TITLE: Italian Guidelines for therapy of Atopic Dermatitis– adapted from Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis).

RUNNING HEAD: Italian Guidelines for therapy of Atopic Dermatitis

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ABSTRACT

Introduction

Atopic dermatitis (AD) therapeutic approach calls for a long term treatment. Treatment options for AD have recently undergone a revolutionary change by the introduction of the first biologic drug. Availability in daily practice of the last version of international AD guidelines, taking peculiarities of the country into account, can contribute to good clinical practice in Italy.

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Objectives

To adapt European Dermatology Forum(EDF) guidelines for atopic dermatitis to the Italian medical-legal context.

Methods

The EDF guidelines were assessed independently by two independent Italian renowned experts in the field and further integrated with articles published and systematically reviewed before May 2019. The first draft was collegially corrected and updated by the members of the SIDEMAST, ADOI, and SIDAPA. Recommendation levels (A; B; C; D)was graded basing on the evidence level(1-4).

Results

The adapted guidelines presented here focus on topical and systemic therapies in AD patients, both children and adults. As opposed to previous Italian guidelines, they include indications about biologics. New relevant evidence available from very recent literature and peculiarities of the Italian medical and legal context have been have been integrated in the revision process.

Conclusions

If compared to general guidelines for AD not adapted to a specific national and cultural context, a revision for specific Italian needs is now available: it comprises the option of impolementing the new biologic treatments and is likely to provide an important contribution to the improvement of clinical practice in Italy. Cooperation between patients, dermatologists, allergologists and pediatricians remains mandatory in AD management. The authors of the present revision recommend an update of the Italian guidelines to be performed at least every second year.

Keywords: atopic dermatitis, atopic eczema, topicals, cyclosporin, azatioprin, methotrexate, phototherapy, dupilumab

1. INTRODUCTION

Atopic dermatitis (AD) is an inflammatory, itchy, chronic or chronically relapsing skin disease, often associated with other atopic mucous membrane diseases, highly concordant in homozygous twins and an overall high family history (Hanifin *et al*., 1980, Wollenberg *et al*., 2016, Megna *et al*., 2017, Weidinger *et al*., 2016). AD prevalence is 20% in children and 2-8% in adults, indeed 10% of the affected deserve a systemic treatment (Wollenberg *et al*., 2016, Wollenberg *et al*., 2018 a, Wollenberg *et al*., 2018 b).

Diagnosis should be made according to the Hanifin and Rajka but these criteria may fit only partially in adults (Weidinger *et al*., 2016) especially in the case of adult onset presentation. The latter occurs in about one-third of adult cases observed in adulthood (Hanifin *et al*., 1980, Weidinger *et al*., 2016).

Once the diagnosis is made the evaluation of the severity of both subjective and objective symptoms is required for choosing the treatment. SCOring of Atopic Dermatitis (SCORAD), Eczema Area and

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Severity Index (EASI), Investigators Global Assessment (IGA), together with Dermatology Life Quality Index (DLQI), are free obtainable, worldwide used scores to evaluate AD severity. Additional scales may be used to measure of specific symptoms such as itch and sleep disturbances. Among these scales the Patient-oriented Eczema Measures for Eczema (POEM), Numerical Rating Scale (NRS), and the Visual Analogue Scale (VAS) are frequently used. (Wollenberg *et al*., 2018 b).
To date, no validated score allows an all comprising global evaluation of both objective and subjective symptoms. SCORAD, with its three level of severity (mild: <25; moderate: 25-50; severe: >50) should support the choice of the therapeutic approach (Wollenberg *et al*., 2016,). EASI is frequently used in the clinical objective evaluation of the severity of the disease, utilizing non univocal scores to define mild, moderate, and severe AD (Wollenberg *et al*., 2018 a, Wollenberg *et al*., 2018 b).
No pathognomonic biomarkers are available, however, the level of total or allergen specific IgE or the prick test to allergens allow to distinguish intrinsic AD (non-IgE associated) from the extrinsic form (IgE associated) (Wollenberg *et al*., 2016,).
In the course of the last decades important advances were made in understanding the pathogenesis of AD; new elements of the pathogenesis such as dysregulated Th-2 polarization of the immune response, impaired maturation of keratinocytes, deficient skin barrier function, abnormal microbial colonization with increased susceptibility to skin infections (Wollenberg *et al*., 2018 a) have been identified. The present adaptation of the European guidelines (Wollenberg *et al*., 2018 b, Ring *et al*., 2012 a, Ring *et al*., 2012 b) aims to adapt, enrich and contextualize the current evidences towards important and relevant strategies for management of AD in Italy.

2. METHODS

The EDF Consensus based guidelines (Wollenberg *et al*., 2018 b, Ring *et al*., 2012 a, Ring *et al*., 2012 b) (on which the present work is based) are an update of the 2012 guidelines (Ring *et al*., 2012 b), integrated with evidence-based national guideline from Germany (Werfel *et al*., 2009), the Health Technology Report (HTA) report (Hoare *et al*., 2000), as well as the position paper of the ETFAD/EADV (Darsow *et al*., 2010). In 2015, during a meeting in Copenhagen, two authors were chosen to prepare a the first draft of the guidelines; this draft was prepared on the basis of full articles only, published before March 2015. Eventual discrepancies were debated during the consensus process. Due to the consensus nature of the document, a systematic review of the literature was not performed to provide the first draft. The A specifically appointed European Dermatology Forum (EDF) committee reviewed the first draft, hereby setting as target group dermatologists, pediatricians, allergists general practitioners as well as, more generally any physician involved in the management of AD.

The EDF approved and published guidelines were then assessed independently by a committee of Italian renowned experts in the field. The committee integrated into the original paper the content of relevant papers published before May 2019. To this purpose, a systematic review of the literature in Pubmed, Embase and Scopus with the term “atopic dermatitis” and “atopic eczema” was performed. Only full articles in English, Italian, Spanish, and French were included. The result was a first draft of the Italian Guidelines, which was then submitted to special committees of the Italian Scientific

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Societies SIDEMAST (Italian Society of Medical, Surgical and Aesthetic Dermatology and Venereology), ADOI (Italian Society of Dermatologists and Venereologists Hospital-based and Public Health), and SIDAPA (Italian Society of Allergological Occupational and Environmental Dermatology). The various committees revised the manuscript and delivered a new draft, which was revised one last time by the board members of the GSAC (Cutaneous Allergy Study Group) before being submitted for publication. All representatives of the societies chose to adopt EASI as severity score (mild 1-5, moderate 6-22, severe 23-72 points).

Recommendation levels (A; B; C; D) were graded basing on the evidence level (*1-4*):

A: meta-analysis on randomized controlled trials (RCTs) (*1a*) or single RCT (*1b*)

B: systematic review of cohort studies (*2a*) *or* single cohort study *or* RCTs of limited quality (*2b*) *or* systematic review of case control studies (*3a*) *or* single case-control study (*3b*)

C: case series or case-control study or cohort study of limited quality (*4*)

D: expert opinion (-)

3. AD management from a patient's perspective

AD being a chronic disease with multifactorial pathogenesis, where psychosocial factors play a significant role, its management requires a good communication among the different medical professionals and between medical professionals and patients. Several issues need to be tackeld by both medical professionals and patients in order to achieve, as a result of a long term and fruitful collaboration:

- a proper identification of symptoms and basic management of such symptoms in daily life;
- from the part of the patients, optimal understanding and implementation of the existing therapeutic options;
- ongoing sharing of the latest, updated information regarding new therapeutic options;
- concordance between patients and physicians regarding the treatment goals, especially in cases of severe AD.

4. General measures and avoidance strategies

Identifying possible triggers is mandatory in AD: avoiding them may reduce or even completely clear symptoms thus increasing the duration of the complete remission periods.

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Tobacco secondhand smoke and exposure to traffic exhaust should especially be avoided by AD patietns, but in the case of young children this is of adamant importance. Occupations involving contact with strongly sensitizing and irritating substances should also be avoided by AD patients.

Despite the theoretical rationale, no data appear to be available addressing the topic of airborne allergen avoidance in AD; an expert-based-consensus is warranted.

Avoidance of relevant contact allergens positive to patch tests, occupational sensitizing or irritating substances, pollens during pollen season, and house dust mites in selected cases are recommended (D, -).

The disruption of the skin barrier in AD patients raises the possibility of both sensitization and irritation, which could explain the increased prevalence of contact dermatitis that finally exert a detrimental effect also to AD (Teo *et al*., 2019).

The diagnosis of contact dermatitis in all patients but especially in AD patients should be conducted following the recently available Italian Guidelines in Patch Testing - adapted from the European Society of Contact Dermatitis (ESCD) (Stingeni *et al.*, 2019).

All patients with AD should be vaccinated in accordance with the national vaccination plan (B, 2a); however, this should not take place during the acute flares. However, the intracutaneous smallpox vaccination with attenuated live vaccine, which may lead to the life-threatening *eczema vaccinatum*, is counter indicated in AD (Wollenberg *et al*., 2004).

If a primary immunodeficiency is suspected, then the choice of treatment should be preceded by a thourough interdisciplinary discussion of the case between an immunologist and the treating dermatologist.

Although in nearly 40% of children with moderate-to-severe AD IgE-mediated food allergy can be shown, and although food avoidance may improve AD, avoidance diets do not cure AD, may even have detrimental effects such as progression to immediate-type allergy including anaphylactic reactions, According to Eigenmann et colleagues, "food allergy testing is primarily indicated when immediate-type allergic reactions are a concern (Eigenmann *et al*., 2019). In recalcitrant AD, if food is being considered a possible chronic trigger, a limited panel of foods may be tested. An avoidance diet is only indicated in patients clearly identified as food allergic by an appropriate diagnostic food challenge, and after adequately informing the family of the limited benefits, and possible harms of an elimination diet." (2b, B)

Encouraging date support the maintenance of a varied diet In fact, food diversity (D, 1) should be aimed to when introducing food other than maternal milk. This should happen at 4-6 months of age (B, 1-2). In cases with food allergy documented by oral provocation tests, eliciting foods should be avoided (B, 2b). Breast feeding is recommended until 4 months of age (C, 2-3); if for any reason this should not be possible in AD low risk children, cow's milk formulas may be used (C, 2-3), hereby utilizing a documented hypoallergic formula (B, 1).

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Possible benefits deriving from pre- and probiotics remain a matter of controversy.

Psychosomatic counselling, psychotherapeutic approaches, behavioral therapy techniques, autogenic training, relaxation techniques, psychological and psychosomatic interventions are recommended in selected patients. Physicians should explore a possible presence of corticophobia and in relevant cases seek psychological counseling for the patients (respectively the parents) .(A, 1a)

There is good evidence of the benefit from patient education programs. Increasing us is made of internet based programs. Physicians should explore the disposition of parents respectively adult patients towards such programs and, if possible, recommend their use (Siebert *et al*., 2019, Liang *et al.*, 2018, Yoo *et al*., 2018).

5. Therapeutic approaches

The AD management is illustrated in Figure 1 and is stratified in three main steps: basic therapy (emollients, avoidance of clinically relevant allergens), topical therapy and systemic therapy.

5.1.Basic therapy for a disturbed skin barrier function

A daily, frequent, regular application of emollients (at least 250 g per week in adults) (C, 3b) adjusting to the BSA in children is required. A regular emollients application helps sparing both short (3-6 weeks) and long term (>6 weeks) steroidal therapy (B, 2a) in mild-to moderate AD. Emollient bath oils and soap substitutes are recommended, particularly – during winter - those richer in lipids (C, 3b).

5.2.Topical therapy

Topical therapy comprehends the use of topical glucocorticosteroids (TCS) and topical calcineurin inhibitors (TCI). For their precise dosage see the fingertip unit (Long et al., 1991).

Other topical treatments are based on crisaborole, a PDE-4 inhibitor, and tofacitinb, a JAK inhibitor. This drugs are not yet available in Italy.

5.2.1. Topical corticosteroids (TCS)

The use of TCS in AD is recommended especially in the acute phase (D, -) and in patients with an improved risk/benefit ratio, such as the ones with infrequent relapses (D, -). Assessment of itch severity is used to evaluate response to treatment and dose-tapering is evaluable when itch is largely improved. To avoid steroid side effects (skin atrophy, teleangiectasia, spontaneous scars, *striae distensae*, and hypertrichosis) it is advisable to use steroids only during the acute flares. Potent TCS should not be used in sensitive skin areas (face, neck, folds). Only group II TCS are suggested for long term treatment (D, -), while group III TCS require an appropriate dilution for children <2 years

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(D,-). Proactive therapy may reduce relapses (A, 1b), but is tested in RCTs only for a duration of 20 weeks (A, 1b). As already mentioned, an important issue in AD management is corticophobia: it needs to be recognized and addressed in order to avoid undertreatment and improve adherence (C, 4).

5.2.2.Topical calcineurin inhibitors (TCI)

TCI recommended for AD are tacrolimus and pimecrolimus. Currently, topical tacrolimus is available in Italy as ointment with two different concentrations 0.1% for adults and 0.03% for children, whilst pimecrolimus is available as 1% cream.
TCI have important anti-inflammatory properties in AD (D,-) and are indicated in sensitive skin areas such as face, anogenital and intertriginous areas (A, 1b). TCI are indicated after the acute phase and should be considered after the flare is cleared by TCS (D, -).
Proactive therapy (twice/week) of tacrolimus is shown to reduce the time to relapses (A, 1b). Sun protection should be recommended during TCI use (D, -).

5.1.1. Phototherapy

The following phototherapy sources are widely used in the treatment of AD:
- NB-UVB emitting a maximum peak at 311-313 nm for chronic and moderate AD
- (less frequently) UVA1 (340-400 nm) for more severe phase (Rodenbeck et al., 2016).

In patients with pauci-lesional disease, there is the new option of employing excimer sources (monochromatic excimer light and laser at 308 nm); however, there is no recommendation for the treatment of AD patients (D, -).
Several pilot studies have demonstrated a moderate effectiveness of short wave of visible light at 380 nm (A, 1b).
PUVA therapy is no more recommended for AD, neither in children nor in adults because of the long term risk of malingnacies. Caution is especially warranted in patients previously treated with systemic immunosuppressants (C, 4) (Becker *et al*., 2011, Mavilia *et al*., 2008, Wollenschlager *et al*., 2009, Gamichler *et al*., 2005, Eustace *et al*., 2017).
NB UVB has been considered for the treatment of mild-chronic forms of AD and it is administered three times a week using the same increments employed in the treatment of psoriasis (C, 4). The starting dose is chosen according to the skin phototype. NB-UVB is recommended for children as from the age of 10 years (B, 2b) (Dittmar *et al*., 2001, Tzaneva *et al*., 2001).
UVA1 is recommended for acute severe forms in adult patients. Following standard protocols, this source is delivered five times a week for a maximum period of three weeks. Some studies have suggested that a medium dose (60 J/cm^2) could be as effective as a high dose (120 J/cm^2); more recently, however, it has been shown that in dark skin types a high dose protocol is more effective in treating severe forms in adult patients (C, 4)(Pacifico *et al*., 2019).
Adjuvant use of emollients plus TCS should be considered especially in the initial phase of phototherapy in order to prevent acute flares (C, 4).
Prepuberal patients may benefit from NB-UVB.
Patients beyond the age of 11 years, may also benefit from UVA-1 (D, -).

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5.2.Systemic therapies

Systemic agents for AD may be divided into three main categories: immunosuppressants (Glucocorticosteroids, Cyclosporin A, Azatioprin, Methotrexate, Mycophenolate mofetil), biologics (Dupilumab) and others (antimicrobials).
Immunosuppressants and biologics characteristics are summarized in Table 1.
In the present document, agents cited anecdotally or without evidences are mentioned only if rated at least B.

5.2.1. Oral glucocorticosteroids (OGCS)

The evidences for the use of OGCS in AD are low grade. Short term (up to 1 week) therapy with OGCS is moderately effective and the risk/benefit ratio is unfavorable. The indication for OGCS in children warrants even more caution.
Long-term use of OGCS is strongly discouraged due to the *plethora* of side effects; short term therapy (up to 1 week) may be considered an option, only exceptionally, for mild acute flares in AD (recommended dose: 0.5 mg/kg (D, -). Long term treatment with OGCS is not recommended (D, -).

5.2.2. Cyclosporin A (Cyc-A)

Cyc-A treatment may be considered in chronic, severe cases of AD in adults in a continuous regimen for a duration of up to 2 years (A, 1a). Its use is off-label in children and adolescents, but it may be used in severe AD under careful monitoring of blood pressure and renal function (B,2b). In adults, both short and long term may be effective (D, -). The starting dose should be 5mg/kg/day divided in 2 administrations and the duration of the therapy must be guided by tolerance and efficacy (D, -). No routinely check of cyclosporinemia is required (D, -). Once a clinical improved is achieved a dose reduction should be planned, decreasing the dose by 1 mg/kg/day every 2 weeks (D, -). After 2 years of Cyc-A, clinicians should switch to an another systemic therapy. A further cycle of Cyc-A can be considered, it should not be started 3-6 months from the end of the first Cyc-A cycle (D,-) have passed. Intermittent regimens may be constitute an option to decrease the long-term cumulative dosage (D, -).
Combination therapy with UV is not recommended due to Cyc-A photosensitization property (D,-).
No evidences are available, but CyC-A should be paused 2 weeks before and started again 4-6 weeks after a vaccination (D, -).

5.2.3. Azatioprine (AZA)

AZA may be used off-label both in adults (A, 1b) and children (C, 4) in case of non-response or loss of response or even when other systemic therapies are counter indicated. Particular attention should be paid for TPMT heterozygotic patients. Before starting AZA, thiopurine S- methyltransferase (TPMT) screening is required due to the risk of bone marrow toxicity (A, 1b). The suggested dose range is 1-3 mg/kg bw/day (A, 1b), with 1–1.5 mg/kg/day as maintenance dose. The recommended initial dose amounts to 50 mg/day, a slow increase under control of full blood and liver function is

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possible (D,-). Pregnancy is a relative contraindication (D,-). Combination with UV is discouraged (D,-).

5.2.4. Mycophenolate mofetil (MMF)

MMF is recommended for an off label treatment which should be considered after a failure of or Cyc-A therapy or when the latter is counter indicated. The dose must be not exceed 3 g/day in adults. Off-label treatment is possible also in children and adolescents.
Due to the teratogenic properties of the drug, when MMF is used an effective contraception should be employed *both* in women *and men* (B, 3a).

5.2.5. Methotrexate (MTX)

MTX is considered for an off-label therapy in AD in both children and adults (C, 4) and the dosage are the same approved in psoriasis (D,-).
Due to the teratogenic properties of the drug, during the treatment and 6 months after withdrawal an effective contraception should be employed in *both* women and *men* (B, 3a).

5.2.6. Dupilumab (Dup)

Dup is a fully human monoclonal antibody blocking the common alfa-chain receptor of IL-4 and IL-13. It was the first biologic drug approved in 2017 as first-line treatment for moderate-severe adult AD both in the USA and in EuropeIt is so far the only approved biologic drug for AD. It's safety profile is good: conjunctivitis is the only adverse event more frequently described than placebo in CRTs. Dup is recommended as a disease-modifying drug for adult patients with moderate to severe AD when topical therapies are not effective enough and when systemic therapies are not advisable (A, 1a). Overall recommendation is for long-term maintenance treatment, as the response is maintained for at least 1 year of continuous treatment in the majority of patients (1b).
Daily topical emollients and topical anti-inflammatory drugs (TCS, TCI) – if needed - may be combined with DUP treatment (B, 2b).

5.2.7. Antimicrobial therapy

Long-term topical antibiotics without clinically evident signs of bacterial infection should be avoided due to the sensitization and increase of bacterial resistance (B, 2b). However patients with clinical signs of *Staphylococcus aureus* infection may benefit to short course antibiotic therapy (B, 2b).
Topical antiseptic drugs (such as antiseptic baths based on sodium hypochlorite 0.005%) may be considered, particularly in case of bacterial superinfection (C, 4) or treatment resistance (B, 2b).
Topical or even systemic anti-fungal therapy should be evaluated in case of IgE sensitization to *Malassezia spp* and/or in head and neck variant of AD (B, 2b).
Prompt systemic antivirals are mandatory in case of *eczema herpeticum* (D, 4), and Varicella Zoster Virus (VZV) vaccination remains mandatory for children with AD and their parents because they may trigger severe relapses (B, 2a).

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5.3.Off-label treatments

5.3.1. Biologics therapies

Nemolizumab, an anti- IL-31 receptor A, displayed high efficacy in contrasting itch in AD patients (1b), however its use is connected to an increased incidence of peripheral edema (1b). Particular Caution is therefore warrented if the drug is prescribed to patients unresponsive to dupilumab (D, -). Other biologics such as rituximab (anti-CD20), mepolizumab (anti-IL-5), omalizumab (anti-IgE), ustekinumab (anti-IL-12/23) are presently not recommended for AD(C, 4).

5.3.2. Small molecules

Apremilast, a phosphodiesterase-4 inhibitor, may reduce severity of symptoms of AD (skin lesions, itch and quality of life impairment). It increases the intracellular AMPc leading to a downregulation of AD cytokines such as IL-2, Il-5 and IL-13. It may be considered in cases which prove unresponsive to in-label treatments (D, -).

Another promising small molecule is tofacitinb, a JAK inhibitor. It may to reduce SCORAD by 60-70% within 8-29 weeks. Despite the encouraging preliminary results, not enough evidences support its use in AD patients (C, 4).

5.3.3. Systemic therapies

Alitretinoin belongs to retinoids family and has a robust literature advocating its use in atopic hand eczema only in not-childbearing adult patients resistant to topical corticosteroidal therapy (A, 1b).

As other retinoids, alitretinoin has teratogenic effects and should be avoided in patients envisaging pregnancy. In AD lesions in other body sites than hands, Alitretinoin appears to be ineffective, as reported by a limited number of data currently available literature (C, 4).

The use of first and second generations H1R antihistamines in treating AD derived pruritus should be episodically reserved to patients with itch resistant to topical corticosteroids and emollients (1b,A). Their long term use may, however, affect sleep quality in children and should be avoided (D, -). For H4R antihistamines results are , to date, not yet available.

In selected severe AD patients immunoadsorption may be considered (C, 4).

Mast cell stabilizers (-), leukotrien antagonists (B, 2a) and intravenous immunoglobulins (D, 4) are not recommended for AD.

5.3.4. Other therapies

Allergen-specific immunotherapy (ASIT) should be taken into consideration in subsets of severe AD patients with a proved (patch test positivity or history of exacerbations) allergy to house dust mite, birch, grass pollen (B, 2a).

Phytotherapy, Chinese herbal medicine, acupuncture, homeopathy, bioresonance, massage and aromatherapy, autologous blood therapy, vitamin or oral unsaturated fatty acids supplementations are not recommended in AD treatment.

Unsaturated fatty acids delivered topically in the context of dermatologically tested creams may be considered in selected cases (D, -)

Thermal spring water may be recommended in mild to moderate AD patients (B, 2a-2b),

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6. Conclusion

These guidelines are based on currently available evidence regarding AD treatments. It is recommended to update them very 2 years, on the basis of a systematic review. The multiple aspects of AD therapies reflect the complex pathophysiology of AD. Symptoms may currently be effectively treated and in some cases they may disappear. The innovation of biologics acting on immune mediators and receptors bears the promise for an effective future target therapy for AD. Good physician-patient communication remains essential and educational programs will still prove helpful in the future.

Reference

1. Becker, D., Langer, E., Seemann, M., Seemann, G., Fell, I., Saloga, J., *et al*. (2011). Clinical efficacy of blue light full body irradiation as treatment option for severe atopic dermatitis. *PLoS ONE*, **6**, e20566.
2. Darsow, U., Wollenberg, A., Simon, D., Taïeb, A., Werfel, T., Oranje, A., *et al*. (2010). ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol*, **24**, 317–328.
3. Dittmar, H.C., Pflieger, D., Schopf, E., Simon, J.C. (2001). [UVA1 phototherapy. Pilot study of dose finding in acute exacerbated atopic dermatitis]. *Hautarzt*, **52**, 423–427.
4. Eigenmann, P.A., Beyer, K., Lack, G., Muraro, A., Ong, P.Y., Sicherer, S..H, *et al*. (2019). Are avoidance diets still warranted in children with atopic dermatitis? *Pediatr Allergy Immunol*, doi: 10.1111/pai.13104. [Epub ahead of print]
5. Eustace, K., Dolman, S., Alsharqi, A., Sharpe, G., Richard Parslew, R. (2017). Use of phototherapy in children. *Pediatric Dermatol*, **34**, 150-157.
6. Gamichler, T., Breuckman, F., Boms, S., Altmeyer, P., Kreuter, A. (2005). Narrowband UVB phototherapy in skin conditions beyond psoriasis. *J Am Acad Dermatol*, **52**, 660-670.
7. Hanifin, J.M., Rajka, G. (1980). Diagnostic features of atopic dermatitis. *Acta Derm Venereol*, **92** (Suppl), 44–47.
8. Hoare, C., Li Wan Po, A., Williams, H. (2000). Systematic review of treatments for atopic eczema. *Health Technol Assess*, **4**, 1–191.
9. Liang, Y., Tian, J., Shen, C.P., Xu, F., Wang, H., Li, P., *et al*. (2018). Therapeutic patient education in children with moderate to severe atopic dermatitis: A multicenter randomized controlled trial in China. *Pediatr Dermatol*, **35**, 70-75.
10. Long, C.C., Finlay, A.Y. (1991). The finger-tip unit--a new practical measure. *Clin Exp Dermatol*, **16**, 444-447.
11. Mavilia, L., Mori, M., Rossi, R., Campolmi, P., Puglisi Guerra, A., Lotti, T. (2008). 308 nm monochromatic excimer light in dermatology: personal experience and review of the literature. *G Ital Dermatol Venereol*, **143**, 329–337.
12. Megna, M., Patruno, C., Balato, A., Rongioletti, F., Stingeni, L., Balato, N., *et al*. (2017). An Italian multicentre study on adult atopic dermatitis: persistent versus adult-onset disease. *Arch Dermatol Res*, **309**, 443-452.

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13. Pacifico, A., Iacovelli, P., Damiani, G., Ferraro, C., Cazzaniga, S., Conic, R.R.Z., *et al*. (2019). 'High dose' vs. 'medium dose' UVA1 phototherapy in italian patients with severe atopic dermatitis. *J Eur Acad Dermatol Venereol*, **33**, 718-724.
14. Ring, J., Alomar, A., Bieber, T., Deleuran, M., Fink-Wagner, A., Gelmetti, C., *et al*. (2012 a). Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *J Eur Acad Dermatol Venereol*, **26**, 1176–1193.
15. Ring, J., Alomar, A., Bieber, T., Deleuran, M., Fink-Wagner, A., Gelmetti, C., et al. (2012 b). Guidelines for treatment of atopic eczema (atopic dermatitis) part I. *J Eur Acad Dermatol Venereol*, **26**, 1045–1060.
16. Rodenbeck, D.L., Silverberg, J.I., Silverberg, N.B. (2016). Phototherapy for atopic dermatitis. *Clin Dermatol*, **34**, 607-613.
17. Siebert, M.J., Qureshi, Y., Chu, T., Goff, H.W. (2019). Validation of an Evidence-Based Educational Smartphone Application for Atopic Dermatitis. *Dermatitis*, **30**, 176-177.
18. Stingeni, L., Bianchi, L., Hansel, K., Corazza, M., Gallo, R., et al. (2019). Italian Guidelines in Patch Testing - adapted from the European Society of Contact Dermatitis (ESCD). *G Ital Dermatol Venereol*, **154**, 227-253.
19. Teo, Y., McFadden, J.P., White, I.R., Lynch, M., Banerjee, P. (2019). Allergic contact dermatitis in atopic individuals: Results of a 30-year retrospective study. *Contact Derm*.. doi: 10.1111/cod.13363. [Epub ahead of print]
20. Tzaneva, S., Seeber, A., Schwaiger, M., Honigsmann, H., Tanew, A. (2001). High-dose versus medium-dose UVA1 phototherapy for patients with severe generalized atopic dermatitis. *J Am Acad Dermatol*, **45**:503–507.
21. Weidinger, S., Novak, N. (2016). Atopic dermatitis. *Lancet*, **387**, 1109-1122.
22. Werfel, T., Aberer, W., Augustin, M., Biedermann, T., Fölster-Holst, R., Friedrichs, F., *et al*. (2009). Atopic dermatitis: S2 guidelines. *J Dtsch Dermatol Ges*, **7**(Suppl 1), S1–S46.
23. Wollenberg, A., Barbarot, S., Bieber, T., Christen-Zaech, S., Deleuran, M., Fink-Wagner, A., *et al*. (2018 a). Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. *J Eur Acad Dermatol Venereol*, **32**, 657-682.
24. Wollenberg, A., Barbarot, S., Bieber, T., Christen-Zaech, S., Deleuran, M., Fink-Wagner, A., *et al*. (2018 b). Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. *J Eur Acad Dermatol Venereol*, **32**, 850-858.
25. Wollenberg, A., Engler, R. (2004). Smallpox, vaccination and adverse reactions to smallpox vaccine. *Curr Opin Allergy Clin Immunol*, **4**, 271–275.
26. Wollenberg, A., Oranje, A., Deleuran, M., Simon, D., Szalai, Z., Kunz, B., *et al*. (2016). ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *J Eur Acad Dermatol Venereol*, **30**, 729–747.
27. Wollenschlager, I., Hermann, J., Ockenfels, H.M. (2009). Targeted Targeted UVb 308 nm (NB UVB) therapy with excimer laser in the treatment of atopic dermatitis and other inflammatory dermatoses. *Hautartz*, **60**, 898-906.
28. Yoo, J.B., De Gagne, J.C., Jeong, S.S., Jeong, C.W. (2018). Effects of a Hybrid Education Programme for Korean Mothers of Children with Atopic Dermatitis. *Acta Derm Venereol*, **98**, 329-334.

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Figure 1: Therapeutic algorithm in children and adults based on EASI severity index.

EASI mild: 1-5 points, EASI moderate: 6-22 points, EASI severe: 23-72 points

§: In-label treatment, °: Contraindications to assess in Table 1, *: Indication for Atopic Dermatitis.

Modified from Wollenberg et al.

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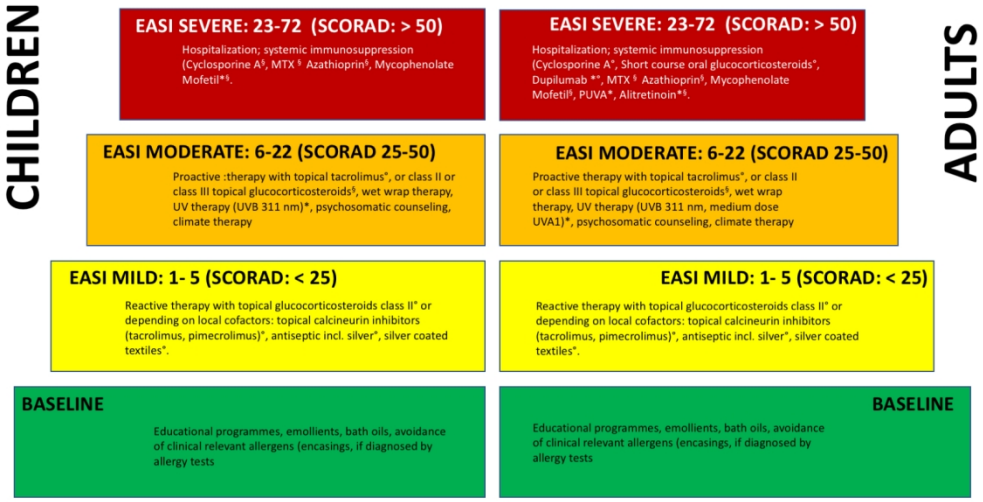

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Table I. Summary of the main characteristics of immunosuppressants and biologics adopted in AD

	CycA	**MTX**	**Aza**	**Myc**	**Oral Cort**	**Dup**
Recommendation	Acute flare	Long term maintenance	Long term maintenance	Long term maintenance	Short term	Long term maintenance
Lab tests	CBC, cratinemia, seric magnesium, seric potassium, seric sodium, seric .	CBC, transaminases, GGT, ALP	CBC, TPMT, LDH, ALT, AST, GGT, ALP	CBC, creatininemia, glycemia, Hb1c	CBC, glycemia, Hb1c	CBC, ocular exam.
Response timing, weeks	2	8-12	8-12	8-12	1-2	4-6
Relapse timing, weeks	<2	>12	>12	>12	<2	>8
Starting dose	*Adults*: 4-5 mg/kg/day *Children*: 5 mg/kg/day	*Adults*: 5-15 mg/week *Children*: 10-15 mg/m2/week	*Adults*: 50mg/day *Children*: 25-50mg/day	*Adults*: 1-2 g/day *Children*: 20-50 mg/kg/day	*Children & Adults*: 0,2-0.5 mg/kg/day	*Adults*: 600 mg loading dose *Children*: currently under investigation
Maintenance dose	*Children & Adults*: 2.5-3 mg/kg/day	*Adults*: usual 15-25 mg/week *Children*: increase of 2.5-5 mg/week, decrease 2.5 mg/week until the lowest responsive dose	*Children & Adults*: 2-3 mg/kg/day, decreased to 1-1.5 mg/kg/day in case of TPMT heterozygote	*Adults*: 2-3 g/day *Children*: increase of 500 mg every 2-4 weeks until 30-50 mg/kg/day	Not for maintenance	*Adults*: 300 mg/2weeks *Children*: currently under investigation
Renal or hepatic failure	Correct for renal creatininemia	Hepatic failure is a controindication	Contraindicated in case of severe hepatic failure	In case of renal filtration <25 ml do not overgo 2g/day	No correction	No adjustment
Main side effects	++: Renal dysfunction, hyperlipidemia, tremor, headache, hypertension, irsutism. +:Leucopenia, pyrexia, myalgia, cramps, acne, hypertransaminasemia, nausea, diarrhea, gingival hyperplasia, peptic ulcer, flushes, Hyperglycemia, anorexia, hyperuricemia, hyperkalemia, hypomagnesemia	++: Abdominal pain, nausea, vomit, stomatitis, +: Rash, itch, interstitial pneumonia, headache, anemia, bone marrow low activity, pneumonia, herpes zoster	++: Infections. +: Alopecia, hepatic dysfunctions, pancreatitis, leucopenia	++:Herpes zoster, herpes simplex, leucopenia, thrombocytopenia, anemia +: pneumonia, airways inflammation, cutaneous neoplasia, pancytopenia, leukocytosis, acidosis, hypo-hyperptassiemia, hypocalcemia, hypercolestorlemia, hypophosphatemia, hyperuricemia	++: gastric ulcers	++: Injection site reaction +: cephalea, conjunctivitis, oral herpes,
Conception	Possible	*Pregnacy*: contraindicated *Fathering*: conflicting data	*Pregnacy & Fathering*: conflicting data, possible under strict monitoring	*Pregnacy*: contraindicated *Fathering*: conflicting data	Possible	No data yet

management.

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Legend: CycA: Cycloporine A, MTX: Methotrexate, Aza: Azathioprine, Myc: Mycophenolate mofetil, Cort: Corticosteroids, Dup: Dupilumab.

++: Very common (≥1/10), +: Common (< 1/10 and ≥ 1/100)

*All drugs should be avoided in case of hypersensitivity of the active compounds or even to excipients.

Children: <18 years

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