a reduced risk of CMPA. For this reason, Sabouraud-Leclerc et al. suggest a daily supplementation of 10 ml of first milk until diversification in exclusively breastfed children at risk of atopic diseases, after discussion with the family (16).

If formula feeding is preferred, it is important to use a non-hydrolyzed first age formula, as hypoallergenic (HA) formulas may not reduce the risk of CMPA and FA (16, 22). Soy protein formula is unlikely to protect against CMPA and should not be introduced in the first 6 months because of potential harm (high concentration of phytate, aluminum, and phytoestrogens) (22).

#### 3. INFANT'S DIET (SOLID FOOD)

In the last two decades, there has been a paradigm shift from food allergen avoidance to early consumption of potentially allergenic foods in infancy to prevent the development of FA (24). Several observational studies have shown that delayed introduction of food allergens may be associated with an increased risk of FA (16,20,25).

The EAACI Task Force recommends the introduction of half a well-cooked egg, not raw or uncooked pasteurized egg, twice a week as part of complementary feeding between 4 and 6 months of age, as the consumption of 2 grams of egg white protein per week may prevent egg allergy. This recommendation is mainly based on the results of the Prevention of Egg allergy with Tiny Amount Intake (PETIT) study (22,23,24). In populations with a high prevalence of peanut allergy, the introduction of peanut in an age-appropriate form as part of complementary feeding between 4 and 6 months of age is recommended based on the results of the LEAP and its follow-up (LEAP-on) study (20,22,23). It is important that the introduced allergen is consumed regularly, i.e. several times per week, to avoid the development of an allergy. Early introduction of potential food allergens, such as egg and peanut, does not have a negative effect on breastfeeding or fruit and vegetable consumption, nor does it have a nutritional effect, except for a higher fat intake with early introduction of peanut, but still in the normal range (16,23,25). There are currently no recommendations for early introduction of peanut in countries with a low prevalence of peanut allergy, or for early introduction of tree nuts or wheat (16,22,23). Evidence for early introduction of fish (before 9 months of age) to prevent allergic sensitization, rhinitis and asthma is limited. Fish can be introduced after 6 months of age because of the important nutrients and omega-3 fatty acids in fish (24).

Thus, the window of opportunity to introduce food tolerance is around 4-6 months of age, especially for highly allergenic foods and highly atopic infants (16). A medical evaluation by an allergist in infants with severe AD and/or FA before introducing common food allergens into the diet remains important. This assessment needs to be done within a reasonable timeframe so that long delays do not increase the risk of sensitization.

Finally, attention should be paid to dietary diversity in the first year of life for all children as it may be associated with a reduced risk of developing allergic diseases such as asthma, AD, allergic rhinitis, food sensitization or FA (24,26). Dietary diversity is the number of different foods, food groups of food allergens eaten over time, taking into account the eating habits of each family. Tolerance development will be stimulated if there is more exposure to food allergens in the diverse diet during the first year of life. On the other hand, dietary diversity may play a role in allergy prevention by increasing the intake of nutrients (omega-3 fatty acids and non-digestible fiber) and modifying the gut microbiome (24).

#### 4. DIETARY SUPPLEMENTS

Currently, according to the EAACI guidelines, there is no recommendation for or against vitamin or fish oil supplementation in healthy pregnant and/or breastfeeding women and/or infants due to inconclusive results in various studies for the prevention of FA, mainly due to methodological limitations (16, 22). Similarly, there is insufficient evidence to support supplementation with prebiotics, probiotics, and symbiotics in healthy pregnant and/or lactating women and/or infants to prevent FA (16, 22). Because these supplements do not cause harm in healthy women and infants, health care professionals should consider the pros and cons for each individual patient (22).

### *B. Cutaneous factors*

AD is a risk factor for the development of FA. The risk of FA increases with the early onset, severity, and duration of AD. In addition to the genetic predisposition (filaggrin loss-of-function mutations, , corneodesmosin gene mutations) to AD, the skin is continuously exposed to environmental factors, including natural (e.g., food, aeroallergens, viruses, bacteria, fungi) and artificial (e.g., detergents, high pH creams, lotions) triggers (17). These factors can lead to skin barrier dysfunction, epicutaneous damage and allergic sensitization in patients with a genetic predisposition to allergic diseases.

In addition, the skin microbiome plays an important role in epicutaneous sensitization, with *Staphylococcus aureus* colonization being a risk factor for AD. It is associated with the severity and worsening of AD and consequently with an increased risk of food sensitization and allergy (17,26).

Because of the strong association between epicutaneous sensitization and FA, it has been suggested that improving the skin barrier of infants and thus reducing the duration and severity of AD may prevent the development of FA. This can be achieved either by improving the barrier through hydration with emollients or moisturizers, or by reducing potential damage to the skin barrier by avoiding potentially harmful substances or irritants. The Cochrane systemic review by Kelleher et al. showed moderate evidence that skin care interventions such as emollients during the first year of life in healthy infants are probably not effective in preventing AD and increase the risk of skin infections. They were unable to draw firm conclusions about FA (27). The recent systematic review by Zhong et al. published that prophylactic and continuous application of emollients in early infancy may prevent AD, especially in high-risk patients (28). The development of AD during the first 32 weeks of life could be prevented by daily application of a moisturizer in the STOP-AD randomized controlled trial by Chaoimh et al. In contrast, there was no significant effect of emollients on the prevention of allergic sensitization (29). If emollients can delay AD, the window of opportunity to induce oral tolerance by early introduction of allergenic foods increases. Currently, there is no recommendation for the standard use of emollients in infants with or without atopy risk. Further research is needed in this regard, with particular attention to the patient population that would benefit, the composition of emollients, the duration of preventive use, etc.

On the other hand, AD is also an inflammatory process. Therefore, targeting inflammation by early and adequate treatment with topical steroids may reduce the severity of AD and prevent food sensitization and allergy. It has been shown that the severity of AD, as measured by the Scoring Atopic Dermatitis (SCORAD), correlates with food sensitization (16). Therefore, anti-staphylococcal treatment is important because *Staphylococcus aureus* dysbiosis may lead to uncontrolled inflammation (16,26). The retrospective cohort study by Miyaji et al. showed that proactive topical treatment in infants with moderate-severe AD was associated with an almost twofold reduction in FA by 24 months if topical treatment was started before 4 months of age versus after 4 months of age (30). Therefore, it is important to treat all infants with AD early and appropriately with emollients and topical corticoids to restore the skin barrier. A trilipid-based emollient would be more effective in reducing transepidermal water loss (TEWL) than a paraffin/alcohol/petroleum-based emollient. The composition of the trilipid-based emollient consists of a 3:1:1 ratio of ceramides, cholesterol and free fatty acids, mimicking the skin's natural lipid composition. The PEBBLES pilot study by Lowe et al. found that twice-daily prophylactic use of the tri-lipid emollient EpiCeramTM during the first six months of life was associated with a reduced incidence of AD and food sensitization at 12 months of age (31).

A third possible preventive measure is to limit the presence of allergens in the infant's environment, as skin barrier dysfunction in infants with AD facilitates the penetration of food allergens from topical application or from the environment. The use of skin creams containing peanut protein is associated with peanut allergy (17,26). There is also an association between repeated use of oat extract containing emollients and the prevalence of oat allergy in children with AD. Studies have shown that the consumption of almonds and peanuts in the home is highly correlated with the concentration of almonds and peanuts in the dust of an infant's bedding and play area, even if the infant does not eat almonds or peanuts (16,17,26).

## Conclusion

The epidemic of FA is a growing global public health problem. In recent years, many studies have supported the dual allergen exposure hypothesis: cutaneous or inhalational exposure to allergens may promote IgE-mediated allergy, while early ingestion of allergenic foods may lead to oral tolerance. Thus, there has been a paradigm shift from food allergen avoidance to early consumption of potentially allergenic foods in infancy to prevent the development of FA. Between 4 and 6 months of age, it is important to introduce half a well-cooked small egg to prevent egg allergy, and in populations with a high prevalence of peanut allergy, a heaped teaspoon of diluted peanut butter (2 grams of peanut protein) to prevent peanut allergy. The allergen must be consumed regularly throughout childhood to prevent allergy. Further studies are needed to investigate the effect of early introduction of other potential food allergens. On the other hand, the risk of FA increases with the early onset, severity and duration of AD. Currently, there is no recommendation for the use of emollients in infants with or without atopy risk. More research is needed. However, there is evidence that early and appropriate treatment of all infants with AD with emollients and topical corticoids to restore the skin barrier may reduce the severity of AD and prevent food sensitization and allergy. Dietary protein-based emollients should be avoided, and indirect contact of the infant's skin with peanuts and tree nuts should be avoided (e.g., washing hands before touching the infant) if the infant has not previously ingested them.

## Conflict of interest

The author has no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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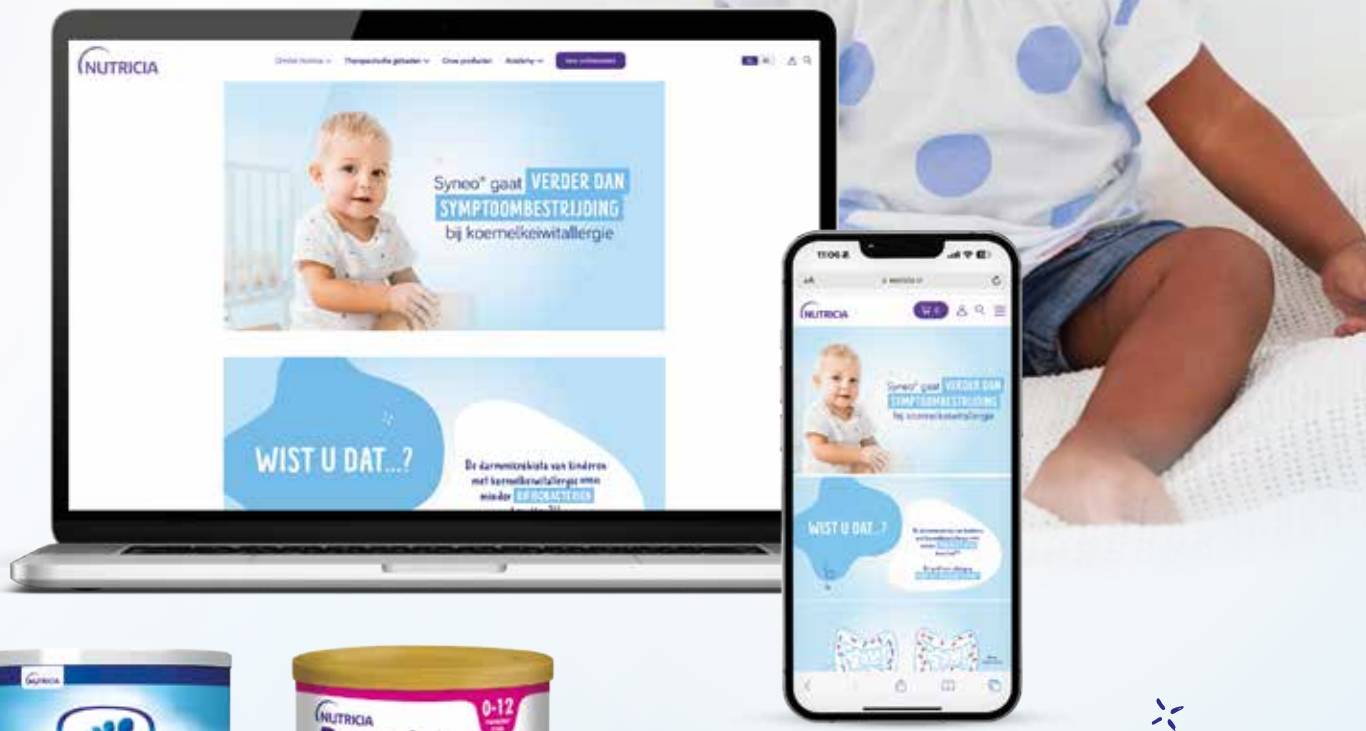



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# Eczema and allergy: the chicken or the egg ?

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## Keywords

Eczema ; atopic dermatitis ; allergy.

## Abstract

Eczema is a common problem in general paediatric consultations. Treatment of eczema is essential because irritated and inflamed skin stimulates the onset of sensitisation and subsequent allergy, particularly food allergy. Treatment is currently based on non-aggressive corporal hygiene, daily application of emollients and early treatment of flares with topical corticosteroids.

In severe cases, an allergic aetiology is often suspected. Early-onset eczema before the age of 6 months and/or steroid-dependent eczema are more likely to be allergic in origin. In these cases, cow's milk is the main culprit, either in artificial milk or via breast milk. Eviction would help to reduce the intensity of the disease. In the older children, an allergic trigger is found in only 10% of cases.

However, a very large number of patients have asymptomatic sensitisation (positive skin prick test and/or positive specific IgE) which should not be confused with allergy. In fact, if eliminating the food does not improve the cutaneous symptoms, it is not only useless but may even promote a breach of tolerance and increase the risk of becoming truly allergic to that food.

## Introduction

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease in children. In its moderate to severe form, it has a significant impact on quality of life, for example through sleep disturbance, but also because of the cost and time involved in treatment.

The prevalence of AD is difficult to estimate because of the different terms are used to describe it. It is to be between 10 and 20% in the paediatric population, according to different studies, and has been increasing steadily in recent years. This increase is mainly observed in developing countries where the prevalence is low, with a stabilisation in countries where the prevalence is already high (1,2).

## AD : a multifactorial disease

There is undoubtedly a genetic predisposition. Indeed, about 70% of patients with AD have a positive family history of atopy, and the odds ratio for developing AD is 2-3 times higher in children with 1 atopic parent and 3-5 times higher if both parents are atopic (3).

Genetic mutations explain this trend, including loss-of-function mutations in filaggrin (FLG), a structural protein of the epidermis, but also mutations in the lipidic cement, keratinocytes and antimicrobial peptides. These mutations lead to a dysfunction of the skin barrier, allowing water to escape to the outside, leading to a skin xerosis and allowing the penetration of pathogenic microorganisms and allergens into the skin tissue, promoting superinfections and the development of secondary allergic sensitisation.

There is also a dysfunction of the immune response, with an imbalance between the Th1/Th2 response, promoting the IgE-mediated response, on the one hand, and the secretion of cytokines self-sustaining the capacity of the immune response on the other. Furthermore, an involvement of the *Staphylococcus aureus* superantigen has also been demonstrated.

However, the recent increase of AD as well as of other atopic diseases is too rapid to be explained by genetics alone. So, there is an involvement of the environment. In this sense, the hygiene hypothesis suggests that the transition from a rural to an urban lifestyle has reduced children's exposure to some pathogenic microorganisms, and consequently altered the Th1-Th2 balance. By limiting repeated exposure to microbes, the Th1 response is less provoked, and the Th2 response is more promoted inducing atopic manifestations in infants and young children living in a more sterile environment. Other environmental factors have also been taken into account: breastfeeding, changes in dietary habits (obesity), smoking, exposure to domestic furry animals, exposure to dust mites and cockroaches, overheating of homes, pollutants and climatic factors, lack of exposure to UVB, use of alkaline detergents, perfumes and preservatives (4 - 7).

## AD: diagnosis and treatment

The diagnosis of AD is clinical. The UK Working Party diagnostic criteria for atopic dermatitis were established in 1994 and have been widely used in studies and are easy to use in everyday practice.

A history of itchy skin plus at least 3 of the following criteria :

- visible flexural dermatitis involving the skin creases, such as the bends of the elbows
- personal history of flexural dermatitis (or dermatitis on the cheeks and/or extensor areas in children aged 18 months or younger)
- personal history of dry skin in the past 12 months
- personal history of asthma or allergic rhinitis (or history of atopic disease in a first-degree relative of children aged less than four years)
- onset of signs and symptoms before the age of two years.

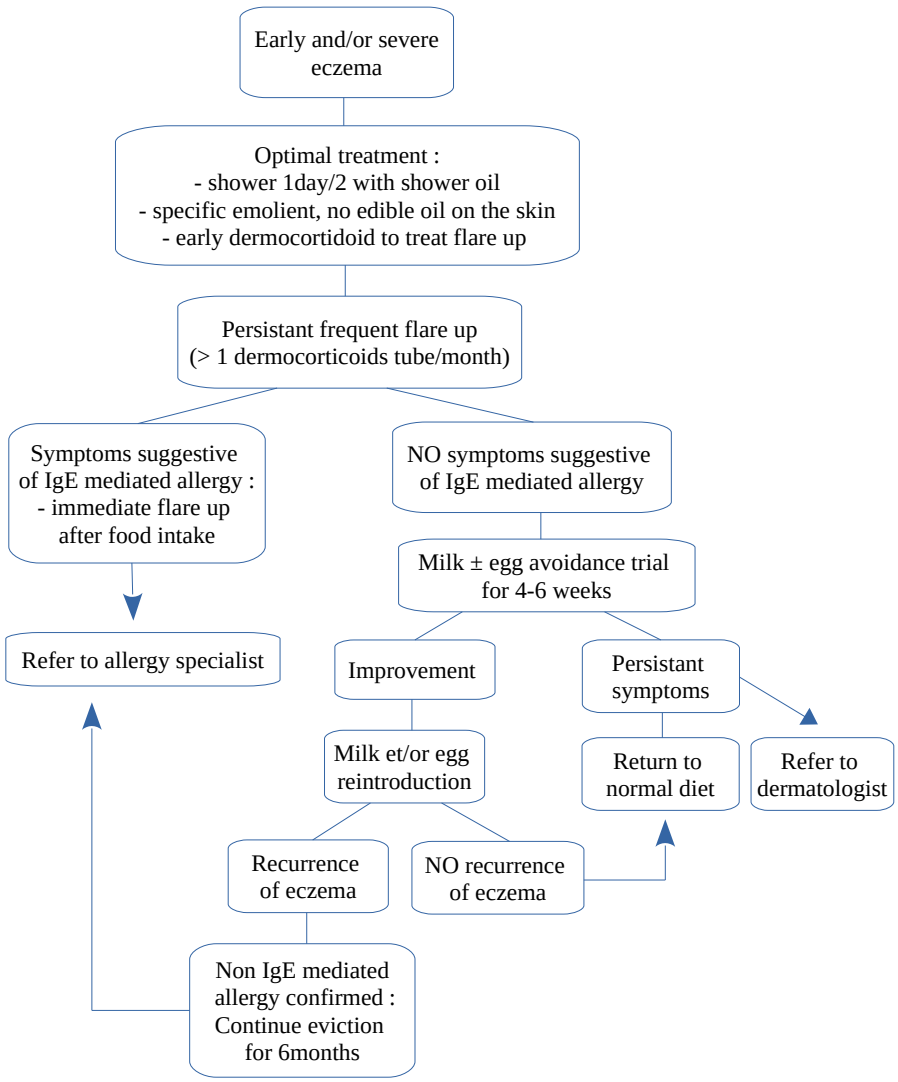
There are also several severity scores (EASI: eczema area and severity index, SCORAD: severity scoring atopic dermatitis index, POEM: patient-oriented eczema measure), but these are cumbersome and not always very useful in current practice.

The cornerstone of treatment is local care. Hygiene measures to strengthen the skin barrier (short warm baths 1-2 times a week, frequent daily application of cutaneous emollients) and regulation of the immune response by early anti-inflammatory treatment (with dermocorticoids and calcineurin inhibitors, the latter only reimbursed in Belgium from the age of 2 years).

There are two approaches: reactive treatment of flare-ups and proactive treatment even outside flare-ups to limit them. The ongoing PACI study is an RCT that aims to determine the best approach (8).

A decision tree for the management of eczema is shown in Figure 1.

**Figure 1:** Decision tree for the management of eczema.




## AD and allergic triggers

In case of severe eczema, an allergic trigger is often sought. A thorough medical history is essential. In fact, systematic testing is not recommended. A suggestive history of food allergy or a moderate to severe eczema with little or no response to optimal topical treatment should raise suspicion of an underlying allergy. On the other hand, unwarranted investigation leads to many false positive reactions. Indeed, there is a high prevalence of asymptomatic food sensitisations in AD (9). Misinterpretation of test results (specific IgE's or prick tests) can lead to severe elimination diets with negative effects on quality of life, but also to avoidance or postponement of tolerance and even induction of food allergy (10).

The EAACI (European Academy of Allergy and Clinical Immunology) recommends testing for food allergens in case of eczema in the following situations (11) :

- AD and immediate reaction to one or more foods
- Persistent, moderate to severe AD with no history of immediate reaction to a food
- Foods suspected by the patient or his family with no obvious history of immediate reaction.

Skin prick tests (SPT) and specific IgE's have a good negative predictive value of 95%, but a bad positive predictive value of only 50%. Atopy patch tests are more sensitive but less specific. However, they are not recommended by EAACI due to their lack of standardisation.

Depending on the equipment available, one test or the other may be preferred. The SPT, which consists of pricking the skin with a lancet through a drop of a commercially available allergen extract or fresh food, is usually preferred because of its low cost, speed of execution and interpretation, and the ability to test for multiple allergens at once. On the other hand, they are generally preferred by children over blood testing. However, in general practice, specific IgE's are often preferred for practical reasons due to lack of experience and/or appropriate equipment.

If a food trigger is suspected, the food challenge remains the gold standard to confirm the allergy before setting up an elimination period or after a trial elimination diet. In the case of eczema, an elimination period of 4 to 6 weeks followed by a reintroduction to confirm the food's involvement in the symptomatology is essential. In the specific case of a positive test for a food that has not yet been introduced into the child's diet, caution is required as there is a risk of real allergy due to allergic sensitisation and the first introduction must be made under medical supervision.

Especially in case of early onset eczema (<6 months of life) and / or corticosteroid-dependent eczema, it is more likely to act as an allergic trigger. In this case, it is mainly cow's milk, either in formula or via breast milk, but it can also be egg or peanut (12). Elimination of the food would help to reduce the severity of the disease. In older children, an allergy is found in only 10% of cases.

## AD and subsequent food allergy

In 2008, a new hypothesis on the aetiology of food allergy emerged (the dual exposure allergen hypothesis). The site of a food's first encounter with the immune system determines the subsequent tolerance or allergy to that food (Figure 2).

**Figure 2:** Chicken or egg? The dual exposure allergen hypothesis.

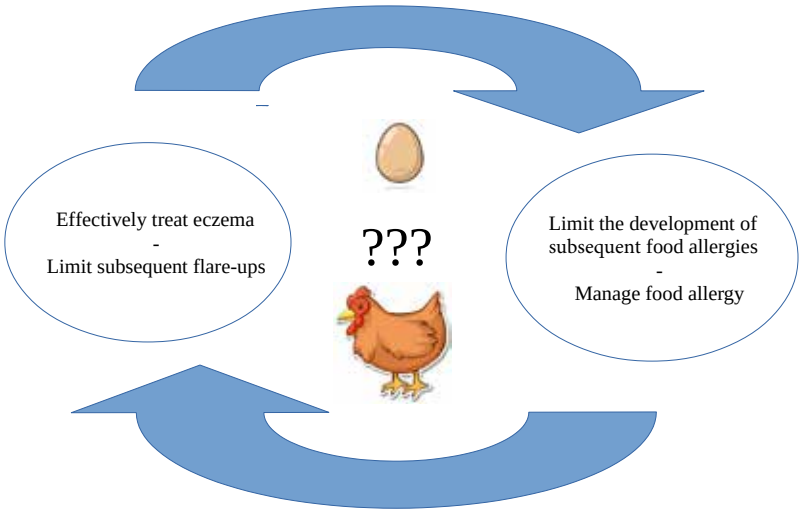



Image : www.freepik.com

The digestive tract is mainly tolerogenic, whereas the cutaneous route is more likely to lead to allergy (13). Since then, several other elements have complicated this theory, e.g. implication of vitamin D levels, skin flora (14).

In children carrying one or more loss-of-function mutations in the filaggrin gene, a dose-response relationship has been demonstrated between early life environmental exposure to peanut protein in house dust and subsequent sensitisation and allergy to peanuts (15).

We can therefore understand that early introduction of foods promotes their tolerance and that a delayed introduction increases the risk of allergy. The latest recommendations are to introduce the main allergens (egg and peanut) as early as 4-6 months.

Similarly, it is recommended that potential allergens should not be applied to weakened and damaged skin. We should avoid creams made with food proteins and prefer creams containing few ingredients (16).

Treatment of eczema should also be started early to reduce the risk of developing a subsequent food allergy. However, it remains a major challenge because of the significant corticophobia, of both the family and some of the patient's health care providers (physicians, paramedics, pharmacists ,…) (17).

## Conclusion

Take home messages

- AD is a common skin disease in children with a significant impact on quality of life.
- The tolerogenic role of gastrointestinal exposure versus cutaneous exposure needs to be recognised.
- Restoring the cutaneous barrier is very important.
- Fighting corticophobia is one of our tasks.
- Early introduction of allergenic foods (egg and peanut between 4-6months) must be advocated.
- Advise food avoidance only when justified by history, allergy testing (specific IgE and prick testing) and/or oral food challenge..
- Referral to an allergologist may be necessary for severe AD not controlled by dermatocorticoids.

## Conflicts of interest

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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# Drug hypersensitivity reactions: an overview

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## Keywords

Drug hypersensitivity; hypersensitivity; immunoglobulin E; T-lymphocytes; penicillins; diagnostic errors.

## Abstract

Drug hypersensitivity reactions (DHRs) account for 10% of all adverse drug reactions.

DHRs are clinically classified as immediate, mostly drug-specific IgE antibody (sIgE) -mediated, and nonimmediate, mostly T-cell mediated, reactions. Gathering insights into the underlying pathophysiological mechanism is crucial for correct orientation of further diagnostic work-up of DHRs. Therefore, a thorough history focusing on elements such as signs, symptoms, timing, index drug, re-exposition is of paramount importance. In case of immediate DHR, diagnosis may comprise skin testing with immediate readings, sIgE antibody quantification, specialized *in vitro* diagnostics. In nonimmediate DHR, sIgE antibodies are not useful and skin tests are performed with delayed readings. In difficult cases with negative or uncertain test results, eventually a drug challenge might be required to document or refute diagnosis.

Correct diagnosis of DHRs is very important. Unverified and false diagnoses of "drug allergy", mainly "penicillin allergy", have evolved into a plague with increasing medical and financial burden. On the other hand, misdiagnosis entails a risk for potentially life-threatening and fatal reactions upon re-exposure. Therefore, quick referral for an allergy workup in case of a possible DHR is recommended.

## Introduction

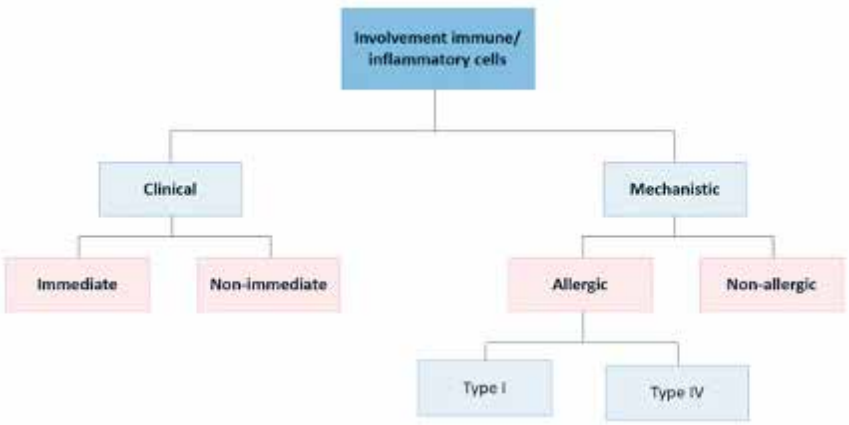
Adverse drug reactions (ADRs) are defined as unintended, harmful effects resulting from exposure to a compound for diagnostic, prophylactic, or therapeutic purposes. Most ADRs directly dependent on the pharmacological properties of the drug (e.g. bleeding by anti-coagulants). Drug hypersensitivity reactions (DHRs) on the other hand, comprise symptoms resulting from effects extending beyond the pharmacological targets of a drug and can result from the activation of immune cells, inflammatory pathways, or both. DHRs account for 10% of all ADRs. According to the World Allergy Organization (WAO), DHRs occur in 1% to 2% of all admissions and in 3% to 5% of the hospitalized patients. The true prevalence in the community is unknown. However, despite absence of correct prevalence data in children, DHR are estimated to be less frequent than in adults, possibly because of less exposure to drugs.

As shown in *Figure 1*, DHRs can be classified based upon their clinical presentation (chronology and morphology) and/or based upon their underlying pathophysiological mechanism.

According to the underlying pathophysiologic mechanism, DHRs can be further subclassified as allergic or non-allergic. Allergic hypersensitivity involves specific activation of drug-reactive T- and/or B-cells of the adaptive immune system (1). T-cells are involved in both immediate and nonimmediate allergic reactions. In contrast, B-cells are only involved in IgE-mediated immediate allergic reactions. Traditionally, 4 types of allergic DHRs are described according to the Gell and Coombs classification (table 1) (2). Type I (mostly mediated by drug-specific IgE antibodies (sIgE)) and type IV (cell mediated) reactions are the most frequent encountered reactions.

In contrast, non-allergic immediate DHRs (IDHRs) involve activation of

**Figure 1**: Classification of drug hypersensitivity reactions.



immune cells and release of mediators by direct mechanisms independent from the adaptive immune system response (e.g., mast cell activation via activation of the mas-related G protein-coupled receptor type X2 (MRGPRX2) or due to pro-inflammatory mediators increased by COX-1 inhibition). Established MRGPRX2-agonists are opiates, quinolones, and neuromuscular blocking agents (3, 4, 5). However, these drugs can also trigger sIgE-dependent basophil and mast cell degranulation. Non-allergic nonimmediate DHRs (NIDHRs) can also result from pharmacological interaction between a drug and MHC of the antigen-presenting cell or T-cell receptor (6).

As shown in figure 1, from a clinical point of view, DHRs are clinically classified as immediate and nonimmediate reactions, designated respectively as IDHRs and NIDHRs. Immediate reactions usually occur within 1 hour, also depending on the route of exposure, and the clinical presentation varies from single organ involvement (e.g., urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm) to potentially life-threatening anaphylaxis (*see figure 2*). Mechanistically, most IDHRs rest upon the activation of tissue-resident mast cells and/or circulating basophils. In contrast, NIDHRs occur more than 1 hour after the exposure (often 48-72h later) and mainly manifest as a maculopapular exanthema or, much rarer, as serious cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome. These NIDHRs involve the activation of drug-specific T-cells, but not mast cells nor basophils. However, correct allocation of the individual patient to one of these phenotypes can be extremely difficult, if at all possible. Therefore, rapid referral of a patient with a possible drug allergy including a detailed description of the clinical presentation is crucial.

Gathering insights into the underlying pathophysiological mechanism is crucial for correct orientation of further diagnostic work-up of DHRs. A thorough history (and revision of medical records) is of paramount importance. Information about signs (photos when available), symptoms, time of onset of the DHR, treatment of the DHR, index drug, indication for the β-lactam antibiotic, other medication concurrently used, persistence of the signs and symptoms after stopping the medication, re-appearance of the signs and symptoms in absence of the index drug and re-administration of the same drug after the reaction, must be obtained. This information is necessary to differentiate between an IDHR or a NIDHR. Moreover, history (e.g., on the timing of the reaction in response to the last dose of the drug) can be helpful for individual risk stratification. A recent study of our research group showed that an urticarial eruption that appearing within 1 hour after the first intake and regressing within 1 day was significantly more frequently observed in patients with a positive skin test/serum specific IgE assay (1-1-1 criterion) (7).

**Figure 2**: Sings/symptoms of immediate drug hypersensitivity reactions.

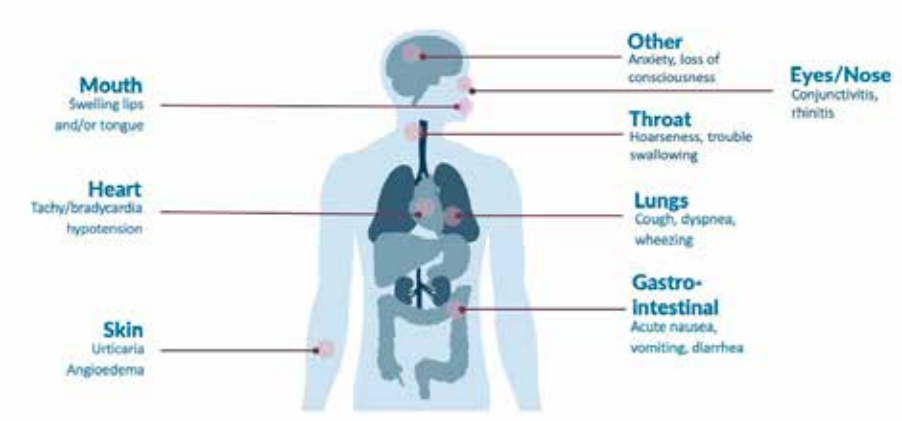
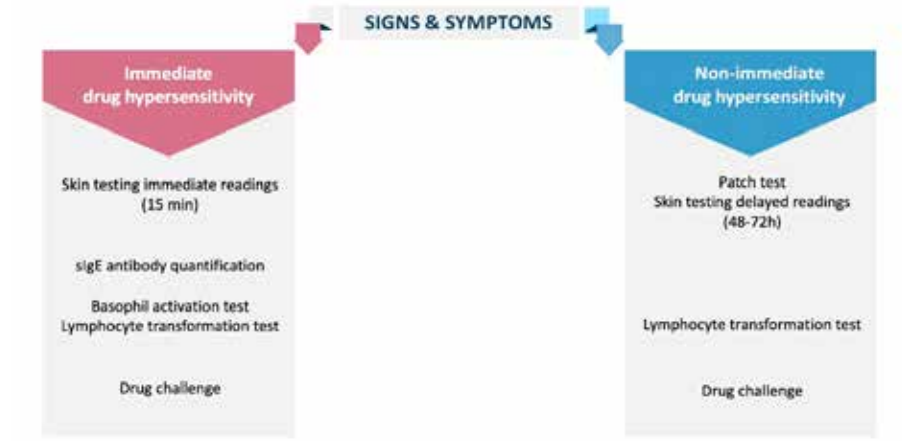



**Figure 3**: Algorithm for the diagnosis of immediate drug hypersensitivity reactions (IDHRs) and nonimmediate drug hypersensitivity reactions (NIDHRs) (adapted from (17)).




However, the discrimination between IDHR and NIDHR is not always straightforward. Sadly, very often, patients do not remember the exact timing and clinical features of their "index reaction", as it often occurred decades ago during childhood or adolescence. In these cases, finding out the clinical phenotype is often extremely difficult, if possible at all. In such patients, international guidelines recommend combining diagnostics for immediate and nonimmediate reactions (8). It goes without saying that such a combined approach increases risk and cost. Therefore, quick referral for an allergy workup in case of a possible DHR is recommended.

## Confirmatory diagnostics

As mentioned before, further diagnostic work-up is guided by history and the suspected underlying pathophysiological mechanism. Figure 3 shows the diagnostic algorithm of IDHRs and NIDHRs according to the current recommendations (9, 10).

### *IDHR*

#### Paired serum tryptase

The pathophysiology of IDHRs relies upon the activation and degranulation of mast cells and basophils. Tryptase is a trypsin-like protease that is mainly stored in intracellular mast cell granules. Alfa- and β- protryptase monomers are released spontaneously by resting mast cells. Other α- and β- protryptase monomers are converted

to mature tryptase which is released upon mast cell degranulation. Consequently, an increase in serum tryptase is supportive for mast cell activation.

Thus, paired quantification of acute and basal tryptase is recommended in patients with a suspected IDHR. Acute tryptase should ideally be measured 30 to 120 minutes after the onset of the reaction. Basal tryptase levels should be obtained before the event or at least 24 hours after resolution of all signs and symptoms. The current consensus formula for mast cell activation is a serum acute tryptase level equalling or exceeding 1.2x baseline serum tryptase +2 (11). So even if the value of tryptase at the time of the reaction seems to be normal, that is below 11.4 µg/L, a basal tryptase must be obtained in order to exclude mast cell activation. Noticeably, the absence of mast cell activation does not exclude an IDHR.

Further diagnosis of IDHRs is limited to the demonstration of an IgE-dependent reaction, as no diagnostic is available to demonstrate alternative processes such as mast cell activation via off-target occupation of MRGPRX2 (5). IgE-dependent reactions can be documented *in vitro* by quantification of specific drug-reactive IgE (sIgE) antibodies and in vivo skin prick tests and/or intradermal tests with immediate readings.

#### Skin testing

Today, skin prick testing (SPT) and intradermal testing (IDT), constitute the primary confirmatory step in the diagnostic work-up of an IDHR. Skin prick tests are performed on the ventral part of the forearm and imply a saline buffer solution (negative control) to exclude cutaneous hyperactivity, histamine 10 mg/mL (positive control) to assess skin test reactivity and the involved drugs. SPT are read after 15 minutes and considered positive when the wheal equals or exceeds 3 mm with a surrounding flare. IDT are read after 20 minutes and, for most drugs considered positive when the wheal, accompanied by an erythema, equals or exceeds 5 mm or is doubled as compared to the injection bleb.

Even though skin tests are the first step in the diagnostic work-up of a potential DHR, there are still some disadvantages to be mentioned.

First, skin tests are sometimes unreliable, such as in patients with cutaneous anergy or patients taking antihistamines both leading to false negative readings. False positive results, on the other hand, can be seen in patients with dermographism. Second, skin testing is not always recommended (e.g., for fluoroquinolones and opiates, skin tests have no added value due to low specificity) (12). Third, skin test performance is highly dependent on the methodology and operator used. Furthermore, for many drugs, the maximal non-irritant concentration (NIC) for skin tests have not been established and have mainly been established in healthy control individuals or have been generalised for all compounds in a certain drug class without correct validation. Besides, NICs might vary for IDHRs and NIDHRs (13). Further validation of NICs is crucial for optimization of sensitivity and specificity of skin tests.

#### Quantification of total and drug specific IgE antibodies

Quantification of total and drug specific IgE (sIgE) antibodies can be used in the diagnosis of IDHRs. However only a limited number of drug-specific assays are available and sensitivity and specificity of sIgE assays for drugs vary significantly (14). Recently, it has been suggested that, to optimize sensitivity, the threshold for positivity of sIgE has to be lowered to 0.10 kUA/L instead of 0.35 kUA/L. However, a recent study of our research group (15), showed that all patients with a suspected immediate, non-life-threatening, hypersensitivity to amoxicillin or a non-specified penicillin and a sIgE to penicillins between 0.10 kUA/L and 0.35 kUA/L, underwent a drug challenge without any problems. Diagnosis of penicillin hypersensitivity should not rest upon a low sIgE result alone.

#### Drug challenges

Drug challenges (DCs) are the reference test to correctly diagnose IDHRs (16). However, DCs entail a risk for (severe) complications and even DCs are not absolutely predictive for the clinical outcome of subsequent exposure with a risk for false negative results (17). Therefore, DCs should be preceded by skin and/or sIgE testing. However, sometimes, in low-risk patients a direct drug challenge can be considered. Traditionally, DCs imply the administration of incremental doses of the suspected drug(s) with a minimum interval of 30 minutes under strict hospital surveillance with emergency room facilities. A minimum observation period of 2 hours after the last dose is recommended. A challenge test is only considered positive when objective symptoms (e.g. hypotension, urticaria, angioedema, wheezing,…) can be observed.

#### Basophil activation test (BAT), mast cell activation test (MAT) and lymphocyte transformation test (LTT)

As DCs are hampered by the risk of severe, life-threatening reactions and are demanding in resources, time consuming and costly (17), flow-based analyses of basophil activation (BAT) as potential complementary diagnostic for immediate drug allergy have been studied. Although the BAT has become a pervasive test for IDHRs, expert consensus has not been reached. For example, for β-lactam antibiotics, the sensitivity of BAT varies between 13 and a too optimistic 67% (18, 19). The reasons for this poor sensitivity mainly relate to a basophil non-responder status as seen in 10-15% of our patients and rapid negativization of BAT over time (20). Negativization also applies to sIgE and skin tests (21, 22). Importantly, the loss of reactivity in skin testing, quantification of sIgE and BAT, is not necessarily accompanied by loss of clinical reactivity. Whether the passively sensitized mast cell activation test (MAT) might overcome these limitations is a matter of ongoing attractive research. However, because of the rapid decline of sIgE titers, it seems unlikely the MAT will close the gap in the diagnosis if IDHRs to β-lactams. T-cell tests, such as the lymphocyte transformation test (LTT) and variants such as flow-based analysis of activation markers and cytokine expression have only been rarely adopted to document IDHRs (23).

### *NIDHRs (type IV)*

#### Skin testing

Skin testing procedures for NIDHRs include patch testing and delayed readings of the IDT. Patch testing is a simple and safe diagnostic with a low risk of systemic reactions. In a patch test the drug is generally dissolved in petrolatum and this mixture is applied to the skin of the back. Readings are done after 72-96 hours. Patch testing is considered positive when erythema, infiltration and papules can be observed. Patch testing is the method of choice in patients who experienced SCARs (17). In cases of positive patch tests, further IDTs should be avoided, whereas in cases of negative patch test, IDTs can eventually be performed (9, 10) provided there is no contraindication such as drug-induced autoimmune diseases, severe exfoliative skin reactions and severe vasculitis syndromes .

The technique of IDTs is already described higher. However, for NIDHRs delayed readings of IDT after 48-96 hours are necessary. Delayed readings of IDT are considered positive when an induration surrounded by erythema exceeding 5mm occurs (24). In maculopapular exanthema (MPE), IDTs have a higher sensitivity as compared to patch testing. Therefore, in MPE IDTs are performed without prior patch testing (24).

However, like skin tests for immediate drug allergy, non-irritating concentrations have not yet been established and skin tests are not absolutely predictive. Consequently, again, many patients will need additional DCs to confirm or refute diagnosis.

### Drug challenge

As in IDHRs, DC is the reference test for diagnosis of NIDHRs after negative skin testing including delayed readings of IDT and/or patch testing (17). DCs are contraindicated in patients with SCARs and patients with hematologic reactions, e.g. vasculitis (17). As exemplified higher, traditional DCs imply administration of incremental doses of the suspected drug(s) in a single-day. However, for NIDHRs signs and symptoms are expected to occur hours to days after the DC. Prolonged DCs, extending over several consecutive days seem to be of limited use in the diagnosis of nonimmediate drug hypersensitivity (25). It is of utmost importance to balance accuracy, safety, cost, and labor intensity of diagnostic procedures in beta-lactam allergy. Currently, there is increasing evidence for direct challenges in mild NIDHRs. A recent systematic review and meta-analysis (26) showed that in these "low risk" children direct challenges without prior skin testing are effective and safe. However as acknowledged by the EAACI Task Force report (9), hitherto, there is no clear and uniform definition of "mild" and "low-risk". Further studies on this subject are needed with specific focus on children as their risk profile differs from adults.

### Lymphocyte transformation test and variants

There are many in vitro techniques to identify causative agents for NIDHRs such as the LTT, cytokine/mediator detection assays, multiplex bead-based immunoassay and ELISpot. The LTT is the most standardized method but failed to enter mainstream use. The main limitations of the traditional LTT are the need for radioactive thymidine, long culture duration (4-7 days) and poor sensitivity (27). Other in vitro tests, like cytokine detection assays, have also been used, but they are still being evaluated. In the last few years, the advent of performant multicolor flow cytometers has paved the way for the development of novel and more practicable techniques (28). The main advantages of these flow cytometric assays over traditional LTT are speed (48-72h vs. 6 days) and the fact that they do not require a radioisotope. A study of our research group showed that the intracellular quantification of CD154 is an attractive instrument to document both nonimmediate allergies to amoxicillin (clavulanic acid). Most importantly, the test yielded positive results in patients with negative skin tests who needed additional DCs to document diagnosis and it seems that drug-specific T-cell responses might be longer detectable after the index reaction than other diagnostic techniques (29). However, further research is required.

### The scourge of unverified "penicillin allergy"

β-lactam antibiotics (β-LABs), especially penicillins, are one of the predominant causes of drug hypersensitivity reactions (DHRs) with significant morbidity and mortality. Alternatively, unverified and false "penicillin allergies", mainly to the first-line preparations natural penicillin and aminopenicillins, have evolved into a plague with increasing medical and financial burden. A recent study on the prevalence of self-reported penicillin allergy in a Belgian outpatient population showed that 12% of the individuals attending the outpatients' allergy clinic claimed to have a "penicillin allergy". However, over 90% of the cases with such a spurious "penicillin allergy" tolerate a challenge with the alleged culprit(s) (30). Importantly, unverified "penicillin allergy" constitutes an almost life-long condition that generally starts as an ill-described, ambiguous and undocumented history in childhood/adolescence going unchallenged in adulthood.

The negative consequences of spurious allergy are undeniable, not only for the individual patient, but also for society. Actually, spurious "penicillin allergy" is associated with erroneous avoidance and unnecessary substitutions, readmissions, poorer outcomes, prolonged hospitalizations, increased costs and last but not least increased rates of *Clostridium difficile* and antimicrobial resistance. On the other hand, misdiagnosis entails a risk for potentially life-threatening and fatal reactions upon subsequent exposure.

**In conclusion**, judicious diagnostic work-up by a trained physician is absolutely necessary in every case of both witnessed or self-reported "penicillin allergy. The importance of a correct and complete description of the index reaction, eventually complemented with pictures of skin lesions, cannot be overemphasized. Every referring physician who witnesses a potential drug hypersensitivity reaction should provide a complete and correct report. This information is critical for guidance of further diagnostic testing and will help to avoid unnecessary tests, which is especially important in children. Further efforts to simplify and optimize the diagnostic approach, to control the plague of alleged "penicillin allergy" and to correctly label patients as truly allergic are needed.

## Conflict of interest

The authors have no conflict of interest to declare with regard to the subject discussed in this manuscript.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# Cow's milk protein allergy (CMPA): the value of synbiotics in nutritional management

with excerpts from an interview with Dr Elvira Levy, paediatric gastroenterologist at St-Pierre University Hospital in Brussels

**Infants with cow's milk protein allergy (CMPA) have more digestive, skin and respiratory disorders than other infants. They suffer more frequently from infections. Their intestinal microbiota has more pathogenic bacteria and fewer beneficial bacteria than in non-allergic infants. This is known as dysbiosis. The link between microbiota, allergy and infections probably reflects the importance of a normal microbiota in the establishment of adequate immunity. The adoption of a hypoallergenic diet containing a synbiotic can improve the symptoms of infants with CMPA.**

The prevalence of CMPA ranges from 0.5% to 3% [1] depending on the location in Europe, with higher figures in the north than in the south. Its incidence decreases with age, but some children may still have an allergy to cow's milk protein after the age of four.

## More often unwell

Most of the manifestations of CMPA occur in the digestive system (50-60%), the skin (50-60%) and the respiratory tract (20-30%). These include regurgitation and vomiting, crying, asthmatic manifestations, skin manifestations, loss of appetite, blood or mucus in the stools, etc. These symptoms resemble those of numerous other conditions. Consequently, none of them is pathognomonic [2]. However, their incidence is significantly higher among infants affected by CMPA. Gastrointestinal symptoms affect CMPA infants 55% more than others, while the incidence of eczema is 57% higher and that of urticaria 52% higher than in non-allergic infants. There is also a much higher incidence of colic [3].

Dr Levy: **"Some complaints are very similar to those of other gastrointestinal disorders: regurgitation, reflux, vomiting, fussy eating. CMPA infants suffer higher rates of atopic dermatitis, respiratory infections and irritability than other infants. They cry more often."**

Table 1:
**Clinical manifestations suggestive of CMPA**

| Severe manifestations | Moderate to mild manifestations |
|---|---|
| Gastrointestinal system | Gastrointestinal system |
| • Insufficient development | • Regurgitation and vomiting |
| • Iron-deficiency anaemia | • Diarrhoea or constipation |
| • Enteropathy | • Colitis |
| Skin | • Colic, abdominal pain |
| • Severe atopic dermatitis (exudative) | Skin |
| Respiratory system | • Atopic dermatitis |
| • Laryngeal oedema | • Angioedema |
| General | • Urticaria |
| • Anaphylaxis | • Swollen lips |
| | Respiratory system |
| | • Rhinitis |
| | • Conjunctivitis |
| | • Wheezing |
| | General |
| | • Irritability |

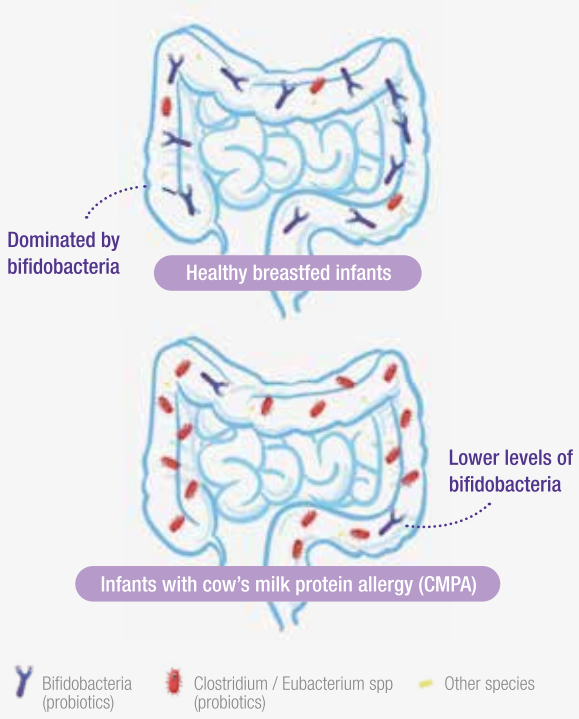
According to De Greef *et al.* (2012).

More infections are seen in infants with a cow's milk protein allergy than in others. Studies show the following: +74% gastrointestinal infections, +20% skin infections, +9% respiratory infections, +30% otitis [3]. Clinical experience is similar for all these aspects. Table I shows the clinical manifestations that suggest CMPA.

## Dysbiosis and CMPA

The microbiota of infants with CMPA is different from that of healthy infants. It contains more pathogenic bacteria (*Streptococcusand Clostridium* species) and fewer bifidogens than that of non-allergic infants (Figure 1). There is therefore an imbalance in the biological diversity of the intestinal microbiome. This is what is known as dysbiosis. However, a balanced microbiome is necessary for the proper maturation of the immune system. This is because the intestinal bacteria and their metabolites are in constant relationship with the immune system via the immune cells of the mucous membrane [4]. It is therefore easily understood that an imbalance of the microbiota causes disturbances in the establishment of normal immunity. This is a complex and dynamic process that takes place during the first year of life. Dysbiosis can therefore result in allergic manifestations.

Figure 1:
**Difference in the composition of the intestinal microbiota between a healthy breastfed infant and a CMPA infant.**




Dr Levy: **"Dr Levy: The intestinal microbiota of the infant with cow's milk protein allergy shows dysbiosis. Beneficial bacteria such as bifidobacteria are less present than in the healthy breastfed infant. Conversely, their microbiome contains more pathogenic bacteria species such as *Streptococcus* and *Clostridium*."**

## Find the best diet

Breast milk is the best food for infants. If CMPA is suspected and the mother is breastfeeding, the experts [5] recommend to follow a strict diet free from cow's milk protein. The breastfeeding mother should take calcium and vitamin D supplements if the levels are below normal. In IgE-mediated allergies, there is usually a temporal relationship between the ingestion of the allergen and the onset of symptoms. IgE screening and prick testing contribute to the diagnosis. In the case of a non-IgE-mediated allergy, the diagnosis is based on the clinical history of signs and symptoms and on their improvement after eviction of the suspected allergen. The challenge test helps to confirm the diagnosis when the clinical picture is unclear. When the clinical manifestations are suggestive and the tests are positive, nutritional management will be carried out according to the severity of the manifestations. For mild cases, an extensively hydrolysed formula will be proposed for two to four weeks. If the symptoms improve, a challenge test will be performed. Any return of the symptoms will require prolongation of the extensively hydrolysed formula until the age of 9 to 12 months. For severe cases, it will be necessary to prescribe an amino acid-based

formula. If there is no improvement, another condition will need to be sought. Improvement is an indication for continued nutritional management (Figure 2) [1].

## Supplementation with synbiotics

Synbiotics, which are combinations of probiotics and prebiotics, can help to improve the microbiome in cases of dysbiosis. Fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS) and human milk oligosaccharides (HMOs) are prebiotics. Suitable probiotics (often *Bifidus* and *lactobacilli*, the most common bacteria in breast milk) allow the development of a bifidogenic medium, which opposes the pathogenic bacteria responsible for inflammation and stabilises the intestinal homoeostasis. Several studies [6-9] show that *Bifidus breve* remains abundant in the intestine when supplementation is provided, and that the proportion of undesirable bacteria decreases. The production of short-chain fatty acids in the intestine increases and the pH of the stools decreases. This is potentially beneficial for immune maturation. Synbiotics are well tolerated, even after one year of follow-up, and height-weight growth is favourable.

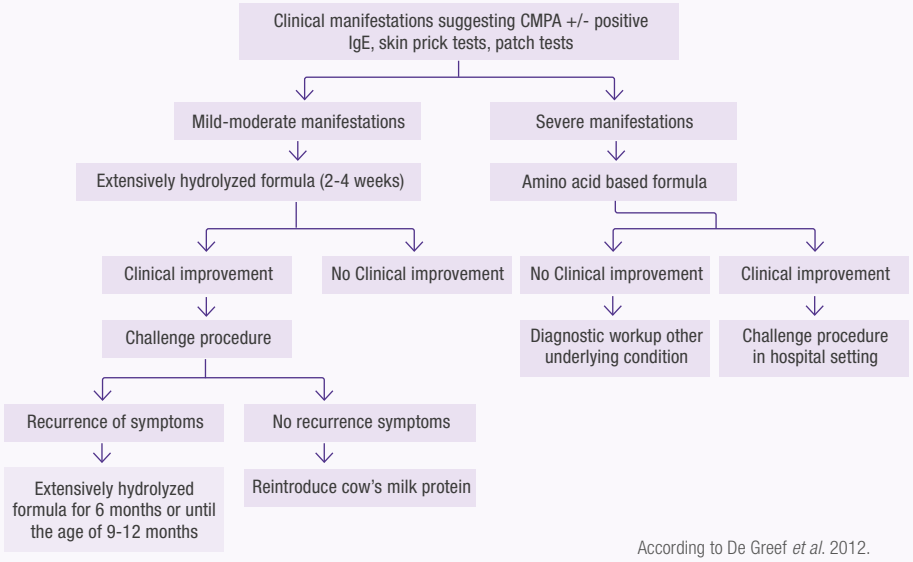
Dr Levy: **"The addition of a synbiotic is well tolerated, and the infant's height-weight growth is good. Manifestations associated with CMPA improve."**

Pathological manifestations associated with CMPA also improve. Topical IgE-mediated dermatitis [10,11] shows an improvement in CMPA infants after three months' use of an extensively hydrolysed infant formula containing a synbiotic. A 25% decrease in the SCORAD severity score is seen (Figure 3). After one year of follow-up, IgE-mediated atopic dermatitis and unmediated atopic dermatitis improve. CMPA infants with asthmatic manifestations (e.g. wheezing) show fewer symptoms (59% reduction in wheezing) (Figure 4) and have less need for asthma medication [12]. Respiratory infections are fewer among the CMPA infants who were fed a diet containing the synbiotic than among those who were not [8]. This results in lower recourse to antibiotics (-50%) and a 60% decrease in the frequency of hospitalisations [6]. Gastrointestinal disorders are less frequent and less severe [8,11]. Hospitalisations for digestive and other disorders, as well as the taking of medications, are reduced. In total, these studies concern more than 800 infants. No side-effects were recorded, and the infants had normal growth. There were also no adverse effects after one year of follow-up.

## In conclusion

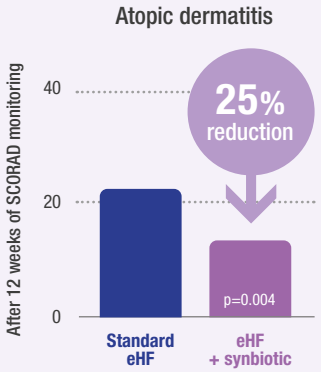
- Breastfeeding is best for the infant. It contains all the components favourable to correct immunity.
- Infants with CMPA have an altered intestinal microbiome. They are more at risk of atopic dermatitis, asthmatic manifestations, infections and digestive disorders, especially colic.
- If the CMPA infant is being breastfed, the breastfeeding should not be stopped, but the mother should follow a diet free from cow's milk protein. Prescribe calcium supplements if necessary. Provide dietician support for the mother.
- In the absence of breastfeeding, especially where there are allergic, skin, respiratory or gastrointestinal manifestations, an extensively hydrolysed formula can be tried, ideally with synbiotic. This can rebalance the microbiota and thus promote immune maturation, reduce the risk of infections and improve the pathological manifestations associated with CMPA. No side-effects have been observed, and safety has been demonstrated.

**Figure 2: Decision tree for diagnosis and CMPA infants.**




According to De Greef *et al.* 2012.

**Figure 3: Evolution of the severity score for atopic dermatitis**




eHF: hypoallergenic extensively hydrolysed formula.

Image based on the results of the study by Van der Aa *et al.* (2010).

**Figure 4: Evolution of respiratory symptoms (wheezing)**

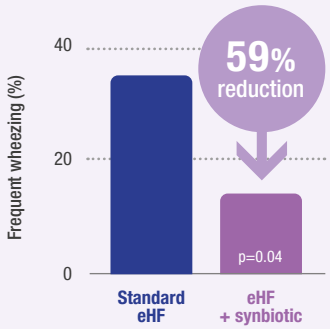



Image based on the results of the study of Van der AA *et al.* (2011).

IMPORTANT: Breastfeeding is best for babies. This information is exclusively intended for healthcare professionals.
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# Allergy to bee and wasp stings in children: state of the art

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## Keywords

Hymenoptera - Bee and wasp allergy – Anaphylaxis – Venom immunotherapy.

## Abstract

Hymenoptera stings are the second most common cause of anaphylaxis in children after food allergies. Identifying the culprit insect is often challenging. Venom-induced anaphylaxis occurs rapidly, within minutes of stinging, and involves multiple organ systems. Diagnosis is based on clinical history and confirmation of IgE-mediated sensitization by skin tests and determination of serum whole venom specific IgE levels. Component resolved diagnosis can provide clarity in cases of double sensitization.

The cornerstone of acute management of venom-induced anaphylaxis is intramuscular injection of adrenaline. Further management of severe hymenoptera allergy includes preventive measures to avoid accidental contact and immunotherapy. Venom-specific immunotherapy is safe and highly effective in reducing future systemic sting reactions.

## Epidemiology

Wasps, bees and, to a lesser extent, hornets make up the majority of Hymenoptera responsible for allergic sting reactions in the European region (1). Hymenoptera stings are the most common cause of anaphylaxis in adults, and the second most frequent cause of anaphylaxis in children after food allergy. European epidemiologic studies report a prevalence of systemic reactions after insect stings ranging from 0.3 to 7.5%. In children, the prevalence is lower, ranging from 0.15 to 0.8% (2-3).

Identification of the culprit insect can be challenging for several reasons. Patients often fail to notice the stinging insect due to panic after the sting, and studies have shown that distinguishing between the different species can be challenging, even for professionals (4). Insects can be distinguished by their appearance and characteristics. Wasps are usually thinner with a small waist and their bodies are marked with bright yellow and black stripes, while bees tend to be rounder in shape with a thick central body, with a softer orange/brown color (Figure 1). Contrary to what we would expect, honeybees are more aggressive towards humans than wasps, especially when they feel their nest is threatened. However, wasps sting more often because they tend to hover around humans, in particular they are attracted to sugared food and drinks. Hornets are large wasps that rarely sting. The honeybee's sting apparatus is more likely to remain lodged in the skin compared to a wasp's stinger. However, whether or not the stinger remains in the skin, can be indicative of the culprit insect but is not a definitive identification factor (5).

## Sting reactions: clinical features, risk factors and impact on quality of life

Fortunately, most people develop only minor local reactions after a sting. Uncomplicated local reactions consist of redness and painful swelling at the site of the sting. Most resolve within a few hours to days. In about 10% of cases, a large local reaction (LLR) can occur. This is a gradually enlarging redness and swelling that can be very extensive (up to an entire limb) and last for several days (5).

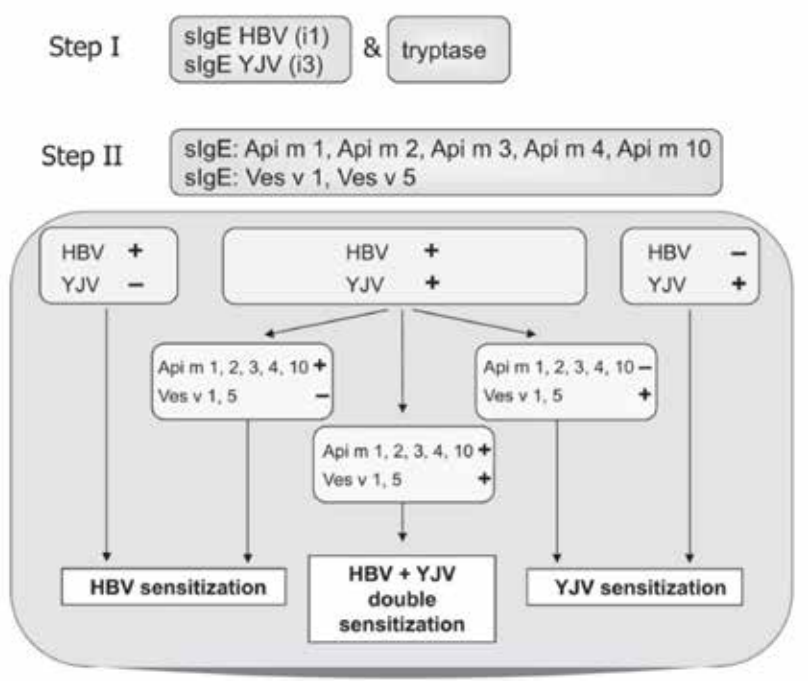
In rare cases, a systemic reaction may occur after a sting. This can range from mild cutaneous reactions (itching, urticaria, angioedema) to more severe reactions. The most dangerous systemic reaction is anaphylaxis. Venom-induced anaphylaxis occurs rapidly, usually within minutes after a sting and involves signs and symptoms in different organ systems distant from the sting site: skin (urticaria, angioedema), respiratory (dyspnea, cough, stridor), gastrointestinal (vomiting, diarrhea, nausea), cardiovascular (hypotension, tachycardia, cardiac arrest), or nervous system (dizziness, syncope, tingling sensation, sense of impending doom). Occurrence of sting-induced anaphylaxis is more common in adults and with bee stings. Adequate acute treatment results in recovery, although there is a small chance for a biphasic course, with recurrence of symptoms hours later. Fatal reactions are very rare (6-7).

Risk factors contributing to more severe reactions include: severe systemic reaction after a previous sting, older age, certain concomitant medications (beta blockers and angiotensin converting enzyme inhibitors (ACEI)), underlying cardiovascular or mast cell disease (mastocytosis and hereditary alphatryptasemia), and elevated baseline serum tryptase concentration. Beekeepers are at increased risk for more severe reactions due to repetitive exposure.

Rarely, unusual reactions occur after a sting, such as local reactions following an unusual sting location (e.g. uveitis following an eyeball sting), or reactions with atypical presentations, including toxic reactions occurring after multiple stings (e.g. rhabdomyolysis, acute kidney injury, autoimmune thrombocytopenia) (8).

**Figure 1:** external characteristics of bee (left) and wasp.

**Figure 2:** Two-step diagnostic algorithm for discriminating between wasp (Yellow Jacket YJV) and honeybee (HBV) venom. Step I: baseline sIgE measurement. Step II: component-resolved diagnostics in case of double sensitization. Reproduced from Jakob T. et al (16)




Experiencing a moderate to severe allergic sting reaction is a frightening event for both children and their parents, and can lead to significant emotional distress and anxiety during daily outdoor activities. In addition, the need to carry an adrenaline autoinjector at all times has been shown to have a negative impact on quality of life (9).

## Diagnosis of insect sting allergy

Diagnosis is made based on 1/ a clinical history suggestive of anaphylaxis and 2/ confirmation of IgE-mediated sensitization. Making a correct diagnosis can be challenging for several reasons. For instance, there is a high rate of asymptomatic sensitization in the general population, with elevated levels of venom-specific IgE not associated with an increased risk of systemic reactions after stinging in 27 to 40% of individuals (10). Furthermore, identification of the culprit insect is often unreliable, and diagnostic tests are difficult to interpret or do not correlate with the clinical presentation. In addition, loss of sensitization over time can result in false negative test results.

To accurately diagnose bee or wasp allergy, the workup should begin with a thorough history including identification of offending insect and the timing and type of reaction. Only if the history is suggestive for a systemic reaction following a sting, should further diagnostic workup be performed.

The standard workup consists of skin tests and determination of serum whole venom specific IgE (sIgE) levels. A refractory period of 2-6 weeks after the sting should be taken into account, as lower sIgE levels can induce false negative results. If a test performed during this refractory period is negative, retesting at a later date is recommended (11).

Skin tests are performed with standardized whole venom preparations. Current guidelines recommend performing skin prick tests (SPTs) as a first-line diagnostic test, but sensitivity is very low compared to intradermal skin testing (IDT). Addition of IDT increases sensitivity from 49 to 94% - leading recent literature to question the utility of SPTs as a diagnostic test (12). Skin testing is generally safe. As there is a minor risk of (mild) systemic reaction following IDT, stepwise testing is recommended in patients with a history of severe anaphylaxis, although this approach is under debate (13).

The detection of whole venom sIgE antibodies in serum has a high sensitivity (98%) for bee venom allergy, but the reported sensitivity for wasp venom is lower (83-89%) (14). There is an international consensus on a cut-off level of 0.35 kU/L, but in some cases a level of 0.1 kU/L may be clinically relevant (15).

The downside of testing for sIgE to whole venom preparations is the high proportion of double sensitization to bee and wasp venoms. Since there is a high degree of asymptomatic sensitization in the general population, this double sensitization may reflect a genuine double sensitization to both venoms or may be due to cross-reactivity based on shared allergenic proteins or carbohydrate determinants. Component resolved diagnosis (CRD), the use of sIgE to single recombinant allergens, can provide clarity in these cases. Currently, commercially available allergen components are: rVes v1 and rVes v5 for wasp venom and rApi m1 - m5, and rApi m10 for honey bee venom (Figure 2). The use of CRD significantly increases sensitivity up to 95% for bee allergy and up to 98% for wasp allergy (16-17).

There is no correlation between diagnostic test results and the severity of the sting reaction. However, CRD could help predict the effectiveness of venom immunotherapy treatment. Sensitization to several recombinant bee allergens (Api m3, Api m5, and Api m10) has been shown to be a risk factor for the failure of venom immunotherapy due to insufficient allergen content in therapeutic extracts (18).

In patients with a suggestive history but negative test results, additional workup may be considered. With a basophil activation test (BAT), basophil activation is measured by flow cytometry after stimulation of whole blood with venom allergen. BAT can confirm the diagnosis in 60-80% of patients with negative test results (19). However, this test can only be performed in specialized laboratories, limiting its usefulness in routine practice.

Basal serum tryptase (BST) levels should be determined in patients with anaphylaxis after stinging. Elevated BST is associated with an increased risk of severe reactions to Hymenoptera stings and may also be indicative of a diagnosis of mast cell disease.

Finally, intentional sting challenge is used as a diagnostic test in some countries. However, this practice is controversial because it carries a significant risk of severe systemic reactions.

## Management

### *1. Prevention*

The first step in the management of severe hymenoptera allergy, as with most allergies, is prevention. Measures to avoid accidental contact with bees or wasps include:

- Maintaining a high level of vigilance during outdoor activities with a risk of exposure, such as picnic areas.
- Not waving your arms or trying to strike the insect.
- Avoid walking barefoot outside.
- Always cover food and do not leave leftover food out.

- Be careful with beverages in cans or bottles, as wasps can easily get into them; preferably use open cups/glasses with an unobstructed view of the liquid inside.

- Remove wasp nests in the near vicinity.

A common advice is to avoid wearing brightly colored clothing or strong perfumes when residing outdoors – however there is currently no evidence that these attract bees or wasps.

### *2. Acute treatment*

After a sting, the barbed stinging apparatus is ripped from the body of the stinging insect (usually bees, but occasionally wasps), along with the venom sac. The venom is released within the first several seconds after the sting. Prompt removal of the offending insect and/or the stinger may thus help limit the amount of venom injected. In case of presentation minutes after the sting, removal of the stinger is still indicated, albeit not urgent, to prevent a local inflammatory reaction.

Management of LLR is based on symptom relief and includes topical application of cold compresses, treatment with antihistamines and topical corticosteroids to relieve pruritus, oral corticosteroids to reduce delayed swelling, and nonsteroidal anti-inflammatory drugs to relieve pain. Treatment with oral antibiotics is only rarely needed, in case of bacterial superinfection.

The cornerstone in acute management of venom-induced anaphylaxis is the administration of adrenaline by intramuscular injection (0.01 ml/kg of a 1:1000 solution; in case of an autoinjector: 0.15 mg for children from 7.5 to 25 kg, and 0.3 mg for >25 kg). All patients with a history of anaphylaxis should have at least one adrenaline autoinjector readily available. Studies have shown that patients often fail to use the autoinjector correctly. Thorough patient education on when and how to use the autoinjector, including written instructions, is therefore strongly recommended (20,21).

### *3. Prevention of future systemic reactions: venom immunotherapy (VIT)*

The only treatment that can prevent systemic reactions in future stings is venom immunotherapy. The decision to proceed with immunotherapy, depends on the type of reaction and the risk of recurrence in case of future stings. The risk of developing a systemic allergic reaction after a LLR, is low (0.8-7%). Patients with a cutaneous systemic reaction have a 10% risk of developing a similar reaction after a future sting; however, the risk of anaphylaxis is low (<3%). In contrast, patients with anaphylaxis have a high risk of anaphylaxis recurrence with a future sting (30% in children; up to 60% in adults).

Therefore, VIT is indicated in children with a history of moderate to severe systemic reaction after a sting and documented IgE-mediated sensitization to the culprit insect by either sIgE, skin tests or BAT. Initiation and follow-up of VIT treatment should be managed by an allergologist with pediatric expertise. Special caution should be applied in individuals with underlying risk conditions, such as cardiovascular disease, use of ACE inhibitors or beta-blockers, and malignant or autoimmune diseases (VIT should not be initiated until the underlying disease is stabilized). Absolute contraindications for VIT include: asymptomatic sensitization to insect venom, sting reactions without documented sensitization, unstable malignant or autoimmune disease, and unusual (non-IgE-mediated) sting reactions.

VIT acts by inducing immunological tolerance to the culprit antigen and is the only type of allergen-specific immunotherapy for children currently reimbursed in Belgium. It is a highly effective therapy (77-84% in honeybee and 91-96% in wasp venom) and contributes to a significant improvement in quality of life (22). VIT is administered by subcutaneous injections, starting with an up-dosing phase of weekly injections in slowly increasing doses. After several weeks to months, the maintenance dose of 100 mcg of venom (equivalent to approximately 5 wasp or 2 bee stings) is reached. Faster up-dosing (rush) protocols have been shown to be safe and more efficient than conventional VIT (23-24). After the up-dosing phase, treatment continues with the maintenance phase, which involves injections every 4 weeks. With ongoing treatment, the interval between injections may be extended to 6 weeks in the second year of treatment, and to 8 weeks from year 3 on (25). The total duration of treatment is 3 to 5 years; studies show superior long-term efficacy with five years of treatment (26). Most patients maintain an adequate level of protection after discontinuation of VIT; however, a loss of efficacy over time can lead to recurrence of (mostly mild) systemic reactions. Therefore, prolonged – sometimes lifelong – therapy should be considered in several cases, such as in patients with initial life-threatening anaphylaxis, with occurrence of severe systemic reaction during VIT, in patients at high risk of re-stinging (e.g. beekeepers), and in patients with mast cell disorders (27). In these cases, extending the maintenance interval to 12 weeks may be considered, which does not appear to reduce effectiveness and is generally well tolerated.

VIT is generally safe and well tolerated. The most prevalent adverse events are local reactions (approximately 12%); there is a small risk of systemic reactions (up to 3% for wasp, and 7-14% for bee VIT). Premedication with a second-generation antihistamine 1-2 hours prior to injection can be considered, and may even positively affect treatment efficacy. However it should be noted that antihistamine treatment may mask the first symptoms of a severe reaction (28). VIT-induced anaphylactic reactions are predominantly mild to moderate reactions, and respond well to antiallergic treatment, often without the need for adrenaline administration.

## Future prospects

When diagnosing and treating bee and wasp allergy, there are several issues that still raise questions.

First, in terms of diagnosis, it is not always possible to distinguish between asymptomatic and symptomatic sensitization to venom, or between cross-reactivity and true double sensitization. Further development of existing (e.g. introduction of new recombinant allergens) or new techniques is needed to address these diagnostic difficulties.

With regard to treatment with VIT, there are currently no means of assessing the efficacy of immunotherapy. Biomarkers that have been studied are skin prick tests, IgE, IgG4; however, decreasing levels during VIT show no correlation with clinical efficacy (29). BAT may be helpful in monitoring efficacy, but more research is needed (30). The only reliable test to date to estimate the efficacy of VIT is the sting challenge test, which also improves quality of life by eliminating uncertainty about possible reactions to future stings (31).

In patients who experience a systemic reaction during immunotherapy, premedication with omalizumab could be an option. More studies are needed to determine the optimal duration and dosing regimen of omalizumab (32).

## Conclusion

A severe allergy to bees or wasps is a potentially life-threatening condition with a significant impact on quality of life. The diagnosis is confirmed by demonstration of IgE-mediated sensitization using skin tests or determination of specific IgE and component resolved diagnostics. Treatment with venom-specific immunotherapy is safe and highly effective in reducing future reactions

## Conflict of interest

The author has no conflict of interest to declare with regard to the topic discussed in this manuscript.

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# Diagnosis and Management of Allergic Rhinitis in Children

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## Keywords

Allergic rhinitis ; asthma ; immunoglobulin E ; allergens ; child;  allergen immunotherapy.

## Abstract

Allergic rhinitis is one of the most common chronic diseases in children. It is a Th2 type allergic disease. Diagnosis is based on the presence of typical symptoms and evidence of allergic sensitization. Up to one in three children with allergic rhinitis develop asthma, and up to 80% of children with asthma have allergic rhinitis.

The most common allergic triggers are house dust mites, grass, weed and tree pollens, cat and dog allergens, and indoor and outdoor mould.

Local allergic rhinitis is a distinct phenotype characterised by typical symptoms and history of allergic rhinitis with undetectable specific IgE, but a positive nasal provocation test to one or more allergens.

Treatment of allergic rhinitis consists of a three-step approach: allergen avoidance, pharmacological treatment with antihistamines or intranasal corticosteroids, and allergen immunotherapy.

## Introduction

This article is the written report of an oral presentation at the VVK (Vlaamse Vereniging voor Kindergeneeskunde) conference on April 21, 2023 and is based on several guidelines and clinical practice (1-5). It provides an overview of the diagnosis and management of allergic rhinitis in children.

Allergic rhinitis (AR) is one of the most common chronic conditions in children. It is rarely seen in infants, but from the age of 2 years there is a gradual increase in the prevalence by 3-4% a year, with up to 15 % of 13–14 year olds being affected (6, 7).

Although it can have a significant impact on quality of life, it is often under-diagnosed and under-treated.

AR is a Th2 type allergic disease. In a sensitised individual specific IgE to an environmental allergen binds to mast cells and basophils in the nasal mucosa and causes a biphasic reaction. In the early phase, degranulation of inflammatory mediators (histamine, leukotrienes, prostaglandins, platelet activating factor (PAF)…) causes symptoms such as sneezing and rhinorrhoea, within minutes of exposure. In a late phase (hours after exposure) activated eosinophils migrate to the nasal mucosa and release additional mediators that trigger prolonged inflammation and nasal congestion.

## Diagnosis and classification of AR

The diagnosis of AR is based on the occurrence of the typical symptoms and the presence of relevant allergic sensitisation, demonstrated either by skin prick test or specific IgE.

Typical symptoms for allergic rhinitis are: sneezing, itchy and /or runny nose, nasal obstruction and red itchy eyes. Headache, sore or itchy throat, cough and hearing loss can also be experienced. Symptoms can be very bothersome, preventing children from participating in their normal activities. AR can affect sleep, concentration and have an impact on school performance.

Clinical signs of AR include allergic shiners (dark circles under the eyes), Denys Morgan folds (creases under the eyes), allergic salute (nasal crease), open-mouth breathing and facial grimacing due to itchiness. The nasal mucosa often appears oedematous and pale, with clear secretions (8).

There is a strong association with asthma, with up to 1/3 of the children with AR having asthma. Up to 80% of children with asthma have AR (4). This close link has been termed the United Airway Concept and is based on the fact that the upper and lower airways share similar epithelium and immunological mechanisms with an interaction between upper and lower airway inflammation. Even in the absence of clinical asthma, many children with AR have bronchial hyperreactivity (9).

Some studies have shown that treatment with intranasal steroids has a positive effect on asthma, and poorly controlled allergic rhinitis is associated with severe asthma (10, 11).

AR is considered a risk factor for the development of asthma.

The most common allergic triggers for AR include house dust mites, grass, weed and tree pollen, cat and dog allergens, and indoor and outdoor moulds. It is important for the management of AR to identify the allergic triggers for the child.

The presence of specific IgE, or a positive skin prick test does not necessarily mean that the allergen tested is the one triggering the symptoms. For example, a pollen allergic child may have positive specific IgE or skin prick test (SPT) to both grass and tree pollen, but only experience symptoms during the grass pollen season, making tree pollen sensitisation irrelevant and due to cross-reactivity with grass pollen allergens.

Therefore, a careful history of exposure and its relationship to symptoms is crucial.

For pollen-allergic children, it may be useful to monitor their symptoms over a season and correlate them with the amount and type of pollen concentration in the air. In some cases, component-resolved diagnosis may be helpful in distinguishing relevant from non-relevant sensitisation.

Sometimes allergy tests remain negative, despite a strong clinical suspicion of AR. In these children, local allergic rhinitis (LAR) should

be considered. This is a rhinitis phenotype characterised by the typical symptoms and history of AR, but with undetectable specific IgE to aeroallergens and negative skin prick tests, and a positive nasal provocation test (NPT) to one or more environmental allergens. The prevalence of LAR in children with chronic rhinitis is highly variable, ranging from 0-66% in different studies(12). Specific IgE has been detected in the nasal mucosa of 20-40 % of patients with a positive NPT, but the immunopathology remains unclear.

As a NPT is difficult to perform in children. The diagnosis of this condition is often made on clinical grounds and its response to treatment. The most common triggers are house dust mite, grass and tree pollen.

Other causes of rhinitis should also be considered. A differential diagnosis is given in Table 1. Referral to an otorhinolaryngologist may be warranted.

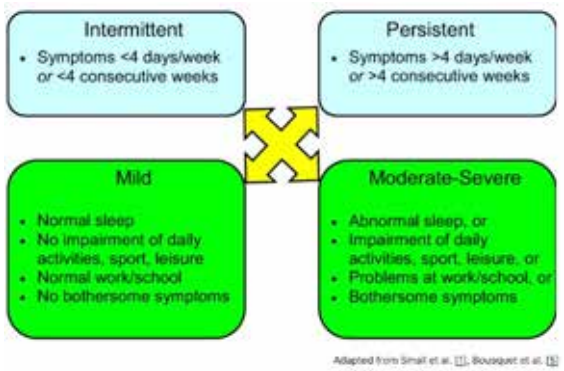
Allergic rhinitis is classified as intermittent or persistent, and in both conditions symptoms can be mild or moderate/severe symptoms (Figure 1). Treatment options vary according to this classification (2). A visual analogue scale is a useful tool to assess symptoms and monitor the effect of treatment.

**Table 1:** Differential diagnosis of allergic rhinitis in children.

| Differential diagnosis of AR in children | |
|---|---|
| **Non-allergic rhinitis** | • Drug-induced<br>• Hormone induced<br>• Gustatory<br>• Vasomotor rhinitis<br>• Idiopathic<br>• Gastro-oesophageal reflux |
| **Infectious rhinitis** | |
| **Structural abnormalities: nasal septum deviation ; choanal atresia or stenosis** | |
| **Adenoid hypertrophy** | |
| **Immunodeficiency** | • Hypogammaglobulinemia<br>• Primary ciliary dyskinesia<br>• Cystic fibrosis (nasal polyps) |
| **Foreign body** | |
| **Benign and malignant tumours** | |
| **Cerebrospinal fluid leak** | |

Adapted from Differentiating Rhinitis in the Paediatric population by giving focus on medical history and clinical examination . Doulaptsi et al. Med Sci 2019;7(3):38

**Figure 1:** Classification of allergic rhinitis according to symptom duration and severity (Small P, Keith PK, Kim H. Allergic rhinitis. Allergy Asthma Clin Immunol. 2018;14(2_suppl):51).




## Management of AR

A three-step approach is recommended for the management of allergic rhinitis.

Allergen avoidance, where possible, is the first step, followed by pharmacological treatment, and if indicated, allergen immunotherapy.

### *Allergen avoidance*

Allergen avoidance is an effective strategy to control the symptoms of AR, but is difficult to achieve.

For house dust mites (HDM), the most important allergen is found in faeces of HDM. HDM feed on tiny flakes of human skin that are shredded mainly in bedding, carpets and curtains.

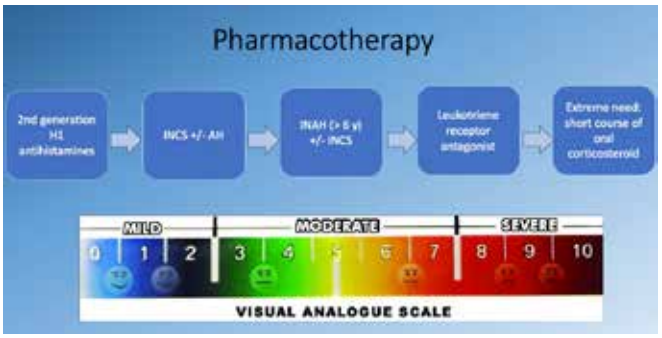
They thrive in humid conditions and are resistant to low temperatures. Washing at 40°C removes about 90%,of HDM allergens, while washing at 60 °C removes 100% of HDM allergens.

Measures to reduce the amount of HDM include the use of acaricides (chemicals that kill mites), impermeable mattress covers, frequent washing and cleaning, air filtration and vacuum cleaning with HEPA (High Efficiency Particulate Air) filters, removal of carpets and curtains and avoiding humidity.

Items that cannot withstand high temperatures, such as soft toys, can be frozen at a minimum of minus 15 °C for at least 16 hours, which will kill the house dust mites but does not remove the allergens (13).

Of all the measures, the use of acaricides appears to be the most effective, although multiple measures are needed to improve symptom control (Figure 2) (14).

**Figure 2:** Environmental control measures to reduce allergen levels and symptoms (Seidman MD, Gurgel RK, Lin SY, Schwarts SR, Baroody FM, Bonner JR, et al. Clinical Practice Guideline: Allergic Rhinitis. Otolaryngology-Head and Neck Surgery. 2015:152(1_suppl):S1-S43).




Pet allergens are present in saliva, urine and skin. There is no evidence for the existence of hypoallergenic animals, although there are differences in the amount of allergens shed by different breeds of dogs and cats. A study investigating the level of dog allergens in the home in so called hypoallergenic dogs compared with non-hypoallergenic dogs found no difference in the levels of dog allergens in the owner's homes (15).

Measures to reduce the level of pet allergens (frequent washing, vacuum cleaning with HEPA filters, avoiding animals in the bedroom) show a reduction in allergens but no effect on symptom scores.

Removal of the animal is the best option but compliance with this advice is often poor. Even if the advice is followed, it can take several months for the house to become allergen-free.

A study in 2010 showed that pet removal has a preventive effect on the secondary development of asthma (16).

Pollen allergen avoidance is difficult.

Keeping windows closed, staying indoors, taking a shower before bedtime, removing clothes from the bedroom, avoiding drying clothes

outdoors or staying indoors when the pollen count is high can be recommended. The Sciensano website ( www.airallergy.be) provides useful information on the amount and origin of pollen in the air.

### *Pharmacological treatment (Figure 3)*

Pharmacological treatment aims to control symptoms.

Treatment options vary according to the type (persistent or intermittent) and severity of symptoms. A step-up treatment plan is recommended with regular assessment of efficacy and adjustment according to symptom control. Patient preference should also be taken into account, for example in the choice of intranasal or oral therapy.

Several guidelines have been published (1-4).

**Figure 3:** Pharmacological treatment: stepwise treatment plan and visual analogue scale (AH = antihistamines, INCS = intranasal corticosteroids, INAH = intranasal antihistamines).

| | Evidence Supports Reduction in Allergen Level | | Evidence Supports Reduction in Symptoms | |
|---|---|---|---|---|
| **Environmental Control Measure** | **Yes** | **No** | **Yes** | **No** |
| Removal of pets | X | | X | |
| Washing pets twice a week | X | | | X |
| Acaricides to kill dust mites | X | | X | |
| Impermeable covers for bedding | X | | | X |
| Air filtration | X | | | X |
| Combined use of multiple control measures | X | | X | |

ANTIHISTAMINES

Second-generation antihistamines are often first line for mild to moderate symptoms, especially when sneezing, itchiness and runny nose are the main symptoms. They have a rapid onset of action and are therefore suitable for mild to moderate intermittent or persistent AR. Cetirizine, levocetirizine, loratadine and desloratadine are FDA approved for use from the age of 6 months.

Their safety and efficacy are well documented. Side effects are rare but include mild fatigue, headache, dizziness or gastrointestinal symptoms. There is no proven difference in effectiveness between the different antihistamines.

The use of first-generation antihistamines is no longer recommended in children because of their sedative properties with impact on cognitive function and their anticholinergic effects.

Intranasal antihistamines are more effective than oral antihistamines and start working within 15 minutes. They can be used from the age of 6 years. Many children do not like to use them because of the bitter taste. Epistaxis or headaches have been reported as side effects (3, 4).

INTRANASAL CORTICOSTEROIDS (INC)

Intranasal corticosteroids are the most effective treatment for AR with good effect on all nasal symptoms. They also improve symptoms of conjunctivitis. INC are the recommended treatment for moderate to severe, intermittent or persistent AR and are FDA approved from the age of 2 years. The onset of action is slow (5 to 12 hours) and clinical improvement usually takes several days. INC can be used alone as first-line therapy alone or in combination with an oral or intranasal AH.

Epistaxis or local irritation are common side effects. Long-term use does not cause damage to the nasal mucosa. Fluticasone propionate, fluticasone furoate, mometasone furoate and ciclosenide have minimal systemic absorption and are considered safe. No growth restriction has been documented with the use of these medications at the recommended doses, but growth monitoring is still recommended.

The duration of therapy is variable and is influenced by the child's allergic profile (intermittent vs persistent AR, intensity of the symptoms). When good symptom control is achieved, a step down in treatment should be considered.

OTHER THERAPIES

Irrigation with normal saline or mildly hypertonic saline has been shown to be a good adjuvant treatment (4).

In Belgium, leukotriene receptor antagonists are mainly prescribed for asthma. Although less effective than INC, their efficacy in mild to moderate AR has been demonstrated. In children with concomitant asthma, they can be a useful step-up treatment. It should be noted

**Table 2:** AIT studies in children.

| Study (year) | Age | AIT Mode (Disease) | Duration | Clinical results | Immunological results |
|---|---|---|---|---|---|
| **Des Roches et al. (1991)** | Children | HDM SCIT (Rhinitis) | 36 mos | ↓ Occurrence in new sensitisation | - |
| **Pajno et al. (2001)** | Children | HDM SCIT (Rhinitis/Asthma) | 36 mos | ↓ Occurrence in new sensitisation | - |
| **Möller et al. (2002)** | Children | Grass and/or birch pollen SCIT (Rhinitis/Asthma) | 36 mos | ↓ BHR<br>↓ conjunctivitis VAS score<br>↓ asthma VAS score | - |
| **Niggemann et al. (2006)** | Children | Grass and/or birch pollen SCIT (Rhinitis/Asthma) | 36 mos | ↓ asthma Improvement in CPT | - |
| **Valovita et al. (2011 & 2018)** | Children | Grass SLIT (Rhinitis/ Asthma) | 36 mos | ↓ asthma symptoms<br>↓ medication use<br>↓ RTSS<br>↓ ICS | ↓ total IgE<br>↓ Grass sIgE |
| **Mosbech et al. (2014 & 2015)** | Adolescent, Adult | HDM SLIT (Rhinitis/Asthma) | 12 mos | ↓ ICS | - |
| **Nolte et al. (2016)** | Adolescent, Adult | HDM SLIT (Rhinitis) | 52 wks | ↓ Total rhinitis SS<br>↓ Daily symptom and medications score<br>↓ VAS score | - |
| **Okubo et al. (2017)** | Adolescent, Adult | HDM SLIT | 12 mos | ↓ Total SS<br>↓ QoL | - |
| **Masuyama et al. (2018)** | Children | HDM SLIT | 12 mos | ↓ Rhinitis SMS | ↓ HDM sIgE followed by decline<br>↓ HDM sIgG4 |

Abbreviations: BHR: bronchial hypersensitivity; CPT: conjunctival provocation test; ICS: inhaled corticosteroid; QoL: quality of life; RTSS rhinoconjunctivitis symptom score; SCI: subcutaneous immunotherapy; SLIT: sublingual immunotherapy; SMS: symptom and medication score; SPT: skin prick test; SS: symptom score; TNSS: total nasal symptom score; VAS: visual analogue scale.

that the FDA has warned against their use because of the possibility of neuropsychiatric adverse effects.

Topical and oral decongestants should be avoided because of their rebound effect and drug-induced rhinitis, although a short course of less than 10 days may be considered.

For severe, uncontrollable symptoms a short course (5 days) of oral corticosteroids is sometimes a last resort, but is not recommended due to its side effects.

### *Allergen immunotherapy (AIT)(5, 17)*

Allergen immunotherapy is the only disease-modifying treatment.

It induces tolerance to the allergen by a shift in the immune system, with suppression of the Th2 responses, decreased production of IgE antibodies, increased IgG 4 antibodies and downregulation of mast cell and basophils. Modified allergens are administered subcutaneously (SCIT) or sublingually (SLIT). Safety and efficacy have been well demonstrated in adults. Although there are fewer studies in children, there is good evidence for pollen and HDM allergic children. An overview of studies exclusively in children is represented in Table 2.

There is no evidence for the use of AIT for other allergens in children. In adults, there is limited high quality evidence for AIT for cat allergy, no clear clinical evidence for dog allergy and low quality evidence for mould allergy (Alternaria).

The use of AIT can be considered in children from 5 years of age with moderate to severe AR with or without asthma and with insufficient symptom control on pharmacological treatment. The recent GINA guidelines have included AIT as an adjuvant treatment option for children with asthma allergic to HDM.

AIT is currently not reimbursed in Belgium.

Short-term beneficial effects are noticeable 2-4 months after starting AIT, with significant improvement in symptom control and a reduction in medication use in 60-85% of the patients.

Long lasting beneficial effects have been demonstrated in the GAP study, with effects on both AR and asthma symptoms 2 years after treatment with SLIT in children allergic to grass pollen (18, 19). The PAT study showed reduction in symptoms in grass and /or birch pollen allergic children up to 10 years after treatment with SCIT as well as a reduction in new development of asthma.

There is currently good evidence for the prevention of asthma in pollen-allergic children for up to 2 years after treatment. For other allergens, such as house dust mite, there is insufficient evidence of a beneficial preventive effect on asthma.

There is insufficient evidence that AIT has a preventive effect on the development of new allergic sensitisations (20).

The choice between the sublingual and subcutaneous route depends mainly on patient preference. There is insufficient evidence to suggest that the latter is more effective than the former. The duration of treatment for both therapies is 3-5 years. SCIT starts with weekly up-dosing, followed by 2-weekly injections for 2 months, then monthly injections, although up-dosing schedules may vary between different products. Local reactions at the injection site (redness, swelling, itchiness) are common (50%). Systemic reactions are rare (0.1%) but is important that the child is observed for 30 minutes and that rescue medication (adrenaline, antihistamine) is readily available (17).

Risk factors for systemic reaction in AIT are uncontrolled asthma, intercurrent infection, a high degree of sensitisation, vigorous exercise after injection, poor compliance, mast cell disease and the use of beta blockers.

SLIT needs to be administered daily and therefore requires good compliance. Common side effects include itchiness in the mouth, swelling of the tongue or lips. Systemic reactions are rare, but it is recommended to give the first dose under supervision. The success of AIT depends mainly on the child's allergic profile, the choice of the right allergens and compliance to therapy. It is possible to combine several allergens at the same time, such as grass and tree pollen. HDM and pollen allergens cannot be mixed, due to degradation of the allergen by enzymatic activity. They should be administered at different injection sites or, in the case of SLIT, at different times.

Contraindications to immunotherapy include severe asthma, active autoimmune disease, malignancy and poor compliance to therapy (5, 17).

## Conclusion

AR is a chronic condition with a significant impact on quality of life, and a risk factor for the development of asthma.

Management consists of allergen avoidance, pharmacotherapy and allergen immunotherapy. AIT may be considered in children from 5 years of age with AR and a documented and relevant sensitisation to pollen and/or house dust mite with moderate to severe symptoms despite adequate pharmacotherapy. It may also be considered for the prevention of asthma in pollen-allergic children.

When deciding between the different treatment options, patient and family's preferences should be take into account.

## Conflicts of interest

The author has no conflicts of interest in relation to the subject matter of this manuscript.

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# What is the place of Fractionated Exhaled Nitric Oxide in the diagnosis and monitoring of pediatric asthma in 2023?

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## Keywords

Fractional Exhaled Nitric Oxide Testing ; Asthma ; Eosinophilic Bronchial Inflammation; Child ; Adolescent.

## Abstract

Fractional exhaled nitric oxide (FeNO) measurement is a partial and indirect estimate of eosinophilic bronchial inflammation. It can be performed in a reproducible, convenient and rapid manner from the age of 5 to 6 years. The FeNO measurement methodology has been validated by a European Respiratory Society / American Thoracic Society consensus. The American Thoracic Society, the National Institute for Health and Care Excellence and the European Respiratory Society have published recommendations with cut-off values for FeNO to guide the diagnosis, treatment and follow-up of asthma in children aged 5-16 years. Internationally validated percentile curves of FeNO values according to height, will allow us to interpret the FeNO value of the child and adolescent in a more statistically relevant way and to have a more accurate tool for diagnosis, phenotyping and follow-up.

## Introduction

Nitric oxide (NO) is known as a pollutant but also as an important regulator in human asthma. Since 1987, we have known that NO is an endothelium-derived relaxing factor that regulates vascular and bronchial tone, promoting dilation. Airway inflammation has been recognised as an important physiopathological feature underlying asthma.

The presence and intensity of T-helper type 2 (Th2)-dependent bronchial pathology is a risk factor for wheezy infants to develop asthma in later life (1,2,3).

As symptoms and lung function measurements poorly reflect airway inflammation, a biomarker providing direct information on inflammatory processes could be of great interest for the diagnosis and management of asthma. It would allow early phenotyping and therefore appropriate treatment of asthma in young children, followed by convenient and regular monitoring.

Therefore, analysis of induced sputum eosinophils has been proposed to assess airway inflammation. In adults, treatment adjustments based on sputum eosinophils resulted in a reduction in the exacerbation rate (4). However, this technique requires expertise and is less suitable for children due to possible discomfort. A non-invasive approach is to measure fractional exhaled nitric oxide (FeNO) (5). The production of FeNO by inducible NO synthase in the lower airways is upregulated in the presence of T-helper type 2 cell inflammation and correlates with sputum eosinophil count (6,7).

Standardised methods for measuring FeNO were developed jointly by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) in 1999 and revised in 2005 (8,9). The guidelines recommend the use of the term FeNO (fractional exhaled NO concentration) to describe the amount of NO in exhaled breath. FeNO is expressed in parts per billion (ppb), which is equivalent to nanolitres per litre. Further technical standards have been published by the ERS (10).

Most of the early studies reported in the literature used ozone chemiluminescence to measure FeNO concentrations and this technology was used in the first US Food and Drug Administration (FDA) approved devices (11). Chemiluminescence methods remain the gold standard and are more commonly used in research settings. Subsequently, more affordable devices based on other technologies (including handheld devices using electrochemical methods) have been approved for clinical use (10,12).

With these validated devices and following the ERS/ATS recommendations, the success rate of exhaled NO measurement increases from 40% at 4 years and 60% at 5 years to 100% at school age (8,9-12,14).

In this modest review of the literature, we will focus on four questions:

1. What factors influence FeNO levels?
2. Is FeNO measurement useful in the diagnosis of asthma?
3. What are the cut-off values for FeNO?
4. Is FeNO measurement useful for follow-up and further guidance of asthma management?

## What factors influence FeNO levels?

Many factors independent of asthma influence FeNO levels (15).

*Increase in FeNO*

- Ethnicity: higher in blacks than in whites
- Age and height
- Sex: higher in males
- Allergic sensitisation
- Consumption of foods containing nitrite, caffeine and alcohol

*Decrease in FeNO*

- Smoke exposure (passive/active)
- Respiratory infection

*Age*

The relationship between FeNO level and the age of the child was highlighted by Buchvald et al. in 2005 in 405 children (14). In the population studied in this paper, the 95% upper limit varied from 15.7 ppb at 4 years of age, 28 ppb at 12 years of age, to 39.2 ppb at 14-17 years of age. Therefore, a single cut-off value of 35 ppb (NICE, ATS) or 25 ppb (ERS) for the diagnosis of asthma in all children is likely to create a problem of validity of interpretation.

*Height*

Wang et al in 2022 attempted to provide us with percentile curves of FeNO values as a function of patient size (Figure 1) using the UK data from non-asthmatic children in the population-based birth cohort Manchester Asthma and Allergy Study (MAAS) (15).

Obviously, these curves need to be validated before they can be used in routine clinical practice, and we will also need percentile type curves for the lower age groups from 4 to 5 years if possible.

## Is FeNO measurement useful in the diagnosis of asthma?

The most widely recognised global consensus on asthma management is the Global Initiative for Asthma (GINA), the latest report of which was published in 2022 (16). This consensus does not differentiate between adults and children for the diagnosis of asthma.

The European Respiratory Society clinical practice guidelines for the diagnosis of asthma in children aged 5-16 years, published in the European Respiratory Journal in 2021, propose an algorithm for the diagnosis of paediatric asthma based on clinical data, spirometry, challenge testing, FeNo and, if necessary, bronchial challenge testing (17).

## What are the cut-off values for FeNO? (Figure 2)

Many clinical guidelines use FeNO as a dichotomous outcome ('positive' or 'negative') to facilitate the diagnosis of asthma in children. However, the cut-off values are not consistent between guidelines. In the NICE guidelines, the paediatric threshold for a diagnosis of asthma is 35 ppb at 50 ml/sec, whereas in the European Respiratory Society (ERS) guidelines it is 25 ppb (17,18). Furthermore, there is a significant overlap in FeNO levels between healthy and asthmatic populations and the range is wide (19).

In 2011, the ATS made suggestions for interpreting FeNO levels in asthma (16):

-A FeNO less than 25 ppb in children aged >12 years and less than 20 ppb in children younger than 12 years suggests noneosinophilic airway inflammation or the absence of airway inflammation and a low likelihood of response to inhaled corticosteroid therapy.

-FeNO greater than 50 ppb in children > 12 years of age or greater than 35 ppb in children < 12 years of age indicates eosinophilic airway inflammation and a high likelihood of response to inhaled corticosteroid therapy.

-Values of FeNO between 25 and 50 ppb in children > 12 years and 20 to 35 ppb in children < 12 years should be interpreted cautiously with reference to the clinical situation.

-An increase in FeNO of more than 20 per cent and more than 25 ppb (20 ppb in children under 12 years) from a previously stable level suggests increasing eosinophilic airway inflammation, but there is wide inter-individual variation.

-A decrease in FeNO of more than 20 per cent for levels above 50 ppb or more than 10 ppb for levels below 50 ppb may be clinically important.

**Figure 1**: Proposed FeNO percentile chart from MAAS cohort (reproduced from: Wang R et al. ERJ Open Research 2022;8:00319-2022 (15).

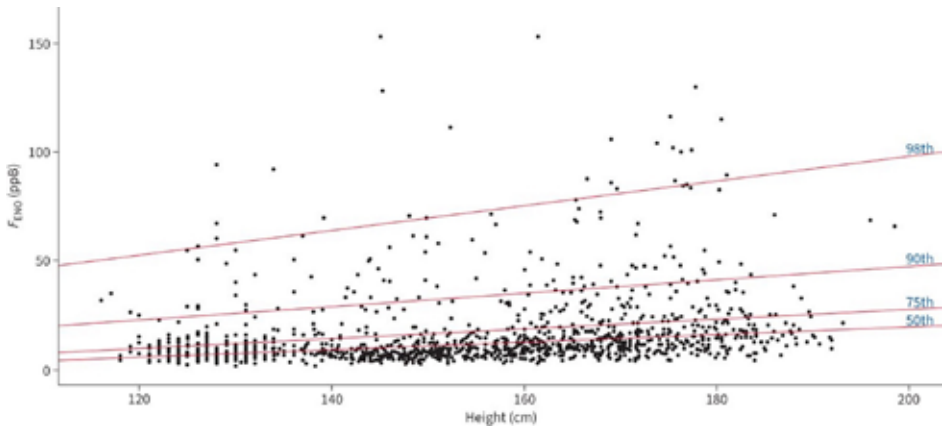


**Figure 2**: Cut-off values, according age, asthma endotype, mentioned in different guidelines: ATS, ERS, NICE, MAAS cohort, Ran Wang.

| In symptomatic patients <6 weeks (cought or dyspnea or wheezing) | ATS | ERS | NICE U-K | Maes cohort Ran wang | |
|---|---|---|---|---|---|
| In favor of a diagnosis of childhood asthma | | 25 ppb | 35 ppp | >perc 90 | > perc98 |
| Ages | | *5-16 years | *5-16 years | 110-200 cm | 110-200 cm |
| In favor of symptomatic eosinophilic airway inflammation | 35ppb | | | sens 58,8 | sens 33,3 |
| and high probability of response to inhaled corticotherapy | < 12 years | | | spec 95,5 | spec 100 |
| Ages | 50 ppb | | | PPV 96,8 | PPV 100 |
| | > 12 years | | | NPV 50 | NPV 39,3 |
| Noneosinophilic airway inflammation or the absence of airway | <20 ppb | | | | |
| inflammation and low probability of response to inhaled corticotherapy | <12 years | | | | |
| | <25 ppb | | | | |
| | > 12 years | | | | |

**Figure 3**: Asthma risk stratification based on percentile cut-off (reproduced from: Wang R et al. ERJ Open Research 2022;8:00319-2022 (15).

TABLE 5 Asthma risk stratification based on percentile cut-off.

| Percentile | Sensitivity, % (n) | Specificity, % (n) | PPV, % (n) | NPV, % (n) | +LR# | −LR¶ |
|---|---|---|---|---|---|---|
| >50th | 78.4 (40/51) | 40.9 (9/22) | 75.5 (40/53) | 45.0 (9/20) | 1.3 | 0.5 |
| >75th | 72.5 (37/51) | 77.3 (17/22) | 88.1 (37/42) | 54.8 (17/31) | 3.2 | 0.4 |
| >90th | 58.8 (30/51) | 95.5 (21/22) | 96.8 (30/31) | 50.0 (21/42) | 13.1 | 0.4 |
| >98th | 33.3 (17/51) | 100 (22/22) | 100 (17/17) | 39.3 (22/56) | ∞ | 0.7 |

#: +LR: sensitivity/(1-specificity). ¶: −LR: (1-sensitivity)/specificity. LR: likelihood ratio; NPV: negative predictive value; PPV: positive predictive value.

While a single diagnostic cut-off may be easy for clinicians to implement in practice, it is clear that the clinical probability of asthma increases with increasing FeNO levels above the recommended cut-off, and reducing this continuous variable to a dichotomous outcome loses an important amount of information (17,19,20).

As mentioned above, pubertal growth spurts influence the trajectory of FeNO, potentially further compromising diagnostic accuracy within this age group when using a single fixed cut-off (21).

The measurement of FeNO using the percentile curves of Wang et al. allows to optimise the rigorous diagnosis of asthma with a simple, not very invasive and inexpensive test. We can see that from the 90th percentile, the specificity of the diagnosis of paediatric asthma increases to more than 95%, with a PPV of 97% for a sensitivity of almost 59% and a NPN of 50% (15).

On the other hand, we know that a patient with another atopic condition, e.g. allergic rhinitis, without the slightest asthma symptom may have an exhaled FeNO at the 90th percentile or above without having asthma by definition.

Therefore

-An exhaled NO test should not be performed in a patient who does not have symptoms suggestive of asthma that are recurrent or have been present for at least 6 weeks.

-The FeNO value should be interpreted according to an algorithm that takes into account the clinical context, baseline spirometry and bronchodilator challenge, if available.

-In inhaled corticosteroid (ICS) naïve patients with chronic symptoms (more than 6 weeks) or recurrent symptoms partially suggestive of asthma (cough, isolated exertional dyspnoea, ...), even in the absence of reversible obstruction on classic spirometry, a value ≥ 35 ppb for NICE recommendations, ≥25 ppb for ERS recommendations, > 90th percentile on Wang's percentile curve, favours the diagnosis of paediatric asthma (Figure 3).

-The value of FeNo > 90th percentile according to Wang et al. could be of great clinical interest after validation, as it is very specific with a high PPV in patients with asthma symptoms.

## Is FeNO measurement useful for follow up and further guidance of asthma management?

Asthma exacerbations contribute significantly to asthma mortality and healthcare costs. It is an important prognostic factor in paediatric asthma according to the long-term goals for asthma management in the Global Initiative for Asthma 2022 (16).

In 2014, our Belgian multi-centre, single-blind, randomised controlled trial of ninety-nine children with persistent allergic asthma concluded that FeNO measurements in childhood asthma management did not improve the proportion of symptom-free days, but resulted in fewer asthma exacerbations associated with increased leukotriene receptor antagonist use and increased inhaled corticosteroid doses (22). Our aim was to keep FeNO below 20 ppb, the rounded 95% upper limit of FeNO levels in healthy children derived from previous studies.

Are these conclusions still valid in 2023?

For the follow-up of asthma, GINA 2022 makes a clear distinction between adults and children: "In children and young adults with asthma, FeNO-guided treatment was associated with a significant reduction in the number of patients with ≥ 1 exacerbation (OR 0.67) and in the exacerbation rate (mean difference -0.27 per year) compared with guideline-based treatment (evidence A); similar differences were seen in comparisons between FeNO-guided treatment and non-guideline-based algorithms (16).

The most recent meta-analysis on this topic was published by Xia Wang et al. in 2022 and selected 23 randomised controlled trials (from 2005 to 2020 with 2723 paediatric asthma patients, 1360 in the intervention group vs. 1363 in the control group) comparing the effects of FeNO-guided asthma management with those not using FeNO in paediatric asthma (23).

According to this meta-analysis: "FeNO-guided asthma management helped to reduce the number of children with asthma exacerbations (risk ratio (RR) 0.73, P < 0.0001) and the frequency of exacerbations (standardised mean difference (SMD) -1.57; P < 0.00001).

We can conclude that, although there is still no consensus on the treatment algorithm guided by the measurement of exhaled NO, the FeNO-guided asthma management strategy could partially improve the outcome of paediatric asthma by reducing the risk of exacerbation, which is an essential prognostic factor in paediatric asthma according to the long-term goals of asthma management (GINA 2022), and by increasing inhaled corticosteroid therapy (16).

Currently, in practice, for follow-up and therapeutic adaptation, we could propose to fully respect the recommendations of the ATS interpretation rules.

The following guidelines can be suggested:

- if an asthmatic patient remains symptomatic for more than 1-3 months despite background treatment with:
  - either an exhaled NO level > 20 ppb (or > perc 75 according to R. Wang) and even more if > 35 ppb (or > perc 90 according to R. Wang) or if the follow-up exhaled NO level increases significantly +20% (baseline >50 ppb) or +10ppb (baseline < 50 ppb).
  - An increase in ICS dose or compliance or improvement in allergen avoidance has a high likelihood of improving asthma control.
  - Corticoresistance cannot be excluded.
  - Without an increase in ICS dose, there is a high risk of exacerbation (if > 35 ppb or > PERC 90 according to R. Wang).
  - Either an exhaled NO value <20 ppb (or < perc 75 according to R. Wang) or if the follow-up exhaled NO value has significantly decreased by -20% (baseline >50 ppb) or -10ppb (baseline <50 ppb).
  - Symptoms are unlikely to be due to eosinophilic airway inflammation.
  - Increasing ICS dose or compliance is unlikely to improve asthma control.
  - Questions to ask about diagnosis, comorbidities, passive smoking...
- When an asthma patient has been asymptomatic for at least 3 months on the same background treatment:
  - either an exhaled NO value > 20 ppb (or > perc 75 according to R. Wang) and even more if > 35 ppb (or > perc 90 according to R. Wang) or if the follow-up exhaled NO value increases significantly by +20% (baseline >50 ppb) or +10ppb (baseline < 50 ppb).
  - Reducing the dose of ICS is likely to reduce asthma control and should be done very gradually and cautiously.
  - Either an exhaled NO level <20 ppb (or < Perc 75 according to R. Wang).
  - A decrease in ICS dose has a low risk of decreasing asthma control and could be achieved quickly.

## Conclusions

Measurement of exhaled NO is simple, fast and reproducible from the age of 5-6 years. The technique is not reimbursed in Belgium. The

measurement modalities in children are well specified by the ERS and ATS consensus.

Even if this is not the case for adults, sometimes smokers and carriers of polypathology, we can consider that, in the paediatric field, the measurement of exhaled NO is useful for the diagnosis of eosinophilic asthma in non-smoking patients, without inhaled corticosteroids, with asthma-like symptoms for at least 6 weeks. This measurement must always be interpreted in conjunction with clinical data and, if possible, the results of spirometry with bronchodilator challenge. The interest of this measurement lies in its strong positive predictive value and high specificity, although a normal value cannot exclude the diagnosis of asthma.

Even if this is not the case in adult patients, FeNO data can improve the management of the background treatment of asthma in children. It could lead to a reduction in the number of exacerbations and avoid inappropriate dosing of inhaled corticosteroid therapy.

The use of size-based percentile curves, or even in the future the use of z-score statistical tools, may allow a more statistically valid analysis of exhaled NO levels and a clearer and more rigorous follow-up.

Pending the validation of these curves, the fixed cut-off values proposed by the ATS and NICE recommendations can be used, i.e. FeNO < 20 ppb at 50 ml/sec, corresponding to a low probability of bronchial eosinophilic inflammation and therefore a low probability of efficacy of inhaled corticosteroid therapy, whereas a value > 20 ppb and even more > 35 ppb corresponds to a higher probability of bronchial eosinophilic inflammation and therefore a higher probability of efficacy of inhaled corticosteroid therapy (8,18).

Thus, a FeNO level of ≥ 35 ppb or ≥25 in a paediatric patient who has been symptomatic for more than 6 weeks without inhaled corticosteroid therapy makes the diagnosis of asthma more likely, but a normal FeNO level cannot exclude the diagnosis of asthma.

## Conflict of interest

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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**RÉSUMÉ ABRÉGÉ DES CARACTÉRISTIQUES DU PRODUIT :** Veuillez vous référer au Résumé des Caractéristiques du Produit pour une information complète concernant l'usage de ce médicament. **DÉNOMINATION DU MÉDICAMENT :** Bexsero suspension injectable en seringue préremplie. Vaccin méningococcique groupe B (ADNr, composant, adsorbé) ; EU/1/12/812/001 ; EU/1/12/812/002, EU/1/12/812/003, EU/1/12/812/004. Classe pharmacothérapeutique : vaccins méningococciques, Code ATC : J07AH09. **COMPOSITION QUALITATIVE ET QUANTITATIVE :** Une dose (0,5 ml) contient : Protéine de fusion recombinante NHBA de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Protéine recombinante NadA de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Protéine de fusion recombinante fHbp de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Vésicules de membrane externe (OMV) de Neisseria meningitidis groupe B, souche NZ98/254 mesurée en tant que proportion de l'ensemble des protéines contenant l'antigène PorA P1.4[2] : 25 microgrammes • [1] produite dans des cellules d'E. coli par la technique de l'ADN recombinant - [2] adsorbée sur hydroxyde d'aluminium (0,5 mg $Al^{3+}$) - [3] NHBA (antigène de liaison à l'héparine de Neisseria), NadA (adhésine A de Neisseria), fHbp (protéine de liaison du facteur H). Pour la liste complète des excipients, voir rubrique 6.1 du RCP complet. **FORME PHARMACEUTIQUE :** Suspension injectable. Suspension liquide blanche opalescente. **DONNÉES CLINIQUES : Indications thérapeutiques :** Bexsero est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par Neisseria meningitidis de groupe B. L'impact de l'infection invasive à différentes tranches d'âge ainsi que la variabilité épidémiologique des antigènes des souches du groupe B dans différentes zones géographiques doivent être pris en compte lors de la vaccination. Voir rubrique 5.1 du RCP complet pour plus d'informations sur la protection contre les souches spécifiques au groupe B. Ce vaccin doit être utilisé conformément aux recommandations officielles. **Posologie et mode d'administration :** Posologie : **Tableau 1. Résumé de la posologie : Age lors de la première dose :** Nourrissons de 2 à 5 mois[a]. **Primovaccination :** Trois doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b, c] - Primovaccination : Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b, c]. **Age lors de la première dose :** Nourrissons de 6 à 11 mois. **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose au cours de la deuxième année de vie avec un intervalle d'au moins 2 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose : Enfants de 12 à 23 mois. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose avec un intervalle de 12 à 23 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose : Enfants de 2 à 10 ans. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • **Age lors de la première dose : Adolescents (à partir de 11 ans) et adultes*. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • [a] La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. - [b] En cas de retard, la dose de rappel ne devrait pas être administrée audelà de l'âge de 24 mois. - [c] Voir rubrique 5.1 du RCP complet La nécessité et le moment d'administration d'autres doses de rappel n'ont pas encore été déterminés. - [d] Voir rubrique 5.1 du RCP complet. - * Il n'existe aucune donnée chez les adultes de plus de 50 ans. Mode d'administration : Le vaccin est administré par une injection intramusculaire profonde, de préférence dans la face antérolatérale de la cuisse chez le nourrisson ou dans la région du muscle deltoïde du haut du bras chez les sujets plus âgés. Des sites d'injection distincts doivent être utilisés si plusieurs vaccins sont administrés simultanément. Le vaccin ne doit pas être injecté par voie intraveineuse, souscutanée ni intradermique et ne doit pas être mélangé avec d'autres vaccins dans la même seringue. Pour les instructions concernant la manipulation du vaccin avant administration, voir la rubrique 6.6 du RCP complet. **Contreindications :** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP complet. **Effets indésirables :** Résumé du profil de sécurité : La sécurité de Bexsero a été évaluée lors de 17 études, dont 10 essais cliniques randomisés contrôlés portant sur 10 565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6 837 étaient des nourrissons et des enfants (de moins de 2 ans), 1 051 étaient des enfants (entre 2 et 10 ans) et 2 677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3 285 ont reçu une dose de rappel au cours de leur deuxième année de vie. Chez les nourrissons et les enfants (de moins de 2 ans), les réactions indésirables locales et systémiques les plus fréquemment observées lors des essais cliniques étaient : sensibilité et érythème au site d'injection, fièvre et irritabilité. Dans les études cliniques menées chez les nourrissons vaccinés à 2, 4 et 6 mois, la fièvre (≥ 38 °C) était rapportée chez 69 % à 79 % des sujets lorsque Bexsero était coadministré avec des vaccins de routine (contenant les antigènes suivants : pneumococcique heptavalent conjugué, diphtérie, tétanos, coqueluche acellulaire, hépatite B, poliomyélite inactivée et Haemophilus influenzae de type b), contre 44 % à 59 % des sujets recevant les vaccins de routine seuls. Une utilisation plus fréquente d'antipyrétiques était également rapportée chez les nourrissons vaccinés par Bexsero et des vaccins de routine. Lorsque Bexsero était administré seul, la fréquence de la fièvre était similaire à celle associée aux vaccins de routine administrés aux nourrissons pendant les essais cliniques. Les cas de fièvre suivaient généralement un schéma prévisible, se résolvant généralement le lendemain de la vaccination. Chez les adolescents et les adultes, les réactions indésirables locales et systémiques les plus fréquemment observées étaient : douleur au point d'injection, malaise et céphalée. Aucune augmentation de l'incidence ou de la sévérité des réactions indésirables n'a été constatée avec les doses successives du schéma de vaccination. Liste tabulée des effets indésirables : Les effets indésirables (consécutifs à la primovaccination ou à la dose de rappel) considérés comme étant au moins probablement liés à la vaccination ont été classés par fréquence. Les fréquences sont définies comme suit : Très fréquent : (≥ 1/10) - Fréquent : (≥ 1/100 à < 1/10) - Peu fréquent : (≥ 1/1 000 à < 1/100) - Rare : (≥ 1/10 000 à < 1/1 000) - Très rare : (< 1/10 000). Fréquence indéterminée : (ne peut être estimée sur la base des données disponibles). Dans chaque groupe de fréquence, les effets indésirables sont présentés par ordre de sévérité décroissante. Outre les événements rapportés lors des essais cliniques, les réactions spontanées rapportées dans le monde pour Bexsero depuis sa commercialisation sont décrites dans la liste ci dessous. Comme ces réactions ont été rapportées volontairement à partir d'une population de taille inconnue, il n'est pas toujours possible d'estimer de façon fiable leur fréquence. Ces réactions sont, en conséquence, listées avec une fréquence indéterminée. **Nourrissons et enfants (jusqu'à l'âge de 10 ans) :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Troubles du métabolisme et de la nutrition : Très fréquent : troubles alimentaires. Affections du système nerveux : Très fréquent : somnolence, pleurs inhabituels, céphalée. Peu fréquent : convulsions (y compris convulsions fébriles). Fréquence indéterminée : épisode d'hypotonie-hyporéactivité, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections vasculaires : Peu fréquent : pâleur (rare après le rappel). Rare : syndrome de Kawasaki. Affections gastrointestinales : Très fréquent : diarrhée, vomissements (peu fréquents après le rappel). Affections de la peau et du tissu souscutané : Très fréquent : rash (enfants âgés de 12 à 23 mois) (peu fréquent après le rappel). Fréquent : rash (nourrissons et enfants âgés de 2 à 10 ans). Peu fréquent : eczéma. Rare : urticaire. Affections musculosquelettiques et systémiques : Très fréquent : arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : fièvre (≥ 38 °C), sensibilité au niveau du site d'injection (y compris sensibilité sévère au site d'injection définie par des pleurs lors d'un mouvement du membre ayant reçu l'injection), érythème au site d'injection, gonflement du site d'injection, induration au site d'injection, irritabilité. Peu fréquent : fièvre (≥ 40 °C). Fréquence indéterminée : réactions au site d'injection (incluant un gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister pendant plus d'un mois). **Adolescents (à partir de 11 ans) et adultes :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Affections du système nerveux : Très fréquent : céphalée. Fréquence indéterminée : syncope ou réaction vasovagale à l'injection, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections gastrointestinales : Très fréquent : nausées. Affections de la peau et du tissu sous-cutané : Fréquence indéterminée : rash. Affections musculosquelettiques et systémiques : Très fréquent : myalgies, arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise. Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois). Déclaration des effets indésirables suspectés : La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : **Belgique :** Agence Fédérale des Médicaments et des Produits de Santé - Division Vigilance - Boîte Postale 97 - 1000 Bruxelles - Madou - Site internet: www.notifieruneffetindesirable.be - e-mail: adr@afmps.be. **Luxembourg :** Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé. Site internet : www.guichet.lu/pharmacovigilance. **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ :** GSK Vaccines S.r.l.,Via Fiorentina 1, 53100 Sienne, Italie. **DATE D'APPROBATION DU TEXTE :** 26/04/2023 (v15). **MODE DE DELIVRANCE :** Sur prescription médicale.

**Références : 1.** SmPC Bexsero. **2.** Schmitt JH, Booy R, Astron R, et al. How to optimize the coverage rate of infant and adult immunisations in Europe. BMC Med. 2007;5:11. doi:10.1186/1741-7015-5-11.

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# Latest update of the guidelines for the treatment in childhood asthma

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## Keywords

Asthma ; chronic airway inflammation ; inhaled corticosteroids ; inhaled beta-agonists ; guidelines ; child ; adolescent.

## Abstract

Asthma is defined as a heterogeneous disease characterized by chronic airway inflammation. In recent years, the treatment strategy for this common disease has changed dramatically. Recently, guidelines for adolescents and younger children have given more attention to the use of inhaled corticosteroids whenever beta-agonists are used. This article reviews the changes in recent guidelines and the underlying evidence.

## Introduction

The Global Initiative for Asthma (GINA) defines asthma as a disease with many phenotypes, characterized by chronic airway inflammation and two defining features: a history of wheeze, shortness of breath, chest tightness or cough and variable expiratory airway limitation (1).

Asthma is a serious global health problem affecting all age groups, with global prevalence of 9,8 % (2). Although the prevalence of asthma in the adult population in Belgium has decreased from 8 % to 5 % over the last three decades, the prevalence of childhood asthma is higher, estimated at 10 % (3, 4).

Since the 1990s, guidelines have been published, by the then newly established bodies such as the British Thoracic Society (BTS) and GINA, and are frequently updated to ensure a coherent, consistent, and updated diagnosis and treatment of asthma (5-7). Asthma guidelines for young children and adults differ in terms of diagnostic tools, medication options and inhaler types. Adolescents (12 years and older) and adults are differentiated from 6- to 11-year-olds.

Since significant adjustments in 2019, only the GINA guidelines have been further updated according to recent evidence and are discussed further below (1).

## Treatment guideline 12 years and older and adults

As mentioned above, guidelines are updated regularly and in 2019 there have been major changes in the management of asthma in adolescents and adults (1). Previous treatment regimens suggested to use one type of inhaler for reliever therapy and another inhaler for maintenance therapy. Up to 70 % of people worldwide with asthma are diagnosed with mild disease, having symptoms more than twice a month but not every day. However, they are at risk of experiencing intermittent severe asthma attacks and requiring hospitalization because of the intermittent nature of symptoms in mild asthma that often leads to poor inhaler adherence, with a consequent risk of exacerbations (8).

A recent Cochrane review shows that the use of low-dose ICS (inhaled corticosteroids) in combination with formoterol on an as-needed basis results in 55 % fewer severe exacerbations compared with SABA (short-acting beta-agonist) as a reliever and leads to fewer emergency contacts and hospital admissions (8).

The reason why formoterol, a known LABA (long-acting beta-agonist) shows good results on an as-needed basis is its unique feature of having a rapid onset (1-3 min after inhalation) in contrast to other LABA's, in addition to the prolonged bronchodilation of about 12 h after inhalation.

A comparison of ICS/formoterol as-needed basis with daily ICS use showed similar asthma control was noticed with the same number of exacerbations requiring systemic steroids, but fewer emergency contacts and hospital admissions, despite lower daily doses of inhaled corticosteroids (on average 154 µg less per day) (8).

Based on this evidence, the therapy regimen was modified for patients older than 12 years, by using only 1 type of inhaler (fixed-dose ICS/LABA combination). This approach is called MART: single inhaler for maintenance and reliever therapy (1).

All studies are conducted with a combination inhaler of budesonide and formoterol (e.g., Symbicort®, Bufomix®, AirBuFo®) but GINA guidelines indicate a possible equivalent effect with beclomethasone/formoterol (e.g., Inuvair®).

The 2021 Cochrane review is based on 4 large trials (SYGMA 1, SYGMA 2, PRACTICAL and NOVEL START), but adolescents were included in only 2 of the 4 trials, the SYGMA 1 and SYGMA 2 trial and represented 12,4% and 9,8% of the study population, respectively, with a mean age of 39,6 and 41 years, respectively (9-12). However, a recent post hoc analysis by Bisgaard found similar results when the MART strategy was used in adolescents. Participants had fewer asthma exacerbations, reduced risk of severe asthma exacerbations, fewer asthma-related symptoms and had an improved FEV1 (13).

Henceforth, the GINA guideline for adolescents and adults includes two treatment tracks, the preferred Track 1 using the MART strategy and Track 2 using as-needed SABA as reliever therapy (Figure 1) (1). Both start with low-dose ICS and build up through steps 2 to 5. In Track 2 an ICS-LABA combination is suggested from step 3, but since these ICS-LABA combinations do not include formoterol, this inhaler cannot be used as a reliever and a SABA inhaler should be used instead.

Additional treatment options for severe asthma (step 5) include add-on LAMA or biologicals. Since March 2023, three biologicals are available and reimbursed in Belgium for childhood asthma: anti-IgE (omalizumab), anti-IL5 (mepolizumab) and anti-IL4Rα (dupilumab), which can only be

**Figure 1:** GINA guideline 12 + years and adults (Source GINA 2023).

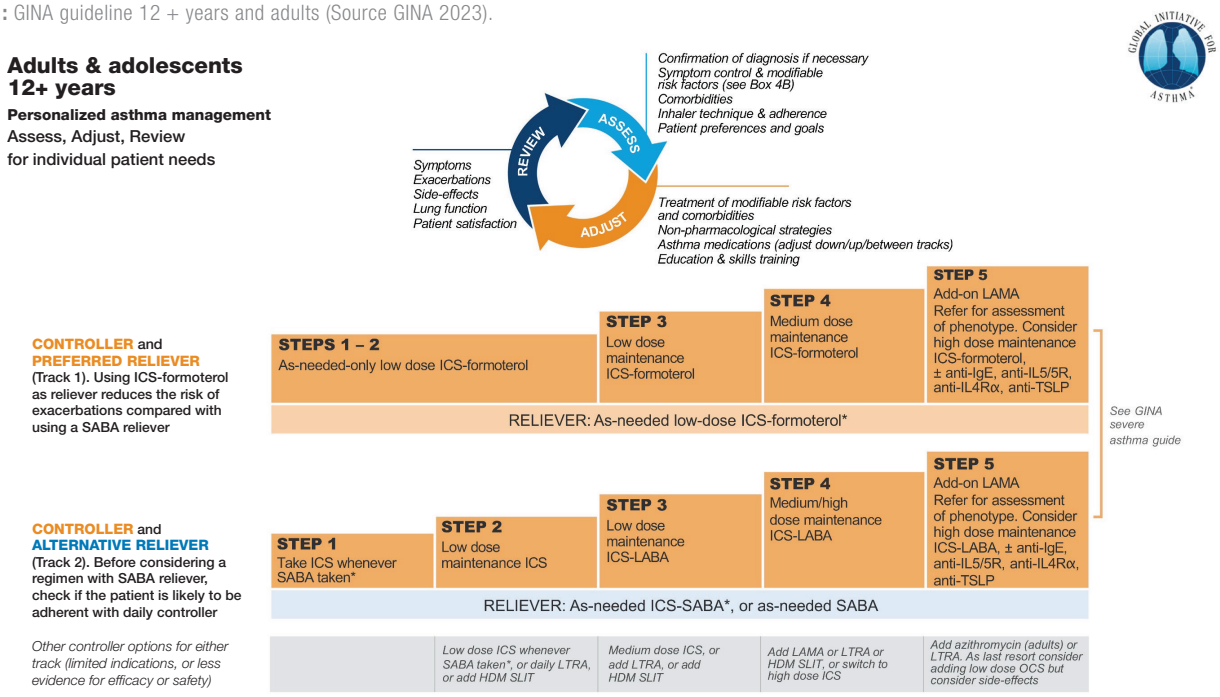
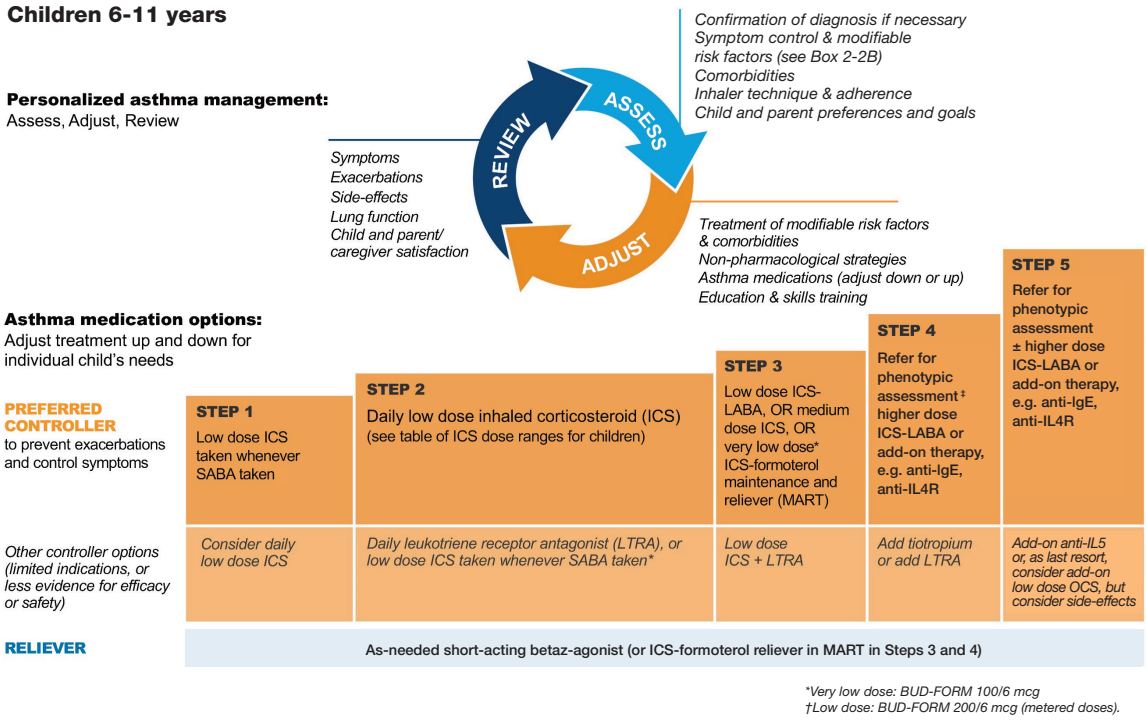



**Figure 2:** GINA guideline in children 6 - 11 year old (Source GINA 2023).




prescribed under strict conditions, the first two for patients older than 6 years and the last only for patients older than 12 years.

In addition, daily LTRA (leukotriene receptor antagonists) or SLIT (sublingual immunotherapy) for house dust mite in allergic patients could be considered from step 2 onwards.

## Treatment guideline 6 – 11 years

Fewer changes are made in the 6 to 11 years regimen. However, since 2022, the guidelines recommend in step 1 to use ICS whenever SABA is used, based on the TREXA trial (14). This RCT compared the use of SABA on an as-needed with ICS-SABA on an as-needed basis and showed a 23% change in treatment failure and exacerbations in the SABA-reliever group versus 8,5 % in the SABA-ICS-reliever group. In addition, there was no growth restriction due to lower doses of inhaled steroids (20 µg vs. 88 µg daily). When using daily ICS, participants grew 1.1cm less than those in the SABA-ICS and the SABA-as needed groups over the course of the 44-week trial.

In addition, there was no additional benefit of using SABA-ICS as a reliever compared to SABA alone as a reliever when using daily ICS. Therefore, they advise to keep SABA as a reliever inhaler from step 2 (Figure 2).

Since 2020 a lower dose of inhaled steroids is recommended for fluticasone propionate, commercially known as Flixotide®, with low-dose inhaled corticosteroids (steps 1 and 2) meaning up to 100 µg daily instead of 200 µg, or in practice 2x1 puffs instead of 2x2 puffs (of Flixotide® 50 µg) in steps 1 and 2 (1).

MART is also added in the 6- to 11-year old regimen from 2021 onwards. Evidence In this age group is currently sparse. One trial in 342 children shows less severe exacerbations compared to daily ICS, with lower doses of inhaled steroids, but no further evidence is available (15). However, the steroid dosage in the inhaler used (80 µg budesonide + 4.5 µg formoterol) is currently not available in Belgium.

In addition, daily LTRA could be considered from step 2, and in step 5, biologicals are suggested as add-on therapy for some cases of severe asthma.

## Furthermore

In the latest GINA guideline, special attention is given to the diagnosis of patients with asthma, preferably before starting treatment, using either spirometry-based testing, if available, or peak expiratory flow (PEF).

It remains important to adjust for modifiable risk factors such as nicotine exposure, beta-blocker use, NSAID use, and allergen exposure, and to treat possible comorbidities such as rhinitis, obesity, gastroesophageal reflux, and depression.

To improve patient adherence, a written treatment plan is recommended, as well as (re)education on correct inhaler use at each visit to the doctor.

## Conclusion

Asthma is a common disease in children and requires up-to-date care. In recent years the treatment guidelines have been adjusted, with significant changes in 2019 in the guideline form Global Initiative for Asthma (GINA) for adolescents, but also for younger children. In this new era, there is more attention for the use of inhaled corticosteroids in combination with a bronchodilator as reliever therapy and for minimizing the dosages and side effects of the steroids used while maintaining a good asthma control.

## Conflict of interest

The author has no conflicts of interest to declare with regard to the subject matter discussed in this manuscript.

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# Biological Therapies for the Treatment of Severe Asthma in Children

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## Keywords

Severe asthma, children, biotherapy, omalizumab, mepolizumab, dupilumab.

## Abstract

Asthma is the most common chronic, non-communicable disease in paediatrics. It is a heterogeneous disease and several phenotypes are described according to symptoms, age of onset, triggers and response to treatment. The characterisation of the inflammatory mechanisms (molecular and cellular), also called endotypes, is more recent and led to the development of more targeted therapies for severe asthma in children, where conventional treatments are not sufficient. Based on the type of bronchial inflammation, there are two endotypes of asthma in children: high T-helpers 2 (TH2) and low TH2. The TH2 endotype is predominant in children, explained by a higher incidence of allergic sensitisation. Three biological therapies, acting on TH2 inflammation, benefit from an intervention from the National Institute for Health and Disability Insurance (NIHDI) in Belgium in children: omalizumab (anti-IgE), mepolizumab (anti-IL-5) and dupilumab (anti-IL-4 and IL-13 a-receptor). When administered in specific situations, these molecules can lead to a significant improvement in patients' symptoms and quality of life. Omalizumab is the best-studied biological therapy in children and is therefore preferred.

## Introduction

Asthma is the most common chronic, non-communicable disease in children. In Western Europe, its prevalence varies from 7.4% (Austria) to 20.9% in the UK for children aged 6-7 years, with a prevalence of 7.5% in Belgium (1). For adolescents aged 13-14 years old, the prevalence varies from 8.3% (Belgium) to 31.2% in the Isle of Man (1). Asthma is a heterogeneous disease characterised by variable respiratory symptoms and airflow limitation, associated with inflammation and airway remodelling. The most common symptoms are cough, chest tightness, shortness of breath and wheezing. In children, asthma is most often manifested by recurrent bronchitis related to viral infections (2). Conventional treatment combines inhaled corticosteroids, short- and long-acting beta2-mimetics and anti-leukotrienes. In 5% of children with paediatric asthma, despite well-conducted treatment with high doses of inhaled corticosteroids in combination with other molecules, the symptoms persist and the asthma is classified as severe, leading to significant morbidity that necessitates sometimes the use of other more targeted therapies such as biological therapies (3). This article, after the description of a clinical case, provides a summary of the different biological therapies that benefit from an intervention of the social security (NIHDI) in Belgium and that are in use for children.

## Case report

An 8 years old boy has been followed for several years in a paediatric pneumology clinic. Despite a well conducted treatment with anti-leukotrienes and high dose inhaled corticosteroids (500µg fluticasone propionate, daily) associated with formoterol (a long acting beta2-mimetic), he presents monthly exacerbations of viral induced asthma, with regular need for oral corticosteroids. He has been hospitalised several times. Between episodes, he presents rapid shortness of breath, frequent dry cough and symptoms of rhino-conjunctivitis. The biology shows a significant sensitization to dust mites (*Dermatophagoides Pteronyssimus 70.8kU/L, Dermatophagoides Farinae* 92.9kU/L), with a total IgE level of 244UA/L, and a blood eosinophilia of 220/mm3. Chest CT scan showed no bronchiectasis, bronchoscopy showed no anatomical abnormalities, bronchoalveolar lavage revealed predominantly lymphocytic inflammation, gastroscopy was normal, there was no immune deficiency, and the sweat test was normal. FEV1 was normal on breath function test. The asthma control score (ACT) was 10/27. Given the morbidity and severity of the symptoms, a biological therapy was started in February 2020 with Omalizumab at a dose of 150mg every 4 weeks, calculated according the weight and the initial IgE level. The first injections were given in the day hospital with monitoring for a few hours, and after 4 injections, the patient was given injections in ambulatory consultation. Since then, the patient has shown a clear improvement of his symptoms. He has not been hospitalized until now and didn't receive any more oral corticotherapy. He could practice sports without symptoms. He has never experienced any side effects from the treatment. His inhaled corticosteroid dose has been reduced by half. His ACT scores range from 22 to 27. He is still on Omalizumab and has been receiving it for 3 years. A discontinuation trial will be considered in the near future.

## Discussion

Several clinical phenotypes of asthma are described according to symptoms, age of onset, triggers and response to treatment. The characterisation of inflammatory mechanisms (molecular and cellular), also called endotypes, is more recent and involves, in addition to the clinic, precise biological assessment and the use of biomarkers. In severe asthma in children, based on the type of bronchial inflammation, two asthma endotypes are distinguished: high T-helpers 2 (TH2) and low TH2 (4). The TH2 endotype is predominant in children, explained by a higher incidence of allergic sensitisation, ranging from 83% to 94% in children aged 6 to 18 years (5-6).

When pollutants, viruses or pneumallergens interact with immune presenting cells (dendritic cells), they migrate to the local lymph nodes where they activate naive TH cells, which in turn differentiate into TH1, TH17 or TH2 lymphocytes. Subsequently, in the TH2 endotype, TH2 lymphocytes secrete interleukin 4 (IL-4), which acts as a signalling intermediate between TH2 lymphocytes and B lymphocytes to increase

**Table 1:** Differential diagnosis of severe asthma.

| Differential diagnosis | Complementary test |
|---|---|
| Tracheomalacia | Bronchoscopy, Rx trachea |
| Bronchopulmonary dysplasia | Chest CT, Spirometry |
| Tuberculosis | IDR, Quantiferon |
| Cystic fibrosis | Sweat test, genetic |
| Primary ciliary dyskinesia | Ciliary study, genetic |
| Bronchiolitis obliterans | Chest CT, Spirometry |
| Immune deficiency | Immune assessment |
| Foreign body inhalation | Bronchoscopy |
| Vascular Ring | Thoracic angioscan |
| Vocal cord dysfunction | ENT Fiberoptic nasopharyngoscopy |
| Exercise-induced hyperventilation | Exercise stress test |
| Hyperventilation syndrome | Psychological assessment |

the production of immunoglobulin E (IgE). IgEs then bind to effector cells (mast cells, basophils and eosinophils) and trigger the release of histamine, leukotrienes and prostaglandins, which promote vascular permeability and smooth muscle contractility. In the airway epithelium, TH2 lymphocytes will secrete IL-5 and IL-13. IL-5 promotes eosinophil maturation and migration, while IL-13 induces mucin production by caliciform cells and modifies airway smooth muscle leading to hyperresponsiveness (2).

Severe asthma affects 5% of paediatric asthma patients. Severe asthma is defined by a high therapeutic pressure associated with clinical and/or functional criteria (7). Therapeutic pressure being a combination of high-dose corticosteroid therapy (Budesonide equivalent ≥800µg/d) and a long-acting beta2-mimetic and possibly anti-leukotriene or long-term systemic corticosteroid therapy. Clinical criteria are chronic respiratory pulmonary symptoms (respiratory symptoms ≥3 times/week ≥3 months) or exacerbations resulting in at least one intensive care hospitalization, at least two hospitalizations or at least two courses of oral corticosteroids within a year. Functional criteria are persistent severe bronchial obstruction with FEV1 Z-score <1.96 on a steroid test. In addition, three other parameters are required: the absence of another diagnosis (table 1), adequate management of precipitating factors, and good adherence and technique to treatment (3, 7-8).

A better understanding of the immunological mechanisms involved in the pathophysiology of asthma has allowed the development of more targeted therapies such as biological therapies. In Belgium, three treatments benefit from an intervention for the management of severe asthma in children: omalizumab, mepolizumab and dupilumab (6).

Omalizumab (Xolair®) is a monoclonal antibody that is specific for IgE. It binds to IgE and prevents the binding of IgE to FcεRI (IgE high affinity receptors present at the cellular surface) on basophils and mast cells, thereby reducing the amount of circulating IgE that can trigger the chain of allergic reactions, and allowing the reduction of blood and tissue eosinophils and inflammatory mediators, including IL-4, IL-5 and IL-13. It is administered to patients from the age of 6 years with allergic asthma, sensitised to at least 1 perennial pneumallergen and with high IgE levels. The dose and frequency of subcutaneous injections (every 2 and 4 weeks) depend on total IgE levels (in Belgium: 6-11 years: ≥200 - ≤1300; ≥12 years ≥76 - ≤700U/ml) and weight (9). It is the most well-studied molecule in children, resulting in improved asthma control, fewer respiratory exacerbations, reduced daily use of inhaled or oral corticosteroids, improved symptom control, and stabilisation or improvement of airway obstruction on breath function tests (6). In a randomised, double-blind study by Busse et al. of 419 patients aged 6-20 years, there was a 24.5% reduction in the number of symptomatic days and a 38% reduction in patients with at least one respiratory exacerbation (10). In the real-life study by Deschildre et al. of 78 children treated for 2 years, asthma control was observed in 80% of patients with an 83% drop in the rate of respiratory exacerbations. However, there was no beneficial gain in FEV1 (11). Response to treatment was observed within 4-6 months after initiation of treatment. Asthmatic patients with frequent exacerbators and with eczema or food allergies responded better in that study. Generally, the treatment was well tolerated. The main side effects are fatigue, arthralgia and hair loss. Anaphylaxis is rare. It is also indicated and benefit from NIHDI intervention in cases of sinonasal polyposis and chronic urticaria (8).

Mepolizumab (Nucala®) is a humanised monoclonal antibody which inhibits the biological activity of IL-5 by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the cell surface of eosinophils. Thus, it inhibits the IL-5 signalling pathway and reduces the production and life span of eosinophils. It is indicated in children aged 6 years in severe refractory eosinophilic asthma with a blood eosinophilia count of >300/mL at initiation and once in the 12 months prior to initiation. The dose is 40 mg in children aged 6-12 years and 100 mg in children aged ≥ 12 years, every 4 weeks, administered subcutaneously. Post-hoc analysis of 37 patients showed a significant decrease in the annual rate of respiratory exacerbation (6,12). There is only one paediatric study in children under 12 years of age. In this study by Gupta et al, administration of mepolizumab to 36 children aged 6-12 years confirmed a significant reduction in blood eosinophilia after 12 weeks, but the impact on asthma symptoms were not evoked in the report (13). Treatment tolerance was good and the main side effects described were injection site pain, headache, fatigue, respiratory infections and a paradoxical worsening of asthma. Mepolizumab is also indicated for the treatment of sinonasal polyposis, eosinophilic granulomatosis with polyangiitis and hypereosinophilic syndrome (12).

Dupilumab (Dupixent®) is a humanised monoclonal antibody directed against the IL-4 receptor α, blocking the receptor shared by IL-4 and IL-5, which is essential for signal transduction. Dupilumab is indicated for the additional background treatment of severe oral corticosteroid-dependent asthma associated with type 2 inflammation, characterised by elevated blood eosinophils (≥150/mL eosinophils in the 12 months prior to and at the time of initiation of treatment) and/or an elevated fraction of exhaled nitric oxide (FeNO) (≥25ppb), in adolescents aged 12 years and older (6). The dose is 600 mg at the first injection, then 300 mg every 2 weeks. In the randomised phase III QUEST study dupilumab vs placebo, 107 adolescents aged 12-17 years were included. There was no significant improvement in the number of respiratory exacerbations. However, there was a significant improvement in FEV1 (14-15). For children aged 6-11 years and weighing between 15 and 60 kg, dupilumab is indicated for severe asthma associated with type 2 inflammation in patients who are inadequately controlled on high-dose inhaled corticosteroids in combination with another background asthma treatment. The dose is 300 mg every 4 weeks. In the VOYAGE study of dupilumab versus placebo in 408 children over 52 weeks, patients had fewer respiratory exacerbations (0.31 in the dupilumab group vs 0.75 placebo group) and improved lung function (+10.5%±1 dupilumab group vs +5.3%±1.4 in the placebo group) (16). The main side effects were injection site reactions, oropharyngeal pain and hypereosinophilia. Dupilumab is also indicated for the treatment of severe atopic dermatitis from the age of 12 years, eosinophilic esophagitis, nodular prurigo and sinonasal polyposis in adults (17).

In practice, the initiation of a biological therapy needs to be made by a paediatric pulmonologist working in an academic setting or an adult pulmonologist. The initiation of biological therapies should be discussed in a multidisciplinary meeting (paediatric and adult respirologist, allergist, ENT specialist, dermatologist, etc.) and a full differential diagnosis should be made before treatment is started. The treatment is initiated the couple

**Table 2:** Reimbursement criteria for biological therapies in Belgium for severe asthma.

| Molecules | Action | Age | Common criteria | Specific criteria | Dose |
|---|---|---|---|---|---|
| **Omalizumab** | Anti-IgE<br>TH2 high allergic asthma | ≥ 6 years | - Medication review by a pharmacist or specialist nurse or physiotherapist<br>- Daily high dose inhaled corticosteroid therapy combined with a long acting beta2-mimetic +/- anti leukotriene or long-term general corticosteroid therapy<br>- At least 2 hospital admissions or 2 emergency department treatments for severe asthma in the previous 12 months, or at least 2 documented severe exacerbations in the previous 12 months (worsening of asthma requiring systemic corticosteroids for at least 3 days and/or hospitalization and/or emergency department visit) | Obstruction confirmed on spirometry ≥ 12 years<br>Confirmation by prick test or RAST of perennial sensitisation<br>IgE levels (children 6-11 years: ≥ 200 - ≤ 1300 IU/ml; >= 12 years: ≥ 76 - ≤ 700 IU/ml) | 75 mg to 600 mg SC every 2 to 4 weeks depending on weight and initial IgE level |
| **Mepolizumab** | Anti-IL-5<br>Severe eosinophilic asthma | ≥ 6 years | | Blood eosinophilia ≥ 300/µL on two blood tests within a year | 40 mg 6-12 years and 100 mg ≥12 years/ 4 weeks, SC |
| **Dupilumab** | Anti-IL-4Ra<br>Severe type 2 asthma | ≥ 6 years | | Eosinophilia ≥ 150/µL on 2 blood tests within a year, associated with FeNO ≥ 25ppb<br>Severe corticosteroid-dependent asthma ≥12 years | ≥ 12 years: 600 mg first injection, then 300 mg every 2 weeks<br>6-11 years and weighing between 15 and 60 kg: 300 mg every 4 weeks |

SC: subcutaneous.

of first times in an inpatient setting with monitoring of cardio-respiratory parameters for a few hours. It is injected subcutaneously into the outer arm by a third party. It can also be injected into the abdomen or the thigh. The reimbursement agreement will be valid for 4 to 6 months initially, and will be renewed for one-year periods thereafter. Table 2 summarises all the elements to be considered. If there is no significant response to treatment, it should be discontinued (6). There are few data on discontinuation of treatment. A discontinuation trial may be discussed after 3 years for Omalizumab. In case of relapse, the biological therapies can be restarted. In the real-life study by Deschildre et al., out of 100 patients, treatment could be stopped in 27 children after 25 to 86 months without relapse. Eight other patients had a recurrence of symptoms when omalizumab was stopped and had to be restarted (18).

## Conclusion

The management of severe asthma in children and adolescents can be a therapeutic challenge. Patients with difficult to control or severe asthma should be referred to an expert centre. A better understanding of immune mechanisms has led to the development of targeted therapies to improve disease control when asthma symptoms persist despite maximum-dose inhaled corticosteroids combined with another molecule. Three molecules currently benefit from social security intervention in Belgium in children: omalizumab, mepolizumab and dupilumab. Omalizumab remains the best studied compound in children. Further randomised paediatric studies are needed to better define the role of biological therapies in the treatment of childhood asthma, and to determine cost-effectiveness, remission of disease and criteria for discontinuation of treatment, as well as indications for switching from one product to another. The choice of biological therapies should always be judicious and be discussed in a multidisciplinary meeting.

## Conflict of interest

The authors declare that they have no conflicts of interest.

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# Skin care interventions in infants for preventing eczema and food allergy

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## Keywords

Skin care ; Eczema ; Food allergy.

## Questions

What are the effects of skin care interventions such as emollients in infants for the primary prevention of eczema and food allergies?

## Context

Eczema and food allergies are both common health issues that typically begin during the first year of life and they often co-occur. Eczema is a chronic inflammatory skin condition which results in dry, cracked and itchy skin. IgE-mediated food allergy have well-characterized symptoms ranging from minor oral and gastrointestinal symptoms, urticaria, angioedema to more severe symptoms such as anaphylaxis, which occasionally results in death. Symptoms usually occur within two hours of ingesting the food. Both eczema and IgE-mediated food allergy are associated with genetic variations that damage skin barrier functions. It is, however, unclear if trying to prevent or reverse an impaired skin barrier at an early age is effective for preventing eczema or food allergy.

Emollients, lipid based products that smooth the skin, are one of the staples in treatment of established eczema as dry skin is one the key symptoms. Moisturizers, which provide water and moisture to the skin, are also often used. Since skin barrier dysfunction is often seen before the development of eczema, using moisturizers or emollients could possibly offer a route to eczema and maybe even food allergy prevention. This review therefore assessed the effects of all skin care interventions aimed at preserving, or limiting damage to, the skin barrier and enhancing skin hydration (1).

## Criteria for study selection

The review included studies that assessed skin care interventions that could potentially enhance skin barrier function, reduce redness, or reduce subclinical inflammation in healthy term (>37 weeks) infants (≤12 months) without pre-existing eczema, food allergy or other skin conditions. These included moisturizers and/or emollients; bathing products; advice regarding reducing soap exposure and bathing frequency; and using water softeners. The randomized controlled studies compared these skin care interventions with standard care or no treatment. The two main outcomes were an eczema diagnosis or Ig-E mediated food allergy by 1 to 3 years of age.

## Summary of the results

In total, the authors identified 33 studies with 25827 participants of which 17 studies with 5823 infants reported on one of the relevant outcomes. Most studies randomized infants to age three weeks to receive a skin care intervention or the standard infants skin care. Intervention duration and follow-up ranged from 24 hours to three years. Of the 17 studies reporting on the prespecified outcomes, 13 used emollients.

Skin care interventions during infancy probably have little to no effect on the risk of eczema diagnosis by 1 to 3 years (standard care: 150 infants per 1000 vs skin care intervention: 155 infants per 1000 (95% CI : 122-197); 7 studies, 3075 infants, moderate-certainty evidence) or the time to onset of eczema (standard care: 24 months vs skin care intervention: 27.9 months (95% CI: 21.1-36.9); 9 studies, 3349 infants, moderate-certainty evidence. Skin care interventions may increase the risk of IgE-mediated food allergy (via oral food challenge) by 1 to 3 years (standard care: 50 infants per 1000 vs skin care intervention: 127 infants per 1000 (95% CI: 50-335); 1 study, 976 infants, low-certainty evidence), but may have little to no effect on the risk of allergic sensitization (via skin prick) by 1 to 3 years (standard care: 90 infants per 1000 vs skin care intervention: 95 infants per 1000 (95% CI: 58-154); 3 studies, 1794 infants, low-certainty evidence). Skin care interventions may slightly increase the parent report of an immediate reaction to a common food allergen at 2 years (low-certainty evidence), but this is only seen for cow's milk which is possibly unreliable due to the overreporting of milk allergy in infants. Skin care interventions in infancy probably increase the risk of skin infections over the intervention period (standard care: 50 infants per 1000 vs skin care intervention: 67 infants per 1000 (95% CI: 51-88); 6 studies; 2728 infants, moderate-certainty evidence). It may also increase the risk of infant slippage over the intervention period (low-certainty evidence) and stinging/allergic reactions to moisturizers (low-certainty evidence), however these effects vary and it is also be possible that skin care interventions make little to no difference and even reduce slippages and sting/allergic reactions.

Subgroup analysis showed that age, hereditary risk, filaggrin (FLG) mutation, duration of intervention, and classification of intervention type did not affect the risk of developing eczema. These analyses could not be performed for food allergy risk. It is unclear whether adherence to treatment affects the relationship between skin care interventions and risk of developing eczema or food allergy.

## Conclusion

Based on low- to moderate-certainty evidence, skin care interventions such as emollients during the first year of life in healthy infants probably do not influence the development or time to onset of eczema in healthy-term infants by age one to three; may increase risk of food allergy; and probably increase risk of skin infection.

## Implications for practice

Regular use of emollients or other skin care interventions is most likely not beneficial in healthy infants to decrease risk of eczema or food allergy, however there could be other reasons for using these products. As the use of these products probably increases skin infections, it may be important for caregivers to practice appropriate hygiene measures when applying the products to the infants' skin.

CI: confidence interval

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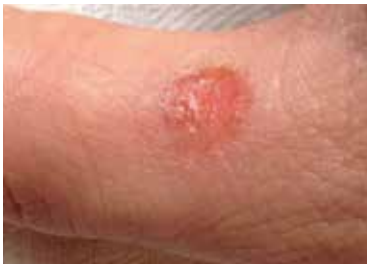

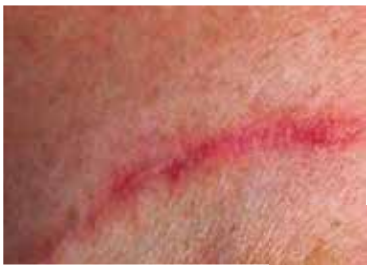

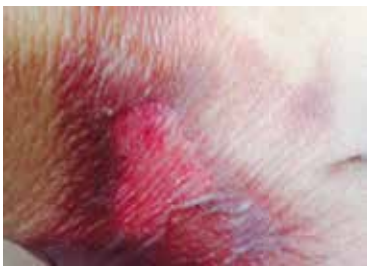

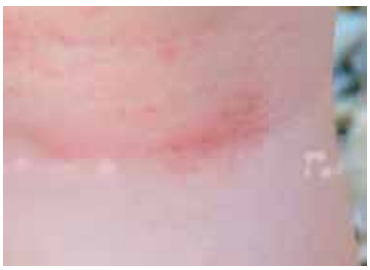

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# Study of airway inflammation as a result of external triggers inducing epithelial cell damage in non-allergic asthma and exercise-induced bronchoconstriction

PhD thesis presented on June 27th, 2023 at KU Leuven, Leuven, Belgium

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## Keywords

Adolescent ; Bronchoconstriction ; Mast Cells ; Asthma ; Athletes ; Inflammation.

In this thesis the impact of external triggers on airway inflammation was investigated, with a focus on adolescent athletes and individuals with asthma. The study explores the complex relationship between airway epithelium, immune cells and bronchoconstriction, particularly in the context of mast cell activation regarding the underlying mechanism. Additionally, it examines exercise-induced bronchoconstriction (EIB) and the influence of environmental factors on airway health in athletes.

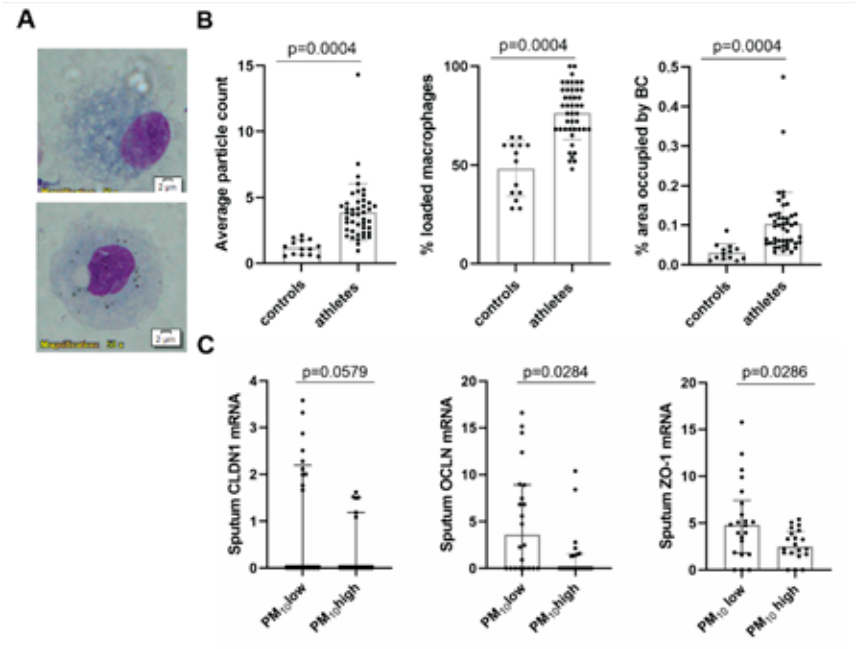
Human airways are continuously exposed to external triggers trough breathing, which can initiate epithelial damage. This may induce an inflammatory response, resulting in bronchoconstriction. It is known that in asthma, which is an heterogenous disease characterized by reversible airway obstruction, there is a complex interaction between airway epithelium and immune cells in the initiation and continuation of airway inflammation. As mast cells are located close to the airway epithelium, we hypothesize they are critical in mediating this response. Released mast cell mediators via both IgE-dependent and IgE-independent mast cell activation are able to induce bronchoconstriction. The role of the newly described Mas-related G-protein coupled receptor member X2 (MRGPRX2) in this cascade is not fully understood (1). Furthermore, the thesis addresses the occurrence of bronchoconstriction in otherwise healthy individuals, a phenomenon known as EIB. Athletes, in particular, face an elevated risk of EIB, with factors such as the intensity of sporting activities and external triggers like cold air in cross-country skiing or chlorine by-products in swimming contributing to its development (2). Even adolescent athletes embarking on their professional careers are susceptible to EIB, underscoring the need for better identification and management of this condition among them (3, 4).

The main objective of this thesis was to study airway inflammation as a result of external triggers inducing epithelial damage. We hypothesize that adolescent athletes, due to their heightened ventilation rates, are more vulnerable to external triggers, which might act as stressor to the airway barrier. The research is structured around three main objectives: first, studying atopy and EIB in intense adolescent athletes; second, delving deeper into the impact of external stimuli on the airways of elite adolescent athletes and asthmatics; and finally, examining the central role of mast cells in airway inflammation.

Atopy has been significantly associated with bronchial hyperreactivity and EIB in adult elite athletes (5). Therefore, a screening tool may help with the early identification of atopy and allergy symptom development, which may impact physical performances in adolescent athletes. An Allergy Questionnaire for Athletes (AQUA©) score of ≥ 6 and fractional exhaled nitric oxide (FeNO) levels of ≥ 15 ppb were identified as prediction tool for EIB in adolescent elite athletes (12-18 years) (6, 7). These results were confirmed in recreational athletes performing at least 12 hours of sport a week (12-18 years). These results showed the presence of atopy in approximately 40% of adolescent athletes in both cohorts, which is higher than in the general population. Furthermore, 14% of recreational athletes reported previous asthma diagnosis and 22% tested positive for EIB. Of these EIB+ athletes, 76% of athletes did not receive a prior asthma diagnosis, which is often used interchangeably in real life practice. These results indicate the need to better identify EIB in adolescent athletes. Investigating different factors linked to EIB, the highest sensitivity was found for AQUA© ≥ 6 and highest specificity was found for reporting wheeze during exercise. Furthermore, previous asthma diagnosis was associated with outdoor athletes, highlighting the impact of the environment during intense exercise. Serum levels of epithelial damage biomarkers were not able to differentiate EIB+ and EIB- athletes, but were associated to training type, training intensity and EIB severity.

Secondly, an in-depth exploration of the effect of external stimuli on the airways of elite adolescent athletes and asthmatics was performed. The effect of intense exercise and environmental exposure to air pollution

**Figure :** Adapted from Goossens et al. Thorax 2023 (8). (A) Illustration of images captured for analysis showing airway macrophages stained by diff-Quick with increasing black carbon load. (B) The average particle count per macrophage, percentage of loaded macrophages, and the percentage area occupied by black carbon for each participant was calculated by a blinded researcher. For each participant 25 macrophages were counted. (normality confirmed, unpaired t-test with Welch's correction). (C) Effect of PM10 on tight junction expression of claudin 1 (CLDN1), occludin (OCLN) and Zonula occludens (ZO-1). (Mann-Whitney)




on the airways of adolescent elite athletes was investigated. Indeed, RNA-Seq analysis of sputum transcriptome showed significantly differentially expressed genes in athletes compared with controls, which were related to inflammation and epithelial cell damage (8). In addition, sputum samples of athletes contained significantly more carbon loaded airway macrophages compared with controls (figure 1A,B), likely the result of their high ventilatory demands during exercise. In addition, significantly lower mRNA levels of OCLN and ZO-1 in athletes exposed to higher particulate matter ≤10µm (PM10) levels compared with athletes exposed to lower levels were observed (figure 1C). Remarkably, the airway response to eucapnic voluntary hyperpnoea (EVH) testing in athletes was associated to prior PM exposure, indicating that exposure to increased air pollution may induce short term increased airway hyperreactivity. Our preliminary RNA-Seq analysis between EIB+ and EIB- athletes suggested a role of epithelial damage, oxidative stress and (neuro)inflammation in EIB. A retrospective analysis was performed of environmental exposures of patients with asthma, including smoking and work-related exposures. Increased epithelial damage in asthmatic patients compared with healthy controls was demonstrated, suggesting that they might be more vulnerable for external triggers. We indeed found significant differences amongst sputum transcriptome of asthmatics exposed to cigarette smoke or work-related exposure to cleaning products compared with asthmatic patients without exposure. A role for the aryl hydrocarbon pathway (AhR) for airway inflammation in asthmatic patients exposed to irritants was suggested.

Lastly, the involvement of mast cells in non-IgE mediated airway inflammation was investigated. In this thesis, a pilot study was performed in asthmatic patients compared with healthy controls to characterize MRGPRX2 expressing mast cells in sputum samples. Sputum mast cells were increased in allergic asthmatic patients compared with controls. However, also increased mast cell activation was observed in non-allergic asthma. MRGPRX2 expression was not associated with allergic or non-allergic asthma phenotype. Furthermore, neuromediator Neurokinin A (NKA) correlated positively with the percentage of mast cells and negatively with FEV1/FVC. These results suggested a role for mast cells in neuro-immune reaction for both allergic and non-allergic asthma patients. To better investigate this role of the mast cell, a human mast cell differentiation protocol was optimized to obtain functional MRGPRX2 expressing mast cells. Stimulation of mast cells with substance P resulted in increased CD63 expression and the classical inhibitor ketotifen was able to inhibit this activation. The optimized in vitro model can be used to explore the role of mast cells in especially MRGPRX2 mediated activation and as screening tool for potential therapeutics.

In conclusion, this research underscores the increased vulnerability of intense adolescent athletes to environmental triggers and epithelial damage. It emphasizes the need for robust screening tools to monitor and identify athletes at risk of EIB. Moreover, the impact of external triggers on the airways extends to asthmatic individuals, where the involvement of non-IgE mediated mast cell activation is proposed. The development of research tools for investigating MRGPRX2-mediated activation holds promise for future studies and therapeutic advancements in this area.

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# ENTEROL® 250 mg

*Saccharomyces boulardii* CNCM I-745

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| 10 | 10,32 € | 10 | 10,32 € | 10 | 10,32 € |
| 20 | 19,36 € | 20 | 19,36 € | 20 | 19,36 € |
| 50 | 38,96 € | | | | |


BIOCODEX

INFORMATIONS ESSENTIELLES. DENOMINATION DU MEDICAMENT Enterol 250 mg, poudre pour suspension buvable. Enterol 250 mg, gélules. *Saccharomyces boulardii* CNCM I-745 COMPOSITION QUALITATIVE ET QUANTITATIVE Enterol 250 mg, poudre pour suspension buvable : Chaque sachet-dose de poudre pour suspension buvable contient 250 mg de *Saccharomyces boulardii* CNCM I-745 sous forme lyophilisée (soit au minimum 6 x $10^9$ cellules reviviscentes au moment de la fabrication et 1 x $10^9$ cellules lyophilisées reviviscentes à la date de péremption). Enterol 250 mg, gélules : Chaque gélule contient 250 mg de *Saccharomyces boulardii* CNCM I-745 sous forme lyophilisée (soit au minimum 6 x $10^9$ cellules reviviscentes au moment de la fabrication et 1 x $10^9$ cellules lyophilisées reviviscentes à la date de péremption). Excipient(s) à effet notoire (voir rubrique 4.4 du RCP) : Enterol 250 mg, poudre pour suspension buvable : fructose, lactose monohydraté, sorbitol. Enterol 250 mg, gélules : lactose monohydraté. Pour la liste complète des excipients, voir rubrique 6.1 du RCP. FORME PHARMACEUTIQUE Enterol 250 mg, poudre pour suspension buvable : Poudre pour suspension buvable. Enterol 250 mg, gélules : Gélule. DONNEES CLINIQUES Indications thérapeutiques • Prévention de la diarrhée associée à l'antibiothérapie à large spectre chez des sujets prédisposés à développer une diarrhée à *Clostridium difficile* ou rechute de diarrhée à *Clostridium difficile*. • Traitement des diarrhées aiguës chez les enfants jusqu'à 12 ans, en complément de la réhydratation orale. Posologie et mode d'administration Posologie : Adulte : 2 à 4 gélules ou 2 à 4 sachets-doses par jour, en 2 prises. Population pédiatrique. Enfant : 2 gélules ou 2 sachets-doses par jour, en 2 prises. Mode d'administration : Gélules : avaler avec un peu d'eau. Sachets-doses : diluer la poudre dans un verre d'eau. Précautions à prendre avant la manipulation ou l'administration du médicament En raison d'un risque de contamination aéroportée, les sachets ou gélules ne peuvent pas être ouverts dans les chambres des patients. Les professionnels de la santé doivent porter des gants durant la manipulation de probiotiques en vue de leur administration, puis les jeter immédiatement après usage et se laver les mains avec soin (voir rubrique 4.4 du RCP). Durée du traitement : Prévention des récurrences ou rechute de diarrhée à *Clostridium difficile* : 4 semaines. Traitement de la diarrhée en complément à la réhydratation orale chez l'enfant : 1 semaine. Contre-indications • Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP. • Patients porteurs d'un cathéter veineux central, patients dans un état critique ou immunodéficients en raison du risque de fongémie (voir rubrique 4.4. du RCP). • Allergie aux levures, spécialement *Saccharomyces boulardii* CNCM I-745. Effets indésirables Les effets indésirables sont classés ci-dessous par système-organe et par fréquence comme définies ci-après : très fréquents (≥ 1/10), fréquents (≥ 1/100, < 1/10), peu fréquents (≥ 1/1.000, < 1/100), rares (≥ 1/10.000, < 1/1.000), très rares (< 1/10.000), fréquence indéterminée (ne peut être estimée sur la base des données disponibles). Classes de systèmes d'organes Fréquence Infections et infestations Très rares : Fongémie chez des patients porteurs d'un cathéter veineux central, et chez des patients dans un état critique ou immunodéficients (voir rubrique 4.4 du RCP), mycose à *Saccharomyces boulardii* CNCM I-745. Fréquence indéterminée : Sepsis chez les patients de réanimation ou immunodéprimés (voir rubrique 4.4 du RCP) Affections du système immunitaire Très rare : choc anaphylactique. Affections vasculaires Très rare : choc anaphylactique. Affections respiratoires, thoraciques et médiastinales Très rare : dyspnée. Affections gastro-intestinales. Très rares : constipation, épigastralgies, météorisme abdominal (épigastralgies et météorisme abdominal ont été observés lors d'études cliniques). Affections de la peau et du tissu sous-cutané. Très rares : prurit, exanthème, Œdème de Quincke. Troubles généraux et anomalies au site d'administration. Très rares : soif. Déclaration des effets indésirables suspectés La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration (Belgique : www.notifieruneffetindesirable.be, adr@afmps.be; Luxembourg : www.guichet.lu/pharmacovigilance). TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE BIOCODEX Benelux NV/SA - Square Marie Curie 20 - 1070 Bruxelles - Belgique - Tél : 0032(0)23704790. NUMERO(S) D'AUTORISATION DE MISE SUR LE MARCHE Enterol 250 mg, poudre pour suspension buvable : BE269026. Enterol 250 mg, gélules en flacon en verre : BE269035. Enterol 250 mg, gélules en plaquette: BE397896. MODE DE DELIVRANCE Délivrance libre DATE DE MISE A JOUR DU TEXTE Mise à jour : 01/2023. Approbation : 03/2023.

2023_ENT_HCP_007

# Trapped fourth ventricle
# Case report and narrative review

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## Keywords

Isolated fourth ventricle ; Trapped fourth ventricle ; Fourth ventricular shunting ; Endoscopic procedures ; Paediatric Neurosurgery ; Post-haemorrhagic hydrocephaly ; Post-infectious hydrocephaly ; Prematurity ; Neonate ; Case report.

## Abstract

A trapped fourth ventricle is a rare complication following successful shunting of cerebrospinal fluid from the lateral ventricles in patients with acquired post-haemorrhagic or post-infectious hydrocephalus. Inadequate drainage combined with ongoing cerebrospinal fluid production leads to progressive enlargement of the fourth ventricle with compression of surrounding anatomical structures. We present the case of a four-month-old girl born extremely prematurely at 25 weeks with bilateral intraventricular haemorrhage whose management was complicated by the rare combination of trapped fourth ventricle and subsequent multiloculated posterior fossa hydrocephalus, presenting a neurosurgical dilemma.

## Introduction

In 2020, approximately 7% of newborns in Flanders were born premature (gestational age less than 37 weeks), of which 1% was born very preterm (gestational age between 28 and 32 weeks) or extremely preterm (gestational age less than 28 weeks) (1). Despite considerable advances in perinatal and neonatal care, complications still occur, including the development of intraventricular haemorrhage (IVH) in 20 to 25% of very low birth weight (<1500 grams) infants, of which 15% is complicated by a parenchymal haemorrhagic infarction (PHI). In 25%, IVH is followed by progressive post-haemorrhagic ventricular dilatation (PHVD) of which 35% will require surgery (2). The management of these conditions is a major challenge for families, neonatologists and the health care system as a whole.

We present the case of a four-month-old girl, born extremely prematurely at 25 weeks with progressive PHVD and lateral ventricular shunting, complicated by the development of a trapped fourth ventricle (TFV) and subsequent multiloculated posterior fossa hydrocephalus after multiple neurosurgical interventions, posing a management dilemma. A comprehensive review of the literature on the current understanding of the pathophysiology, diagnosis and treatment of a TFV is provided.

## Case report

The patient was born extremely prematurely at 25 weeks and 2 days with a birth weight of 740 grams and quickly presented with respiratory distress syndrome requiring intubation for surfactant replacement therapy. She had multiple other complications, including left-sided pneumothorax, prolonged intubation evolving into mild bronchopulmonary dysplasia, late-onset sepsis, spontaneous bowel perforation requiring a temporary double-barrelled ileostomy and retinopathy of prematurity treated with intravitreal injection and laser therapy. In addition, there were significant neurological complications, which prompted the writing of this case report. On the second day postpartum, a bilateral grade 3 IVH of germinal matrix origin with venous infarction in the left terminal vein area occurred. This was complicated by the development of bilateral PHVD, and the formation of left-sided porencephalic cysts (Figure 1). A Rickham® ventriculostomy reservoir was initially placed in the right lateral ventricle to evacuate CSF. Three weeks later, ventriculostomy-associated ventriculitis was suspected and treated with antibiotics. One month after the initial operation, a second Rickham® reservoir had to be placed in the left ventricle due to progressive dilatation of the left ventricle. Serial transcranial ultrasound scans revealed the development of a TFV (35 mm in height and 20 mm in anteroposterior diameter) at the age of four months.

**Figure 1**: brain MRI showing bilateral post-haemorrhagic ventricular dilatation and formation of left sided porencephalic cysts.

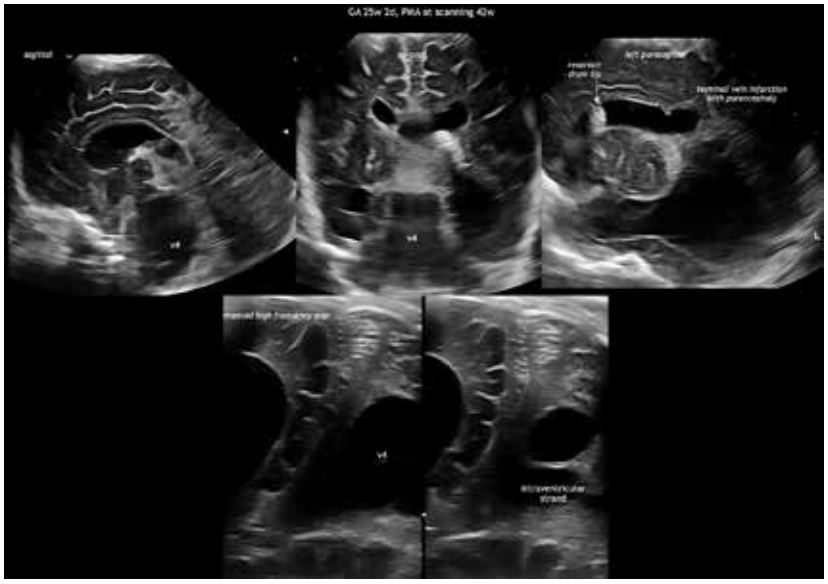

**Figure 2**: brain MRI showing dislocation of the Ommaya® catheter and septation dividing the fourth ventricle into two isolated cysts with consequent brainstem compression.

This appeared to progress rapidly over two days with significant mass effect on the cerebellum and brainstem, leading to clinical deterioration with poor feeding, somnolence and bradycardia. Urgent decompression was achieved by performing an endoscopic fourth ventriculostomy with insertion of another Rickham® reservoir. The operation was successful and in a second stage, the three ventricular reservoirs were replaced by two ventriculoperitoneal shunts (VPS): a Y-shaped branched VPS to divert CSF from the lateral ventricles and another VPS to drain the fourth ventricle. Clinical improvement was observed and ventricular size remained stable on repeated ultrasound scans. On postoperative day 8, recurrent entrapment of the fourth ventricle occurred as consequence of Escherichia coli ventriculitis. Both VPS were immediately removed and replaced with three intraventricular Ommaya® reservoirs which provided adequate decompression.

However, since the last surgery, neurological function had not fully recovered and our patient had persistent axial hypotonia and poor feeding, corresponding to persistent dilatation of the fourth ventricle on ultrasound imaging. One month post-operatively, a brain MRI showed dislocation of the Ommaya® catheter and septation dividing the fourth ventricle into two isolated cysts with consequent brainstem compression (Figure 2). Further neurosurgical intervention was imminent and consisted of removal of the Ommaya® reservoirs and placement of new VPS: a Y-shaped branched VPS for the lateral ventricles and a second multi-perforated VPS for the fourth ventricle cysts. The MRI was repeated one week post-operatively and showed that the fourth ventricular cystic lesions had increased in number and size, with significant pressure on the brainstem and supratentorial extension towards the midbrain (Figure 2). There was an imminent risk of fatal brain herniation if left untreated, and it was decided to perform endoscopic fenestration of the posterior fossa cysts by bilateral ventriculostomy. The neurological status improved postoperatively, but MRI showed further expansion of the posterior fossa cysts with increased transtentorial herniation.

Following multidisciplinary consultation, it was agreed that our patient was unlikely to benefit from further surgical intervention given the increasing surgical complexity, extensive medical history and poor prognosis in terms of severe developmental delay. In consultation with the parents, palliative care was provided to minimise suffering. Twenty days later, aged 4 months, she died in hospital.

Informed consent was obtained from both parents to publish this case report.

## Literature review and discussion

### *Pathophysiology*

TFV, also known as 'isolated fourth ventricle', 'encysted fourth ventricle' and 'double compartment hydrocephalus', is a rare complication following lateral ventricle shunting in patients with acquired post-haemorrhagic or post-infectious hydrocephalus. TFV develops when the shunting system fails to drain the fourth ventricle (3-7).

The primary site of CSF production is the choroid plexus of the ventricles of the brain. CSF flows through the ventricular system from the lateral ventricles to the third ventricle through the foramen of Monro. From here it continues through the aqueduct of Sylvius to the fourth ventricle and then enters the subarachnoid space through the lateral apertures of Luschka and the median aperture of Magendie. Obstruction of the inlet (aqueduct of Sylvius) and three outlets (the paired lateral apertures of Luschka and the median aperture of Magendie) of the fourth ventricle isolates the fourth ventricle from the ventricular system and the subarachnoid space, resulting in TFV. The continued production of CSF causes progressive enlargement of the fourth ventricle with compression of surrounding anatomical structures (brainstem, cranial nerves, cerebellum, central canal of the spinal cord) and increased intracranial pressure (4-6).

TFV is most commonly secondary to the placement of a VPS for the treatment of congenital or acquired hydrocephalus. Dandy-Walker and Arnold-Chiari malformations are the main causes of congenital hydrocephalus associated with the development of TFV (8). Subarachnoid or intraventricular haemorrhage (IVH) and infections (bacterial/fungal meningitis/ventriculitis, VPS infection and cysticercosis) are the main causes of acquired hydrocephalus associated with the development of TFV (9-11). The incidence of TFV in shunted patients has been reported to be 2-3% (7).

The pathophysiological mechanisms of TFV secondary to acquired hydrocephalus are complex and multifactorial. The main mechanism is the onset of inflammation of the ependyma (ependymitis) and subarachnoid space (arachnoiditis) due to haemorrhage and/or infection, leading to fibrosis of the surrounding structures. When the ventricular system is decompressed following shunt placement, adhesions may form at the level of the ventricles and the cerebral aqueduct as a result of chronic ependymitis, leading to occlusion of the aqueduct. Impaired CSF absorption at the level of the arachnoid villi and obliteration of the foramina of Luschka and Magendie are consequences of chronic arachnoiditis. Blood products and cellular debris from haemorrhage and infection may contribute to obstruction of the cerebral aqueduct and foramina. Repeated revisions and manipulations contribute to the overall inflammation (3-6, 10-13). It has also been suggested that 'overdrainage' after shunt placement causes a reduction in supratentorial pressure relative to infratentorial pressure, resulting in upward displacement of midline cerebellar structures into the tentorial incisura. This results in a distortion of the cerebral aqueduct with impaired cerebrospinal fluid flow (3, 5, 11, 13).

In addition, the presence of cellular debris and chronic ependymitis may induce the formation of fibrous adhesions leading to intraventricular septations, creating one (uninoculated) or more (multiloculated) non-communicating fluid-filled compartments, known as multiloculated hydrocephalus, which may occur at different levels of the ventricular system. It is a dynamic disorder with the development of new septae due to hydrodynamic changes and new membrane formation (14, 15).

### *Diagnosis*

TFV usually presents as a sudden clinical deterioration after an initial period of improvement following successful lateral ventricle shunting,

most commonly in patients with post-haemorrhagic or post-infectious hydrocephalus. The time between shunting of the lateral ventricles and the presentation of TFV ranges from 1 month to 12 years (7, 16, 17). In our case, the interval between placement of the first Rickham® ventriculostomy reservoir and diagnosis of TFV was 102 days. A wide variety of symptoms and signs are reported, all related to increased intracranial pressure and compression of surrounding anatomical structures, resembling posterior fossa syndrome. Clinical signs depend on the age of presentation and range from irritability, lethargy, apnoea, spontaneous bradycardic episodes, vomiting, poor feeding, full to bulging anterior fontanel and increasing head circumference in neonates and infants to headache, ataxia and growth failure in older children. Tonic seizures, progressive spasticity, dysconjugate eye movements and cranial nerve palsies (third and sixth cranial nerve palsies) have also been reported (3-7). Clinical diagnosis may be complicated by pre-existing neurological deficits such as developmental delay, cerebral palsy and epilepsy (6, 10). Delayed diagnosis can lead to severe neurological impairment and death (4, 18). Approximately 15% of patients are asymptomatic with an incidental finding of TFV on neuroimaging during follow-up, as was the case in our patient (13). Repeat cerebral ultrasound revealed TFV, which was asymptomatic at the time. However, it appeared to be rapidly progressing with significant mass effect on the cerebellum and brainstem visible on MRI imaging, which subsequently led to clinical deterioration with poor feeding, somnolence and bradycardia.

The problem of discrepant dilatation is often detected by cranial ultrasound and confirmed by magnetic resonance imaging (MRI). The diagnosis is made when an enlarged 'ballooned' fourth ventricle is seen, often accompanied by membranous occlusion of the cerebral aqueduct and compression of the surrounding structures with effacement of the cerebellar tissue, flattening of the posterior aspect of the brainstem and reduced CSF in the prepontine cistern caused by ventral displacement of the brainstem (7, 19). In addition, MRI can be used to differentiate between a TFV, shunt malfunction and cystic lesions. Treatment decisions are based on the size of the lateral ventricles (slit or wide), the length of the aquaeductal stenosis (short or long), compression of the brainstem and cerebellum, and herniation through the tentorial notch on preoperative imaging (16, 20).

### *Treatment*

Asymptomatic TFV with or without brainstem compression is usually treated conservatively without surgery, but, in some cases, with progressive brainstem compression surgery is to be considered (13). Symptomatic TFV requires surgery (20). The optimal surgical treatment has not yet been determined because, for obvious reasons, randomised studies on this topic are not available. The available surgical options are fourth ventricular shunt procedures, endoscopic procedures and a suboccipital craniectomy with outlet fenestration (18, 20).

Fourth ventricular shunts (FVS) are considered the mainstay of treatment to drain the TFV. The catheter can be connected to the existing lateral ventricle shunt with a Y-connector or to a separate system. FVS has a high risk of complications, including shunt malfunction (obstruction, disconnection), infection, intra-cystic haemorrhage, reversible and rarely irreversible cranial nerve dysfunction, fourth ventricle flour injury and brainstem injury (18, 20). Approximately 40% require shunt revision within one year of initial placement (21). In our patient, it was decided to first perform an urgent life-saving decompression through endoscopic fourth ventriculostomy with placement of a Rickham® reservoir, which was later replaced by a ventriculoperitoneal shunt draining the fourth ventricle. To date, there are insufficient case reports to compare the risk of TFV for shunts and reservoirs. Both techniques by definition reduce the flow through the aqueduct and, in reducing the size of the third ventricle, may predispose to adhesions of denuded and infected ventricular walls. Reservoir puncture causes intermittent changes in ventricle size and cerebrospinal fluid flow, in contrast to contrary to the continuous effect of a shunt. This intermittent effect would not theoretically increase the risk of TFV. Shunt complications that were encountered in our case included ventriculoperitoneal shunt infection and ventriculitis, followed by improper CSF drainage due to shunt malfunction requiring shunt revision surgery.

Due to the high complication rate of FVS and advances in endoscopy, other treatment options are now available (22). Endoscopic procedures include aqueductoplasty with or without stent placement (trans frontal trans-third ventricle or suboccipital approach), third or lateral interventriculostomy with or without stent placement (translateral ventricle approach) and fenestration of the obstructed aqueduct with stent placement (trans foramen of Magendie approach). Aquaeductoplasty penetrates the membranous occlusion of the cerebral aqueduct, restoring communication and equalizing pressure between the infra- and supratentorial ventricular system (23). Due to the high risk of restenosis ranging from 39 to 73%, stent placement is recommended even if there is a history of infection (7, 16, 23, 24). The transfrontal trans-third ventricle approach is usually performed in the presence of ventriculomegaly, which is used to facilitate safe endoscopic navigation (20). If the lateral ventricles are well decompressed, the pre-existing VPS is externalised and the ventricles are gradually dilated, or a suboccipital approach is performed. It has been suggested in the to differentiate between short segment aquaeductal stenosis (< 5 mm on MRI) and long segment aqueductal stenosis (> 5 mm) to avoid stent complications, such as stent migration, infection, cranial nerve palsies (especially third and sixth cranial nerve palsies), Parinaud syndrome and brainstem injury. Short segment aqueductal stenosis is eligible for aqueductoplasty with stent placement and long segment aqueductal stenosis for FVS (20). A third interventriculostomy with or without stent placement may be considered in cases of cystic dilatation of the fourth ventricle with upward herniation through the tentorium and distorted ventricular anatomy with unidentifiable anatomical landmarks. The thinnest membranous barrier between the third and fourth ventricles is then perforated, with the risk of damaging the basilar artery and hypothalamus when perforating the third ventricular floor (22-25). Suboccipital craniectomy and microsurgical canalisation of the obstructed aqueduct and fenestration of the outlet membranes is considered in complicated patients or when other approaches have failed (19, 20).

The neurosurgical management of our case was particularly challenging due to the formation of multiple posterior fossa cysts secondary to intraventricular infection, defined as multiloculated hydrocephalus. The presence of compartmentalisation within the fourth ventricle system is extremely rare and may be the most difficult form of hydrocephalus to treat. There is a paucity of data on posterior fossa shunting in the neurosurgical literature, so there is no widely accepted surgical treatment. Cyst fenestration to restore communication between these isolated cystic compartments is the main strategy of treatment, yet the approach remains controversial. The strategy in our case was an initial shunt revision with insertion of a multi-perforated ventricular catheter. Unfortunately, this did not adequately drain the isolated posterior fossa cysts. Endoscopic surgery consisting was then performed with intraventricular septum fenestration, which was also unsuccessful. After enduring numerous shunt revisions with high morbidity, a multidisciplinary decision was made to offer palliative care.

## Conclusion

Advances in perinatal medicine have contributed to significant improvements in the survival of preterm infants. However, a significant number of these infants still suffer from disabling and life-threatening health conditions. The development of a trapped fourth ventricle was a major setback for our patient, who had previously been successfully for PHVD with lateral ventricle shunting. TFV develops when the fourth ventricle becomes isolated due to the occlusion of the inlets and outlets. Continued CSF production with progressive enlargement of the fourth ventricle leads to compression of the surrounding anatomical structures and increased intracranial pressure. Delayed diagnosis can lead to severe neurological impairment and death. Treatment options depend on a number of factors and include fourth ventricle shunting or endoscopic procedures. Neurosurgical management in this case was particularly challenging due to the formation of multiple posterior fossa cysts secondary to intraventricular infection. Early diagnosis of ventriculitis including close monitoring with high-resolution magnetic resonance imaging to detect multiloculated transformation and early treatment are key to a better prognosis.

## Conflict of interest

The authors report no conflict of interest.

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# Editorial Policy

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More than 6 authors: Bervoets L, Van Noten C, Van Roosbroeck S, Hansen D, Van Hoorenbeeck K, Verheyen E, et al. Reliability and Validity of the Dutch Physical Activity Questionnaires for Children (PAQ-C) and Adolescents (PAQ-A). Arch Public Health. 2014;72(1):47.

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Kanneganti P, Harris JD, Brophy RH, Carey JL, Lattermann C, Flanigan DC. The effect of smoking on ligament and cartilage surgery in the knee: a systematic review. Am J Sports Med [Internet]. 2012 Dec [cited 2013 Feb 19];40(12):2872-8. Available from: http://ajs.sagepub.com/content/40/12/2872 DOI: 10.1177/0363546512458223.

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*For an electronic book:* Shreeve DF. Reactive attachment disorder: a case-based approach [Internet]. New York: Springer; 2012 [cited 2012 Nov 2]. 85 p. Available from: http://dx.doi.org/10.1007/978-1-4614-1647-0.

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More examples of other published, particularly material from internet, and unpublished material can be found in the quick Vancouver reference guide (https://guides.lib.monash.edu/ld.php?content_id=48260115) or on the website of the U.S. National Library of Medicine: https://www.nlm.nih.gov/bsd/uniform_requirements.html.

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# SPA® REINE

## De rol van water in de ontwikkeling van de microbiota bij kinderen

**De darmmicrobiota van een baby beginnen zich al in de allereerste levensfase, in moeders buik, te ontwikkelen. Verschillende factoren bepalen de microbiële kolonisatie van de darm. Voeding en goede hydratatie van de baby spelen een belangrijke rol in de ontwikkeling van de microbiële gemeenschappen, die de gezondheid van het kind aanzienlijk beïnvloeden.[1,2]**

De darmmicrobiota vormen een complexe gemeenschap van meer dan 1500 soorten micro-organismen die in het maagdarmstelsel leven. De duizend eerste levensdagen zijn essentieel voor de ontwikkeling van het microbioom en het immuunsysteem van zuigelingen. De darmmicrobiota die worden opgebouwd in deze periode, zullen doorwerken in de gezondheid van de zuigeling voor de rest van zijn leven. De microbiële gemeenschap van het darmkanaal speelt in verschillende opzichten een belangrijke rol in het levensbegin en hebben een rechtstreeks effect op de gezondheid van de zuigeling. Zuigelingen die bepaalde soorten bacteriën missen (*Faecalibacterium, Lachnospira, Rothia* of *Veillonella*), hebben bijvoorbeeld een verhoogd risico op astma op de leeftijd van 1 tot 3 jaar.[1,3]

### *Voeding en microbiota van de baby[3]*

Moedermelk wordt beschouwd als de beste voedingsbron voor pasgeborenen, omdat ze de baby voorziet van alle voedingsstoffen die hij nodig heeft en veel biologisch actieve stoffen bevat. De melk is een bron van symbiotische bacteriën die de aanhechting van pathogenen voorkomen en de kolonisatie van het darmkanaal door nuttige micro-organismen stimuleren. Borstgevoede zuigelingen hebben dynamischere darmmicrobiota en een lagere incidentie van sommige ziekten, waaronder astma. Tegelijkertijd zouden de oligosachariden in de moedermelk de groei van nuttige micro-organismen in het darmstelsel van de zuigeling kunnen stimuleren.

### *Water, de vergeten voedingsstof van de darmmicrobiota?[4-6]*

**Water, dagelijks in grote hoeveelheden geconsumeerd, is een potentiële bron van darmmicrobiële diversiteit**. Toch is er weinig geweten over het effect van water op het darmmicrobioom.

Studies hebben aan het licht gebracht dat de samenstelling van het darmmicrobioom verschilt na het drinken van verschillende soorten drinkwater. In de loop van de ontwikkeling van het microbioom van kinderen correleert de consumptie van water (van verschillende oorsprong) met de signatuur van de darmmicrobiota. Dat wijst erop dat water een bepalende factor kan zijn in de verwerving van het microbioom. Voor volwassenen zijn er beperkte gegevens die wijzen op een verband tussen de bron van het geconsumeerde drinkwater en de samenstelling van de darmmicrobiota.

Een uitgebreid cohortonderzoek met meer dan 3.000 deelnemers heeft aangetoond dat het drinken van verschillende soorten water leidt tot verschillen in de samenstelling van de darmmicrobiota. Er werd vooral vastgesteld dat de darmmicrobiota van mensen die weinig water drinken, verschilt van die van mensen die veel water drinken ($p < 0,05$), met bovendien een grotere aanwezigheid van *Campylobacter*, een bacterie die maag-darminfecties veroorzaakt. De auteurs noemen als mogelijke mechanismen voor de interactie van drinkwater met microbiële gemeenschappen: de zuurtegraad van het water, de opgeloste stoffen en mineralen in het water, de intrinsieke natuurlijke microbiële gemeenschappen en de restchloor en bijproducten van desinfectie die nog aanwezig zijn in het meeste leidingwater.

Zeer recent heeft een studie op babymuizen aangetoond dat de hoeveelheid water die wordt geconsumeerd, ongeacht de mineralisatie van het water, een sleutelfactor is voor de goede ontwikkeling van het microbioom. Verder onderzoek is nodig, maar deze gegevens suggereren dat een goede hydratatie, met mineraalarm water, zoals aanbevolen voor zuigelingen, goed is om de ontwikkeling van de microbiota te optimaliseren.

**De darmmicrobiota zijn een essentiële factor voor de gezondheid, de groei en de ontwikkeling, en dat begint al vóór de geboorte. Talrijke factoren bepalen de totstandkoming van de microbiota** van een baby. Door juist te handelen kan het ontstaan van ideale, gezonde darmmicrobiota bevorderd worden. Er is echter nog veel onderzoek ter zake nodig, vooral om de rol van factoren waaronder de waterconsumptie door de moeder en het jonge kind beter te begrijpen.


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