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).

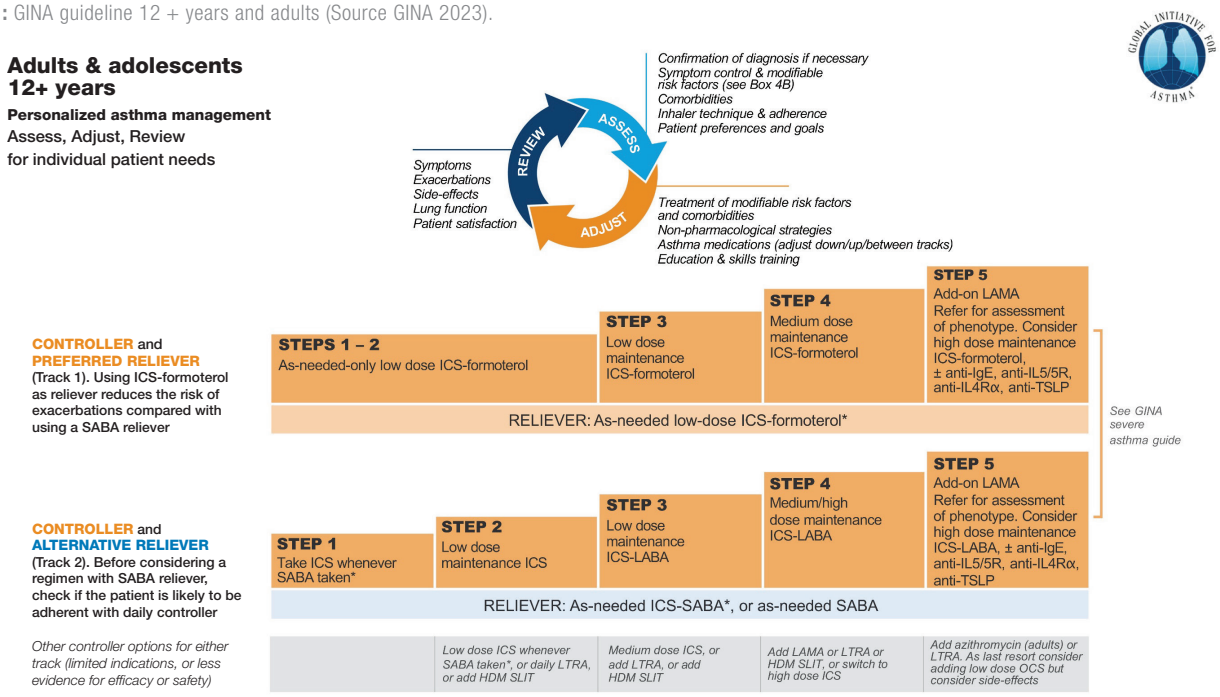
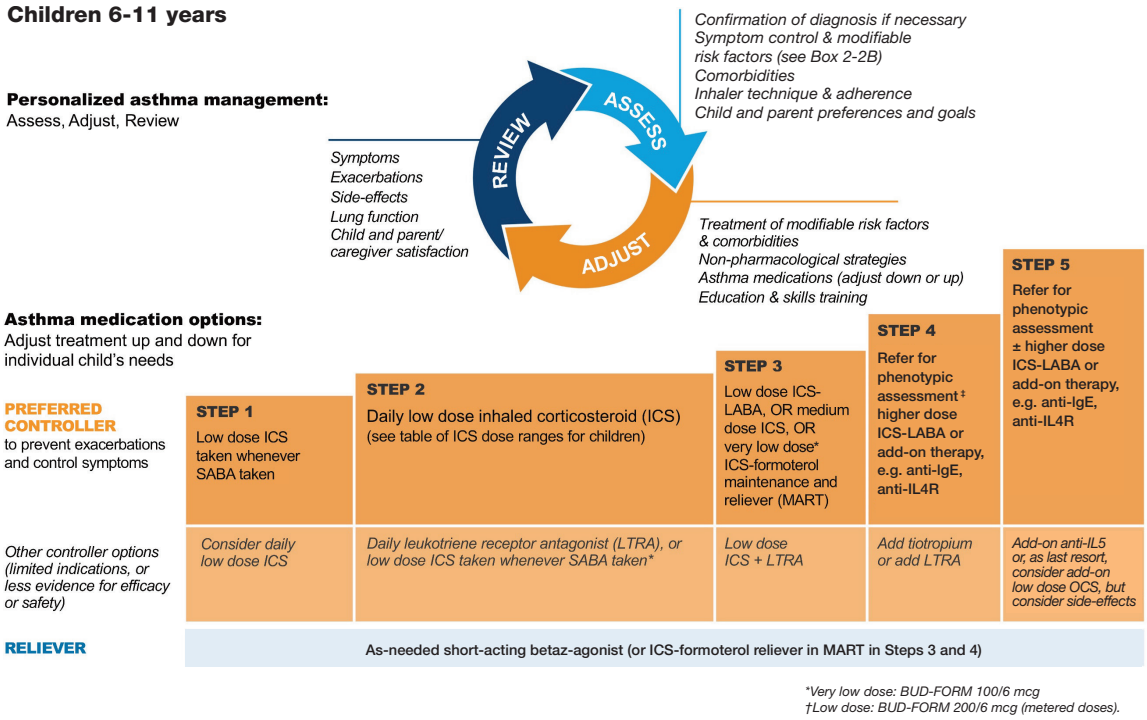


Figure 2: GINA guideline in children 6 - 11 year old (Source GINA 2023).



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 TH2 high allergic asthma	≥ 6 years	- Medication review by a pharmacist or specialist nurse or physiotherapist - Daily high dose inhaled corticosteroid therapy combined with a long acting beta2-mimetic +/- anti leukotriene or long-term general corticosteroid therapy - 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 Confirmation by prick test or RAST of perennial sensitisation 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 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 Severe type 2 asthma	≥ 6 years		Eosinophilia ≥ 150/µL on 2 blood tests within a year, associated with FeNO ≥ 25ppb Severe corticosteroid-dependent asthma ≥12 years	≥ 12 years: 600 mg first injection, then 300 mg every 2 weeks 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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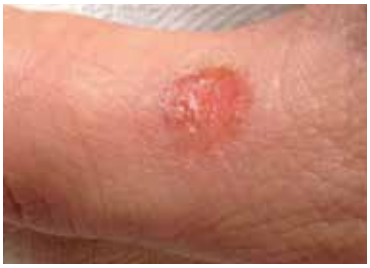
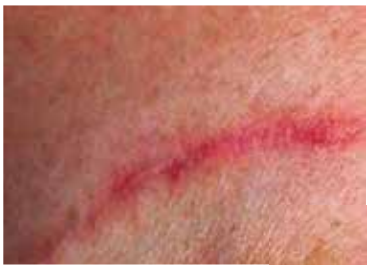


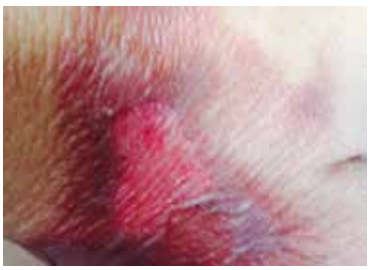
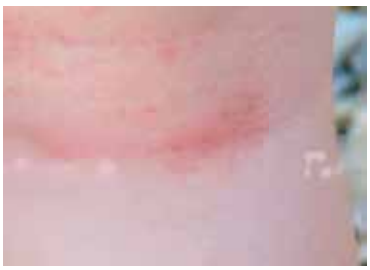

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Study of airway inflammation as a result of external triggers inducing epithelial cell damage in non-allergic asthma and exercise-induced bronchoconstriction

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.

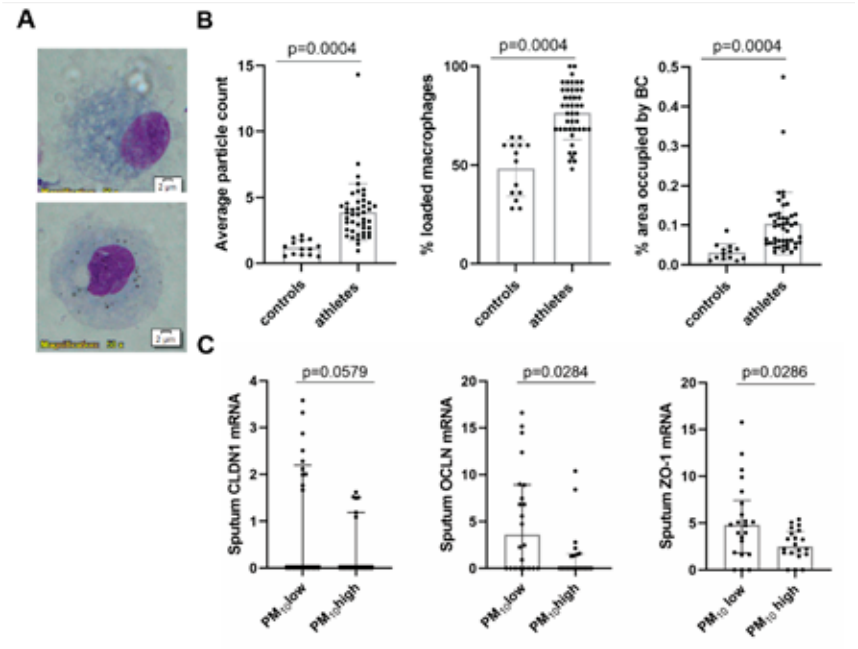
Human airways are continuously exposed to external triggers trough breathing, which can initiate epithelial damage. This may induce an inflammatory response, resulting in bronchoconstriction. It is known that in asthma, which is an heterogenous disease characterized by reversible airway obstruction, 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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