Belgian atopic dermatitis guidelines

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Abstract (144 words)

Atopic dermatitis (AD) is one of the most common, bothersome and difficult to treat skin disorders. Recent introduction of new systemic treatments has revolutionized the management of AD. The goal of this guideline is to provide evidence-based recommendations for the management of patients suffering from atopic dermatitis that easily can be implemented in clinical practice. These recommendations were developed by 11 Belgian AD experts. Comments of all experts on the proposed statements were gathered, followed by an online voting session. The most relevant strategies for the management of and treatment of AD in the context of the Belgian health care landscape are discussed. General measures, patient education and adequate topical treatment remain the cornerstones of AD management. For moderate to severe AD, the introduction of biologics and JAK inhibitors show unprecedented efficacy, although access is limited to a subgroup of patients meeting the reimbursement criteria.

Introduction (4936 words)

Atopic dermatitis (AD) is an inflammatory, pruritic, chronic or chronically relapsing skin disease occurring often in families with other atopic diseases (bronchial asthma and ⁄ or allergic rhinoconjunctivis. AD is one of the most common skin diseases, which affects up to 20% of children and 1–3% of adults in most countries of the world. Importantly, AD is often the first step in the development of other atopic diseases as rhinitis and⁄or asthma, a phenomenon termed « atopic march ». AD usually starts in infancy or early childhood and can persist or recur in adulthood. About 30% of cases arises after puberty.

Most AD-cases are mild, while less than 10% of patients suffer from severe disease. The percentage of severe cases seems higher in adults than children. In the diagnoses of AD several criteria have been established, which are most completely covered by the Hanifin en Rajka-criteria.(1) AD-pathophysiology is multifactorial and complex: Apart from strong genetic influence (80% concordance in monozygous twins, 20% in heterozygous twins), there is an immune deviation towards T helper 2 polarization of the immune system in the initiation phase with increased IgE production in about 2/3 of cases. Additionally, an impaired skin barrier function develops due to abnormal lipid composition in the skinim and deficient formation of epidermal structural proteins formation (filaggrin deficiency, aberrant protease inhibitor activity….). An abnormal microbial colonization develops with pathogenic organisms, such as Staphylococcus aureus or Malassezia furfur (compared with Staphylococcus epidermidis in normal individuals) and subsequent increased susceptibility to skin infection. Finally, there is a remarkable psychosomatic component with a deregulated autonomic nervous system leading to an elevated production of inflammatory factors by various inflammatory cells (e.g. eosinophils). In this Belgian guideline, the recommendations of the Belgian Atopic Dermatitis Working Group (BADWG) for the management and treatment of AD are described.

Methodology:

These recommendations were developed by 11 Belgian experts in atopic dermatitis. Each topic was drafted by 1-2 experts. The evidence for each topic was summarized allowing the generation of specific recommendations. The ETFAD/EADV Eczema task force 2020 position paper (including the evidence levels) was used as a guide and applied to the Belgian context. Additionally, newer treatments were incorporated in this manuscript. Already existing international guidelines were compared and the specific Belgian situation (e.g. drug availability, reimbursement criteria) was taken into account. Comments of all experts on the proposed statements were gathered, followed by an online voting session. Sections without unanimous agreement were adjusted according to the

submitted remarks. A second voting session was conducted after 1 week which led to full agreement on all sections.

Diagnostic criteria

Clinical diagnosis is considered the gold standard, based on a physician's assessment of the patient's signs and symptoms.(2) The most used diagnostic criteria are those defined by Hanifin and Rajka (Table 1). (1) Conditions that may have a similar clinical presentation should have been excluded: allergic or irritant contact dermatitis, cutaneous T-cell lymphoma, scabies, seborrheic dermatitis, ichthyosis, psoriasis, photosensitivity dermatosis, primary immunodeficiency disease or erythroderma of other etiology, such as drug eruption. (3) In rare cases, blood tests for total or specific type E immunoglobulin, skin biopsy for histological examination, patch tests for contact allergy or genetic analysis are useful to exclude other diagnoses and to confirm the diagnosis of AD. (3)

Recommended scores

The "clinical practice set", gathering the validated clinical scores that are useful and practical in routine use, needs to be defined. (4) Currently, the Belgian Atopic Dermatitis Working Group (BADWG) recommends for the assessment and follow-up of patients with moderate to severe AD, especially when systemic treatment is prescribed, the use of at least the three following scores:

- Eczema Area and Severity Index (EASI) for the assessment of objective signs (5) (Supplement 1):

The EASI considers the percentage of skin involvement in four areas of the body (head and neck, trunk, upper limbs and lower limbs) and the severity of the skin lesions in each area according to four criteria: erythema, oedema, excoriation and lichenification. (5)

- Peak Pruritus Numerical Rating Scale (PP-NRS) for the assessment of pruritus; (6):

The PP-NRS specifically assesses pruritus: the patient is asked to quantify his/her worst itch during the last twenty-four hours on a numerical rating scale of 0 to 10, where 0 means no pruritus and 10 means the worst pruritic sensation imaginable. (6)

- Visual analogue scale regarding sleep disturbance in the subjective component of the patient-oriented SCORing Atopic Dermatitis (PO-) SCORAD. (7)

In the academic or specialized setting, additional scores can be useful, especially when caring for patients with moderate to severe disease, including the SCORAD (7), Patient-Oriented Eczema Measure (POEM) (8), Dermatology Life Quality Index (DLQI) (9), and Atopic Dermatitis Control Tool (ADCT) (10).

Management: General measures

1. Allergy testing in children and adults

Work-up of Food allergy/ food hypersensitivity in AD

Immediate reactions, IgE-mediated responses appear on average within 2 hours after consumption of the offending food. They present with angioedema, urticaria, flushing, pruritus, gastrointestinal or respiratory manifestations or anaphylaxis. (11) In children, a rash occurring 6 to 10 hours after this immediate reaction, described as a late IgE-mediated response, can also occur. (12) Isolated, non-IgE-mediated eczematous reactions occur 6 to 48 hours after ingestion, in the form of flare-ups in typical areas of atopic dermatitis. (11) Finally, mixed reactions with immediate symptomatology followed by a late eczematous reaction have also been described. (11). Allergological assessment should be performed in these patients. Prick tests, often performed as a first-line test, have excellent negative predictive value (often >95%), allowing an allergy to be excluded when negative, but low positive predictive value. (11) Likewise, specific IgEs have good negative predictive value but low positive predictive value.(13) Specific IgEs are frequently increased for multiple foods in atopic children, without any clinical relevance. It has thus been shown that less than 40% of patients with specific IgE or positive prick tests had a positive oral challenge test. (14)

Foods to be tested vary depending on clinical history and the prevalence of potential allergens in the patient's age population. Clinical examination can reveal clues to possible allergens such as food allergy in infants with peri-oral AD (the area around the mouth is normally not involved except if there is an irritative eczema e.g. due to saliva) or worsening by specific food intake. In children under 2 years old, cow's milk, egg, soy, wheat, nuts and fish induce >90% of allergies. In older children and adults, foods that cross with birch pollen (via PR10) such as rosacea or nightshade are also frequently implicated in allergic symptoms. (15) Nevertheless, specific IgE levels making it possible to establish a probability of clinical reactivity in more than 95% for the most frequent allergens: cow's milk (≥ 15 kU/L), egg (≥ 7 kU/L), peanuts (≥ 14 kU/L), tree nuts (≥ 15 kU/L) and fish (≥ 20 kU/L), while the cut off values for the wheat (≥ 26 kU/L) and soy ((≥ 30 kU/L) have not been validated. In infants, lower values have been reported especially for egg (≥ 5 kU/L) and milk (≥ 2 kU/L). (12) Finally, these decision points have excellent positive predictive value but poor sensitivity: a specific IgE level lower than the cut-off does not exclude an allergy.

In other cases, when the suspected allergen is another food or when the level of specific IgE is lower than the validated cut-off values, the diagnosis of hypersensitivity must therefore be confirmed by *a double-blind oral challenge versus placebo*, under medical supervision, by a physician competent in the field of allergology. It is recommended to precede this provocation test by an avoidance diet in order to judge the implication of the food in the symptomatology. (13)

The use of "atopy patch tests" have been described for the assessment of food allergies. However, since no standardized test are available, the BADWG states that atopy patch tests currently do not play

a role in routine diagnostic. Although double-blind placebo controlled food challenge (DBPCFC) is the gold standard in allergy testing, only very few centers provide this diagnostic service for large numbers of patients. DBPCFC should be performed in cases with suspicion of food-induced or aggravated AD.

Aeroallergens

Like food allergens, Aeroallergens may elicit immediate or delayed hypersensitivity reactions in atopic patients. The most common Aeroallergens are dust mites (Dermatophagoïdes pteronyssinus and Dermatophagoïdes farinae), pollens, molds and animal epithelia (cat, dog, etc.).

In case of a clinical history suggestive of immediate sensitization (allergic rhino-conjunctivitis, allergic asthma) or delayed (eczematous outbreaks after exposure to possible aeroallergens), exploration by prick tests and / or specific IgE is recommended.

The use of "atopy patch tests" with aeroallergens can be useful but controversial. When done, a reduced series including D. pteronyssinus, D. farinae, birch pollen, cat epithelia and mug wort is regarded as sufficient. (16)

Allergic contact dermatitis (ACD)

The prevalence of ACD in atopic patients has long been debated, but a recent meta-analysis showed no significant difference in the prevalence of ACD to common allergens in patients with or without AD. (17)

The performance of patch tests should be considered in any patient presenting AD whose control cannot be obtained despite appropriate treatment, atypical distribution of lesions, late-onset AD (in adults or adolescents), AD in recent or generalized worsening, localized dermatosis suggestive of contact allergy. (18) Patch tests are not recommended (1) in patients with stable AD and well controlled by treatments, (2) in patients with a surging AD, especially if the back and / or other potential patch application sites are affected, and (3) in patients under current or recent treatment with systemic immunosuppressants or phototherapy.

Importantly, allergy testing should be performed in AD patients with uncontrolled disease despite sufficient patient/parent education and optimally applied therapies (applies to moderate-severe affected patients). Patients should not be put on a specific diet without proven food-allergy diagnosis.

2. Skin cleansing

The skin should be cleaned thoroughly, but with caution. For infants and toddlers, we recommend a short bath twice weekly (max. 5 minutes) with the use of a bath oil. From a dermatological point of view, daily bath or shower is not necessary, but is possible under certain conditions, including duration not exceeding 5 minutes or temperature not exceeding 35°C". Bath oil should not be added immediately at beginning of the bath, but towards the end for about the last 2 minutes. The skin should

not be rubbed for drying, but gently padded to avoid taking the protective oil film from the skin into the towel.

3. Emollients

Emollient therapy is the basis of AD treatment (Table 2). (19, 20) Currently, data on preventive use of emollients in newborns with AD family history is conflicting, with two studies showing reduction of AD during the first year of live, but no preventive effect in a third trial (BEEP study) (21, 22).

In recent years, the concept of emollient plus has been developed, which describes emollients with additional active ingredients. Since these products are not defined as drugs, they do not require registration. Examples of active ingredients are saponine, flavonoids, riboflavones (derived from protein-free oat) or bacterial lysates from Aquaphilus dolomiae or Vitreoscilla filiformis which reduce inflammation and improve skin microbiome diversity in AD patients. (23-25)

4. Dietary intervention

Diet

An actual discussion is the use of pre- and probiotics for prevention and treatment of AD. Currently available trials are still inconclusive, given their heterogeneity in active substances, treatment duration and varying age categories. Thus, no clear evidence-based pre- or probiotic treatment currently exists for prevention and treatment of AD. However, according to allergy prevention guidelines exclusive breastfeeding is recommended for up to 4 months. Subsequently, the timeframe for introduction of food is between 4 to 6 months. (26) In order to prevent peanut allergy, early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts. (27)

Management: local anti-inflammatory therapy (Table 3)

Topical corticosteroids (TCS)

Several factors need to be taken into account when choosing TCS, including potency, the galenic form, patient age and body site treated. Body sites with thin skin and high absorption, including the periorbital region, eyelids and folds/ genitals should be treated with mild TCS (group I and II). These sensitive areas can also be treated with a topical calcineurine inhibitor (TCI), which cause no skin atrophy (tacrolimus, pimecrolimus). Children should be treated with less-potent TCS due to their reduced skin barrier/ increased resorption compared to adults.

Sometimes, twice daily application can improve itch control, but once daily treatment is sufficient in most cases (28, 29) The best way to reduce TCS use is a stringent treatment of flares, followed by

reduction in potency and starting proactive therapy in cases of frequent relapses.(30) Corticofobia (patients or parents fearing side-effects by corticosteroids) is frequent and needs to be addressed during patient education in order to improve treatment adherence. (31-33)

Recommendations

In acute flares, topical corticosteroids remain the cornerstone of AD therapy (–, D). In case of insufficient response, wet wraps can be recommended to increase the efficacy of the topical treatment (1b, A). To prevent relapses, a chronic proactive strategy is useful, e.g. applying topical corticosteroids twice weekly on body areas with recurring AD (1b, A). In more sensitive areas (e.g., intertriginous sites, face, genital area) TCI are particularly interesting to prevent side effects of topical corticosteroids (1b, A).

Tar

Tar containing products have been used for skin diseases including atopic dermatitis (AD) for many years due to their anti-inflammatory and anti-bacterial properties, but their use is declining due to more practical alternatives. (34) Different products are available, such as coal tar (pix lithantracis), coal tar solution (liquor carbonis detergens, LCD), ichthammol (ichthyol, ammonium bituminosulphonate), and pine tar (pix liquida). (35) **The BADWG does not recommend the use of coal tar, because of the lack evidence from well-controlled trials. Only in selected therapy refractory cases it might still be used.**

Systemic therapy

Phototherapy

The clinical observation that a significant proportion of AD patients experiences improvement of disease activity during summer season, UV therapies became a frequently used modality. However, a small group experiences AD flares under sun exposure, which needs to be addressed by thorough history taking.

LIGHT SOURCES AND CURRENT TREATMENT FOR AD

The light therapies most commonly used in Europe today are NB-UVB and UVA1, partly because there are no clinical studies objectifying an increase in the number of non-melanoma skin cancers. (36, 37) Particularly in connection with PUVA, the long-term risks of light therapy must be weighed up, especially in children and patients with a history of immunosuppressive medication.

NB-UVB is the preferred phototherapy for chronic moderate to severe forms of AD the preferred therapy,(38) while high dose UVA1 is reserved for severe phases. (39)

PRACTICAL ASPECTS

In daily practice, the choice of UV treatment is limited by the availability of the equipment; UVA1 cabins are expensive to purchase and maintain. The main disadvantage of UV therapy is the time investment for the patient: 2-3 times a week for 6-12 weeks. Furthermore, UV light is not effective in the treatment of the hairy head and skin folds. At the start of UV, comedication with local corticosteroids and emollients is recommended; if there is improvement, the patient can be switched to emollients only. In practice, phototherapy can improve and control AD: it reduces bacterial colonization and reduces the use of amount/strength of topical corticosteroids by patients, but the benefits vary per individual.

Recommendations

The BADGW recommends the use of narrow-band-UVB over broad-band UVB for the phototherapy in AD (1a, A). Medium-dose UVA1 displays comparable efficacy as narrow-band UVB but is less commonly available (1b, A). High-dose UVA1 can be an interesting option in severe cases (1b, A) . The carcinogenic risk for skin cancer exists in theory for all types of UV treatments. Nonetheless, no increased rates of skin cancer have been demonstrated for NB-UVB in contrast to PUVA (2a, B). Therefore, the BADGW does not place PUVA therapy as a first treatment option. In AD children, phototherapy is rarely used although not formally contraindicated. Similar to adults, NB-UVB is preferred for the treatment of AD in children (-, D).

Antipruritic therapy

Control of inflammation is specific concern for itch control, since it has become apparent that itch in atopic dermatitis is mainly mediated by inflammatory cytokines, including IL-4, IL-13 and IL-31, which explains the anti-pruritic effect of anti-inflammatory measures. (40) Thus, the general measures recommended should also be taken into account.

<u>Local therapy against puritus (Figure 1)</u>

TCS have an anti-inflammatory activity rather than a direct anti-pruritic effect. A meta-analysis has shown that itching could be significantly reduced by 34% in patients treated with TCI compared with vehicle alone.(41) Topical corticosteroids have a rapid anti-pruritic effect and can also be used 'proactively', e.g. twice weekly. (42) Topical calcineurin inhibitors: TCI significantly relieve itching in eczema. The itching disappears completely after the first days of treatment, both in adults and children. There are not enough randomized controlled trials (RCTs) to prove that topical antihistamines are effective for the treatment of itching in AD. Moreover, the use of topical doxepin is avoided because of an increased risk of contact allergy. Antipruritic and analgesic effects are attributed to cannabinoid receptor agonists. There is only one large study, but no RCT, demonstrating a positive

effect of a cosmetic product containing the cannabinoid agonist N-palmitoylethanolamine as adjuvant therapy for atopic eczema. There is no evidence of significant efficacy of opioid receptor antagonists in reducing itching in atopic eczema. There are few studies on the efficacy of polidocanol. It is not registered in Europe but over-the-counter products are available and widely used in some countries. Benzocaine, lidocaine, and mixtures of prilocaine and lidocaine are widely used as short-acting topical anti-pruritics. None of these agents are registered for atopic eczema but some are available over the counter. There are no publications of controlled studies on capsaicin for itch in AD. There is evidence that UV therapy can be used for AD to relieve the pruritus. Narrowband UVB and UVA1 seem to be the most preferred options. (2a,B) (see further section on UV therapy).

Systemic therapy against pruritus

Antihistamines have been used for decades to relieve pruritus in patients with atopic eczema, although scientific evidence of their efficacy in reducing pruritus in AD is very scarce. The first generation is mainly used for its sedative effect, particularly improved sleep in acute situations. In RCTs, opioid receptor modulator nalmefene was used at a dose of 10 and 20 mg 1x/d with significant relief of pruritus. For the only oral antagonist, naltrexone, studies are also known to show clear antipruritic effects at a dose of 25-150 mg daily. However, side effects such as anxiety, arthralgias, dizziness, drowsiness, fatigue, vomiting and headache should also be considered. These agents are currently not registered for treatment of itching in atopic eczema. There is limited evidence for the selective serotonin reuptake inhibitors paroxetine and fluvoxamine with significant improvement in pruritus, but again side effects should be considered.

ANTIBACTERIAL TREATMENTS

Up to 90% of AD patients have extensive colonization with S. aureus (S.a.) even in normal-appearing skin. Recent studies show that in addition to S.a., the imbalance in the skin microbiome also plays an important role in AD-pathophysiology. (43, 44) New developments in emollients are e.g. the incorporation of active ingredients that repair skin barrier function or influence the microbiome with bacterial lysates from Aquaphilus dolomiae or Vitreoscilla filformis species. (24)

A systematic review of 26 studies and 1229 participants could not provide clear evidence for beneficial effects of antiseptic bath ingredients or soaps, nor of antimicrobial agents added to topical therapies in non-infected AD patients. Nevertheless, if there is no response to topical glucocorticoid steroids or calcineurin inhibitors, nor is there obvious infection, the use of topical antiseptics may be considered and they are preferred over topical antibiotics, because of the potential development of bacterial resistance. (45) The use of antiseptics to control S.a-colonization is an additional option. Bleach bath with sodium hypochlorite 0.005% can be an option, especially in children with refractory AD. (46-48)

Nonetheless, this concentration is too low for an antibacterial activity, indicating that other mechanisms may explain its efficacy. (49) In practice, 45 ml natriumhypochlorite 4% should be added to 40 L bath water (ca. 1/4 bath tub) together with 3 units bath oil. The bath should take 10 minutes. Underestimated sources of bacteria are cream and ointment jars, which are up to 53% contaminated, up to 25% with staph aureus. The use of systemic antibiotics is restricted to extensive bacterial surinfection, impetigo or abscesses, taking into account the bacterial resistance profile.
In summary, the following recommendations are valuable: store open emollients in the refrigerator, use pump bottles rather than jars, avoid direct contact with hands, avoid joint use.(50)

Antimicrobial clothing/bandages

Silver impregnated clothing has shown a significant decrease in antimicrobial activity as well as improvement in local SCORAD in a non-blinded, side by side controlled clinical trial. (51) In patients with non-infected AD, use of silver impregnated clothing in combination with cotton clothing did not reduce AR severity. (52-54) However, silver or acid-coated and silk clothing, as well as chitosan (a natural biopolymer with immune-modulating and antimicrobial properties) by reducing the aureus skin colonization step can lead to a reduction in itching. (55) Some of these new modalities are still in a research phase and there is still some uncertainty in the safety of silver-coated clothing in babies and toddlers. ADGIS-coated silver products have not shown clinical benefit in controlled, multicenter clinical trials. (56)

ANTIVIRAL TREATMENTS

Eczema herpeticum (EH) is a disseminated herpes infection. Predisposing factors are early onset of AD, severe or under-treated forms, filaggrin deficiency and high total IgE. (57) Prior treatment with topical corticosteroids does not seem to increase the risk of EH, but topical calcineurin inhibitors do and should be stopped immediately. (58) Treatment of EH consists of systemic treatment with (val)aciclovir, usually given intravenously. (59)
Varicella-zoster virus (VZV) is usually a mild, self-limiting illness in an immunocompetent child. In AD children, however, this virus can cause a secondary local or systemic bacterial superinfection. In children with AD, the recommended vaccinations in the 1st year have been shown to have no associated increased risk of more severe eczema or allergic sensitisation and the immune response to the VZV vaccine is similar to healthy children. (60)
Parents of children with AD may therefore be encouraged to have their children fully vaccinated. Molluscum contagiosum virus (MCV) is a common benign and self-limiting disease, which frequently presents in a disseminated form in AD patients and therefore treatment is advised.

Treat mollusca since they often spread extensively (or even can promote flares), which makes treatment more difficult and harbors risk of scar formation. In very inflamed skin, a short course of topical steroid class II-III for a few days can be used prior to mollusca treatment in order to enhance patient comfort. Curettage and cryotherapy and KOH solutions are treatment options, but are sometimes difficult to achieve in young children. Topical corticosteroids may be continued during MCV infection.

ANTIMYCOTICS

Malassezia species are known to be commensal to non-diseased skin, but in atopic skin they can exert a pathogenic role, possibly by interacting with the local skin immune system and skin barrier function. Antifungal treatment with either topical ketoconazole or ciclopirox olamine or systemic itraconazole/fluconazole can be considered for AD patients with head and neck dermatitis, especially those with a clear IgE-to Malassezia species.

RECOMMENDATIONS

Systemic antibiotic therapy may be considered in AD patients with clinically infected eczema due to Staph aureus (2b,B). Long-term local treatment with topical antibiotics should be avoided in order to avoid the development of resistance and sensitization (2,D). Treatment with topical antiseptics, including antiseptic baths e.g. with diluted sodiumhypochlorite, can be considered in clinically infected eczema (4,C). Treatment with topical antiseptic medication, together with sodiumhypochlorite 0.005% baths, may be considered in therapy resistant, chronic AD patients (2b,B). Eczema herpeticum should be treated instantly with systemic antiviral therapy, e.g. (val)aciclovir (4,D). VZV vaccination is recommended for AD children and parents of AD patients should be urged to have their children complete the full vaccination program (2a,B). Topical or systemic anti-mycotic therapy may be effective in a subgroup of AD patients, particularly those with a head-neck variant or those who show serologically increased IgE mediated sensitization to Malassezia. (2b,B)

PATIENT EDUCATION

The BADGW recommends patient education programs for AD in children and adults. (1a, A) A multidisciplinary age-appropriate group training in the form of an eczema school has the best proven benefit (1a). Eczema workshops improve severity scores, lead to greater treatment adherence, , recognition of the itch-scratch cycle, and exerts additional psychological effects (2a,2b). Nurse-led programs improve efficacy in smearing behavior (3b) and in improving eczema scores (2a), as well as saving doctor time (2b). There is some evidence that direct online access to follow-up dermatological care is equivalent to standard care (2a)

SYSTEMIC THERAPY

Criteria for initiating systemic treatment in AD

In AD, a systemic treatment is recommended if topical treatment with corticosteroids (TCS) or calcineurin inhibitors (TCI) fails to control acute flares despite adequate patient counseling and independent of absolute EASI or SCORAD values (Figure 2; Supplementary Table 1). (61) Currently, systemic treatments are initiated in most cases in addition to a topical treatment. With gain of disease control, topical treatments can be tapered to 2-3 times per week (proactive treatment). (62)

Drugs with the label for managing AD patients with severe disease burden include ciclosporin, dupilumab, tralokinumab, baricitinib, upadacitinib, abrocitinib (upadacitinib and abrocitinib currently not reimbursed in Belgium). Off-label drugs used for managing AD patients with severe disease burden are methotrexate, azathioprine, mycofenolate mofetil. Also UV-therapies (mainly UVB therapy) can be used to treat severe AD, but are not reimbursed in Belgium. Criteria for switching systemic treatment in AD are (1) side effects/ toxicity, (2) unsatisfactory disease control, which is defined as not reaching EASI 75 or itch reduction to 3 out of 10 within 12 weeks of treatment (61, 63).

Conventional immunomulators/immunosuppressants

Systemic corticosteroids should be reserved for acute flares in exceptional cases. An important caveat in the use of oral steroids is the risk of AD-rebound, which in severe cases can lead to erythroderma. Ciclosporin can be used in severe cases of AD in adults, and off-label in children and adolescents. In Belgium, currently a 4 months treatment course with ciclosporin in the last 12 months is prerequisite for the reimbursement of biologics in Belgium. Combination of UV and cyclosporin or azathioprine is contra-indicated. Off-label Methotrexate is effective for treatment of AD in both adults and children. Treatment is possible oral or by subcutaneous injections (which has the advantage of higher effectiveness and better tolerance, but is not reimbursed in Belgium). Mycophenolate mofetil (MMF) or azathioprine may be used (off label) in AD patients, if cyclosporine or methotrexate are either not effective or contraindicated. MMF may be used for treatment of AD in children or adolescents.

Biologics

As a second line systemic option, 2 biologics are currently reimbursed in Belgium: dupilumab and tralokinumab. Dupilumab, a humanised monoclonal antibody blocking interleukins 4 and 13. Randomized trial data show efficacy of treatment of atopic dermatitis with dupilumab over placebo or topical steroids, with improvement in all outcomes of disease severity, including quality of life. Ocular dryness and inflammation may be seen as side-effects as well as redness of the face. Frequently, an

improvement in any concomitant asthma is seen on treatment, but patients should not modify their asthma treatment without pulmonologists advice. (64-66)

Tralokinumab is a fully human monoclonal IgG4 antibody that specifically binds to the type 2-cytokine interleukin-13 (IL-13) and inhibits its interaction with IL-13 receptors. Tralokinumab is indicated for the treatment of moderate to severe atopic dermatitis in adults requiring systemic treatment.

No specific lab monitoring is necessary for dupilumab and tralokinumab. In case of persistent eye symptoms (e.g., conjunctivitis), referral to ophthalmologists is advised (67)

Systemic JAK inhibitors (JAKi) for treatment of atopic dermatitis (68, 69)

First generation JAK inhibitors (JAKis) act on JAK1, JAK2 and JAK3 (e.g. the JAK1/2 inhibitor baricitinib and the JAK1/3 inhibitor tofacitinib). Second generation JAKis (e.g. abrocitinib en upadacitinib) are more specific for JAK1.

JAKis are oral treatments (in contrast to biologics), have well-predictive pharmacokinetics and are not immunogenic. Due to their downstream activity of cytokine receptors, JAKis inhibit multiple cytokines and pathways involved in AD, which lead to rapid improvement of inflammation and itch.

Baricitinib (Olumiant) is a first-generation JAK1/2 inihibitor. In two phase 3 studies baricitinib was compared to placebo (BREEZE-AD1 en BREEZE-AD2). By week 16, 59,4% and 54,9% of patients treated with 4 mg baricitinib reached a EASI75 reduction of skin inflammation, compared to 4,8% in the placebo group. The patient-reported outcomes itch, sleep loss, skin pain, and quality of live improved already within the first week of treatment. The most frequently reported side effects were headache and nasopharyngitis, while no thromboembolic, cardiovascular or hematologic events were noted. (70). Other, not yet reimbursed JAKi also have promising data. Upadactinib is also a selective JAK1 inhibitor. 50% of patients reached a EASI 90 after 16 week of treatment with 30 mg daily. Within 1 week of treatment, significant reduction of itch, sleep loss and other relevant symptoms were noted. Most frequent reported side effects were upper airway infections and acne. (68)

Abrocitinib (Cininqo) is a JAK1 inhibitor. In 2 fase III studies (JADE MONO 1 and JADE MONO 2) 62,7 % and 61% EASI 75 reduction were reached after 12 weeks of treatment with 200 mg abrocitinib daily. Headache, nausea, nasopharyngitis, upper airway infections, reduction of thrombocyte levels and elevation of lipids were reported as side effects.(68) Recommendations on the specific situations of preconception period, pregnancy, lactation can be found in Table 4.

CONCLUSIONS AND OUTLOOK

The complexity of AD pathophysiology explains why the therapeutic arsenals contains many different components. Even if there is a strong genetic predisposition, patients should not be discouraged. Good treatment of eczema is certainly possible and, given the new developments and the elucidation of the

various molecules involved in the pathogenesis, new hopeful prospects for this large patient group have opened up.

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Table 1: Hanifin-Rajka diagnostic features for AD, adapted from original article. (1)

At least 3 major features present	○ Pruritus ○ Chronic or chronically-relapsing dermatitis ○ Typical morphology and distribution according to age: – Facial and extensor involvement in infants and children – Flexural lichenification or linearity in adults ○ Personal or family history of atopy: atopic dermatitis, asthma, allergic rhinitis
At least 3 minor features present	○ Xerosis ○ Ichthyosis and/or palmar hyperlinearity and/or keratosis pilaris ○ Immediate (type I) skin test reactivity ○ Elevated serum IgE ○ Early age of onset ○ Tendency towards cutaneous infections especially *Staphylococcus aureus* and *Herpes simplex* ○ Non-specific hand or foot dermatitis ○ Nipple eczema ○ Cheilitis ○ Recurrent conjunctivitis ○ Dennie-Morgan infraorbital fold ○ Keratoconus ○ Anterior subcapsular cataracts ○ Orbital darkening ○ Facial pallor or facial erythema ○ Pityriasis alba ○ Anterior neck folds ○ Itch when sweating ○ Intolerance to wool and lipid solvents ○ Perifollicular accentuation ○ Food intolerance ○ Course influenced by environmental or emotional factors ○ White dermographism or delayed blanch

Table 2: Use of emollients

Problem	Tips
- Poor tolerance	- Do not use emollients on inflamed skin as it is poorly tolerated and it is advised to treat the acute flare first - Ureum leads to skin moisturization, but can induce skin irritation. In young children, it is recommended to not exceed the percentage of ureum over the biologic age (e.g. 2% in 2 years old children). Adults usually tolerate 5% urea in non-inflammed skin (expert opinion and current practice).
- Skin remains dry	- Emollients should be used after skin cleansing, such as bath or showering, in order to keep the moisture in the skin. - Emollients are available as hydrophilic creams, which contain more water than oil, which should be used if the skin is not too dry or irritated. Ointments should be used on very dry skin, which is often observed in winter.
- Frequency and dosage	Emollients are most effective if applied twice daily. Quantities required are usually high (150–200 g per week in young children, up to 500 g in adults). The required amounts can be estimated using the fingertip unit rule.
- Skin infection	- Emollient tubes are prone to bacterial colonization, therefore we recommend to store emollients in the fridge, use of pumps and bottles is preferred over tubs/pots, avoid touching emollients with fingers and sharing among family members
- Allergy	- Emollients should not contain protein allergens or other known contact allergens, such as fragrances, lanoline or methylisothiazolinone.

Table 3: Use of local anti-inflammatory therapy

Clinical situation	Tips
Inflamed skin	- First-line treatment are corticosteroids, because TCI sting more intensely on inflamed skin. - Anti-inflammatory therapy is used until resolution of AD - Children should be treated with less potent corticosteroids, such as momethason, because less resorption and side effects were reported (71)
Mild AD	- Use corticosteroids during flares
Moderate and frequently relapsing patients	- Following initial daily therapy, a long-term anti-inflammatory treatment is applied twice weekly on frequently affected sites, in combination with emollients, which are used additionally on unaffected skin. (42), (62, 72-74). - A small amount of topical corticosteroids twice to thrice weekly (monthly amounts in the mean range of 15 g in infants, 30 g in children and up to 60–90 g in adolescents and adults), associated with a liberal use of emollients generally allows a good disease control.
Acute, oozing and erosive lesions, and severe AD in children	Wet wraps are highly effective in acute eczema and improve tolerance. The use of wet-wrap dressings with diluted corticosteroids for up to 14 days (usual rather up to 3 days) is a safe crisis intervention treatment of severe and／or refractory AD with temporary systemic bioactivity of the corticosteroids as the only reported serious side-effects
Information tools	**Links for the use of topical therapy:** **https://www.bcfi.be/nl/chapters/16?frag=14233** https://creamcalculator.com https://dermnetnz.org/topics/fingertip-unit

Table 4: Treatment of AD during pregnancy and lactation

Topical treatment	
Anti-inflammatory	- Topical corticosteroids should be first-line (exception: fluticasone propionate which is not metabolized by the placenta) - Pregnant and lactating women should use the lowest possible potency of TCS from class II or class III of the fourth generation TCS - Besides tacrolimus ointment, the use of topical calcineurin inhibitors during pregnancy is not recommended due to the lack of studies and experience
Topical antiseptics	- All antiseptics, with the exception of triclosan, are recommended for use by pregnant women to prevent recurring infections but should not be used as a general measure
Topical antibiotics	- Topical fusidic acid may be used to treat small areas of clinically infected AD in pregnant women. Mupirocin may be used to eradicate staphylococcal infections inside the nose if needed.
Phototherapy	- UVB and UVA1 do not increase the risk for fetal harm in pregnant women. Supplementation of folic acid is recommended during phototherapy.
Treatment of AD-Related Complications	Topical ketoconazole and ciclopiroxolamine and systemic acyclovir as a treatment can be used for fungal or herpetic complications. Oral cephalosporins or flucloxacillin should be used for Staph. aureus induced skin infection, unless bacterial resistance.
Systemic treatment	
Corticosteroids	- may increase the risk for complications including gestational diabetes, preeclampsia, membrane rupture, and preterm delivery - relatively safe if properly monitored during pregnacy - less than 0.1% of the dose is secreted into breast milk
Ciclosporin	- Can be used off-label during pregnancy and lactation
Methotrexate	- In both women and men, methotrexate: should be paused 3 months before conception to reduce the risk for birth malformation
Azathioprine	- If AZA is to be continued during pregnancy, a 50% dosage reduction is recommended. After conception, the use of AZA to treat AD should not be initiated as more effective alternatives exist.
Mycophenolate Mofetil	- Contraindicated in pregnant women with AD and in men with AD 3 months before conception - Secreted in breast milk and is not recommended for treating AD during lactation
Dupilumab	- Lack of experience and scientific data. Do not use during pregnancy or lactation unless stricly necessary. No demonstrated teratogenecity.
Antihistamines	- Only if necessary - Loratadine is preferred, use only sedating antihistamines if necessary

Figure 1: Antipruritic therapy in AD

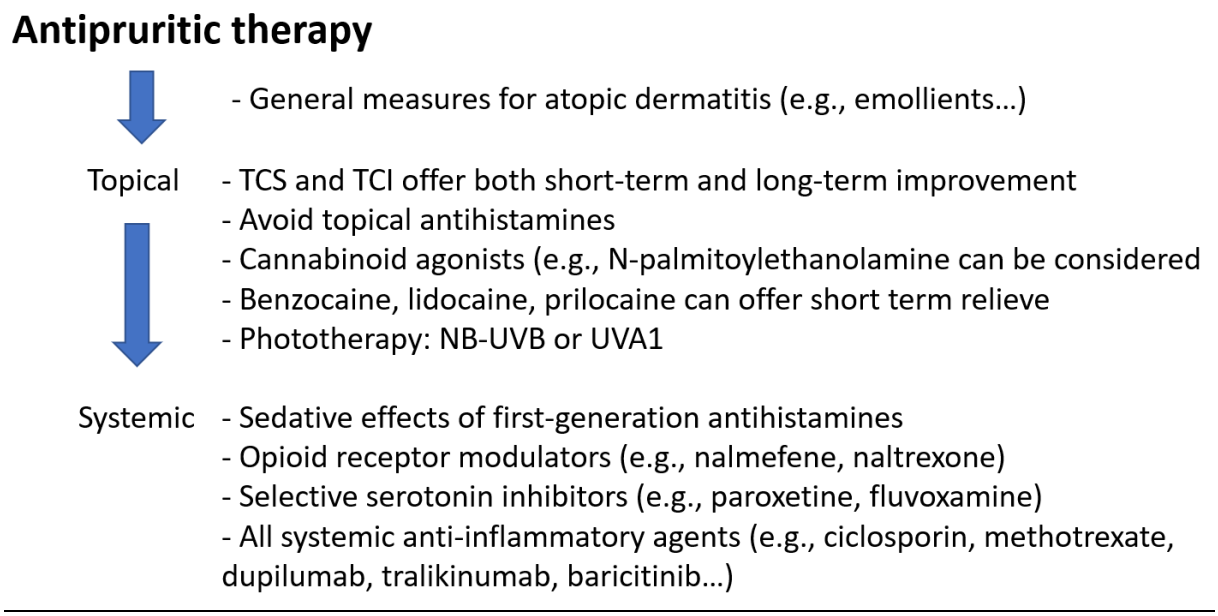
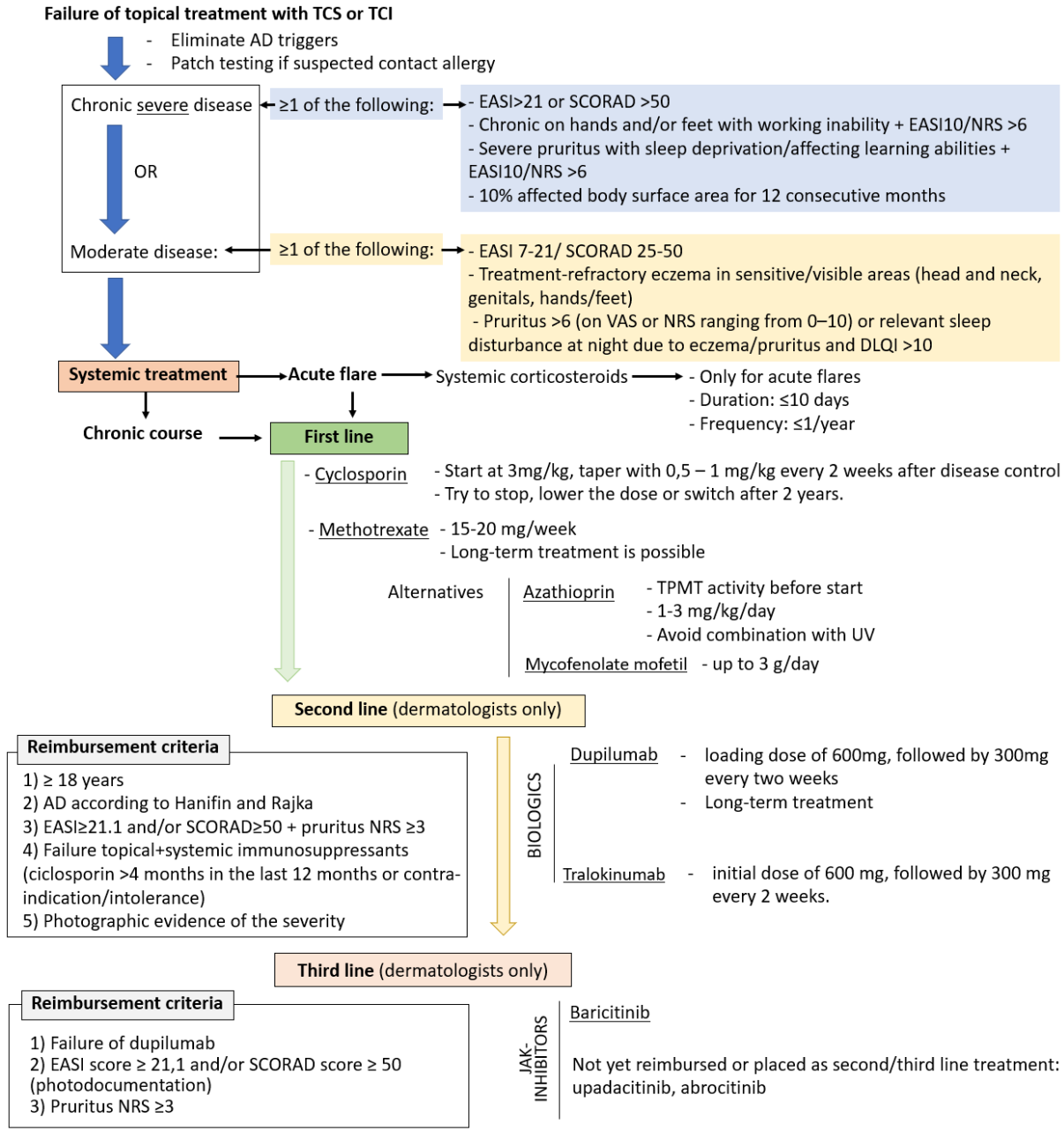


Figure 2: Flow chart of the systemic treatment of AD



Supplementary material:

Supplement 1: links to calculators for recommended scores

- EASI: https://www.dermatools.net/eEASI.html
- PP-NRS: http://www.pruritussymposium.de/numericalratingscale.html
- Visual analog scale regarding sleep disturbance in the subjective component of the (PO-)SCORAD: https://www.poscorad.com/#/ or https://www.dermatools.net/eSCORAD.html

- SCORAD: https://www.dermatools.net/eSCORAD.html
- POEM: https://www.nottingham.ac.uk/research/groups/cebd/resources/poem.aspx
- DLQI: https://www.dermatools.net/eDLQI.html
- ADCT: https://www.adcontroltool.com/

Supplementary Table 1: monitoring of systemic drugs for AD (Modified from Wollenberg A. et al. JEADV 2018;32(6):850-78 and *Nash P et al. Ann Rheum Dis 2020; 0:1–17*)

	Before start	**Follow-up**
Ciclosporin	- Blood pressure - Peripheral blood count (PBC), C-reactive protein (CRP), creatinine, liver function (AST, ALT, γGT), lipids (cholesterol and triglycerides), potassium, magnesium, viral serologies (HIV, Hepatitis B/ C - Consider Mantoux test/Quantiferon - Check vaccination status.	- PBC monthly in the first 3 months of treatment, than every 3 months - Creatinine and blood pressure every month in the first 3 months (in case of elevated creatinine or blood pressure after 3 months, return to taking parameters every two weeks). - Other parameters (liver function, lipids) every 3 months.
Methotrexate	- PBC, CRP, kidney function, liver function (AST, ALT, γGT), HCG, viral serologies (HIV, Hepatitis B/ C) - Consider Mantoux test/Quantiferon - Check vaccination status	- PBC, CRP, kidney function, liver function (AST, ALT, gGT): every 2 weeks during the first month, then monthly. As of month 3, check every 3 months.
Azathioprin	- TPMT (Thiopurine S-methyltransferase) measurement - PBC, CRP, kidney function, liver function (AST, ALT, γGT), HCG, viral serologies (HIV, Hepatitis B/ C) - Consider Mantoux test/Quantiferon - Check vaccination status	- PBC, CRP, kidney function, liver function (AST, ALT, γGT) every 2 weeks for the first month, then monthly. As of month 3, check every 3 months.
Mycophenolate mofetil	- PBC, CRP, kidney function, liver function (AST, ALT, γGT), HCG, viral serology (HIV, Hepatitis B/ C) - Consider Mantoux test/Quantiferon - Check vaccination status	- PBC, CRP, kidney function, liver function: first two weeks of treatment check every week, then every 4 weeks. From week 14, blood check every 3 months.
Dupilumab	- N.A.	- No specific monitoring. - Check for eye symptoms, referral to ophthalmologists if necessary
Tralokinumab	- N.A.	- No specific monitoring. - Check for eye symptoms, referral to ophthalmologists if necessary
Tralokinumab	- N.A.	/
JAK inhibitors	- PBC, CRP, kidney function, liver function (AST, ALT, gGT,), lipids	- PBC, CRP and liver function after 1 and 3 months, then every 3 months.

	(cholesterol and triglycerides), HCG, viral serologies (HIV, Hepatitis B/ C) - Consider Mantoux test/Quantiferon - Check vaccination status, especially varicella zoster vaccination	- Lipid check after 3 months,