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NEWS & VIEWS

Algorithms in Allergy and Clinical Immunology

Medical algorithm: Treatment of atopic dermatitis in early childhood (part II)

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The diagnostic work-up of atopic dermatitis (AD, atopic eczema) was discussed in part I.[1] This part of the medical algorithm focuses on the therapy of AD in early childhood and is based on recent literature and international guidelines.[2-4]

The management of AD is mainly based on disease severity, which has already been discussed in part I. Basic therapy of the disturbed skin barrier is always necessary, that is, also for children that do not suffer from active lesions. Normally, topical treatment is the first choice. Phototherapy or systemic therapy are indicated if topical anti-inflammatory treatment fails (and patient adherence and compliance have been addressed) or in cases of (very) severe disease (step-up approach, see Table 1[2,3]).

Basic therapy consists of emollients to moisturize the skin and improve barrier function, advice on daily skin care and hygiene/bathing, and avoidance of trigger factors (including allergens). Adherence to (basic) therapy and correct drug use has to be addressed. Individual nonallergic trigger factors should be identified and patients and their parents need to be counseled in order to know how to cope with these factors (which are not always avoidable). If confirmed by allergy testing and deemed relevant (eg, specific food), counseling also needs to be focused on allergen avoidance, possible cross-reactions, and alimentary substitutes. Therapeutic patient education (eg, "eczema school") and written instruction plans are of great importance because many patients with AD can achieve disease control with optimized skin care and mild topical treatments.[5]

Mild AD can usually be controlled with reactive therapy in addition to basic therapy. Moderate-severe AD often requires subsequent proactive therapy with modern topical corticosteroids (TCS) with favorable risk/benefit ratios (with or without wet wraps) or topical calcineurin inhibitors (TCI). The choice for the best approach with regard to corticosteroid potency and class depends on age and body site (eg, lower potency for the face vs higher potency for the trunk). In general, children should be treated with TCS class II-III (European classification system, moderate to potent) and infants with diluted preparations. The choice for vehicles (oil-in-water vs water-in-oil) for topical corticosteroids depends on lesion characteristics (moist vs dry), and patient preference/adherence. The fingertip unit (FTU) method should be explained for optimal dosing: one fingertip of cream for an area of two adult palms. There is conflicting evidence on once vs twice-daily application.[6] TCI also can be used off label in children <2 years.[3] The choice of topical anti-inflammatory drug depends on local cofactors (eg, in moderate-severe AD it is recommended to start with TCS instead of TCI because the latter can evoke stinging in inflamed skin). Topical phosphodiesterase inhibitors are a recently approved treatment alternative.

For all patients, depending on the individual situation and disease course and severity, other nonpharmacological options can be used. Silver-coated textiles can be used to decrease *Staphylococcus aureus* colonization on the skin (conflicting evidence). Psychological counseling can be considered with regard to individual family psychodynamics. Climate therapy at high altitude is beneficial for atopic dermatitis, probably due to UV exposure, avoidance of allergen exposure, and decreased stress.[7]

For severe AD, or for cases that do not respond well to topical therapy, wet wrap therapy can be initiated in inpatient or outpatient settings.[8] Ultraviolet (UV) therapy is used reluctantly in early childhood due to the cumulative UV dosage, time necessary, and anxiety in the UV cabin. If used, narrowband ultraviolet B (311 nm) or

TABLE 1 Discussion of the therapeutic options mentioned in the algorithm for the treatment of atopic dermatitis (AD) in early childhood

Drug	Comments	Side effects
	Topical	
Corticosteroids	The mainstay of therapy; for reactive and proactive use. Extensive experience with the Fingertip Unit method (see text).	With prolonged use: skin atrophy, hypertrichosis, depigmentation, and telangiectasias. Systemic absorption, particularly in dysmature infants.
Calcineurin inhibitors	Safe, also <2 years of age (off label).	Initially stinging/burning on the application sites.
PDE4 inhibitors	Recently approved in >2 years of age.	Temporary stinging/burning on the application sites.
Wet wraps	Good alternative to systemic medication for crisis intervention or averting hospitalization.	Folliculitis. Systemic absorption/cushing in prolonged use. Not indicated during puberty because of side effects of the corticosteroids (striae).
Antiseptics	Topical disinfectants may be used but evidence is conflicting.	Rarely allergic reactions.
	Systemic	
Phototherapy	Not commonly used in early childhood (feasibility). If used, preference for narrowband ultraviolet B (311 nm) or ultraviolet A1.	Claustrophobia in small children, erythema/burns, premature aging of the skin, photocarcinogenity.
Antibiotics	Topical antibiotics are not advised; in case of superinfection systemic antibiotics are warranted.	Gastrointestinal problems, allergies/drug reactions (rare).
Cyclosporine A	Approved from the age of 16.	Hypertension, nephrotoxicity, tremor, hyperlipidemia.
Methotrexate	Safe in children but off label and effect takes longer than cyclosporine A. Folic acid supplementation recommended.	Hepatotoxicity, gastrointestinal discomfort.
Azathioprine	Off label.	Superinfection, nausea, hepatic function abnormality, malignancies.
Mycophenolate mofetil	Off label.	Superinfection, anemia, leukopenia, diarrhea.
Dupilumab	Biologic (injection). Approved from the age of 12.	Conjunctivitis, injection site reactions.

Note: Abbreviation: PDE4, phosphodiesterase 4.
Green = on label; Yellow = off label.

ultraviolet A1 is preferred. As first biologic for AD treatment, the interleukin (IL)4/13 receptor antagonist dupilumab has been approved in ages ≥12 years and is sometimes used off label in early childhood.[9] Its main side effects are eye inflammation (including noninfectious conjunctivitis and blepharitis), injection site reactions, and herpes simplex virus infections. Approval for children aged six years and older is expected soon. All other systemic medication is off label in early childhood. However, there is ample clinical experience with use of cyclosporine A (fast-acting and approved in Europe from age 16 years) and methotrexate, a safe alternative but clinical improvement takes longer. Cyclosporine A is nephrotoxic and may lead to hypertension, so blood pressure and renal function have to be monitored. Methotrexate is hepatotoxic. Other options are azathioprine (side effects: infection, nausea, and cancer) and mycophenolate mofetil (side effects: infection, anemia, leukopenia, and diarrhea). Regular blood tests are necessary to screen for hematological, hepatic, and renal side effects. There is limited evidence that omalizumab has a TCS-sparing effect.[10] Systemic corticosteroids are not recommended because of side effects (eg, growth impairment) and risk of rebound after discontinuation. Antibiotics should

FIGURE 1 Medical algorithm for the therapeutic management of atopic dermatitis (AD) in early childhood, based on severity. Adapted from: Wollenberg A et al, J Eur Acad Dermatol Venereol, 2018.[3] [A]For criteria, see part I of this medical algorithm. [B]Disease severity scales can be used but might not be practical. Severity (global assessment) can alternatively be assessed by body surface area involvement, lesional features and locations, and disease impact on quality of life. [C]Please refer to part I of this medical algorithm. [1]Not commonly used in early childhood (feasibility). Preference for narrowband ultraviolet B (311 nm) or ultraviolet A1. [2]Cyclosporine is licensed from age 16 and dupilumab from age 12 in Europe (approval for children aged 6 years and older is expected soon). All other systemic options are off label. [#]Choice depending on local cofactors. For moderate-severe AD, it is recommended to start with a corticosteroid. Choice of corticosteroid class (European classification shown) depending on age and local cofactors. [%]Off-label treatment option. *Special attention if age <3 mo or recurring infections: in early-onset severe AD, certain primary immunodeficiency syndromes such as Omenn syndrome, selective IgA-deficiency, Hyper-IgE-syndromes and Wiskott Aldrich syndrome, genetic disorders with an impaired barrier function, such as Comel-Netherton syndrome and peeling skin syndrome, and some inherited metabolic diseases such as biotin deficiency or phenylketonuria should be considered as differential diagnoses

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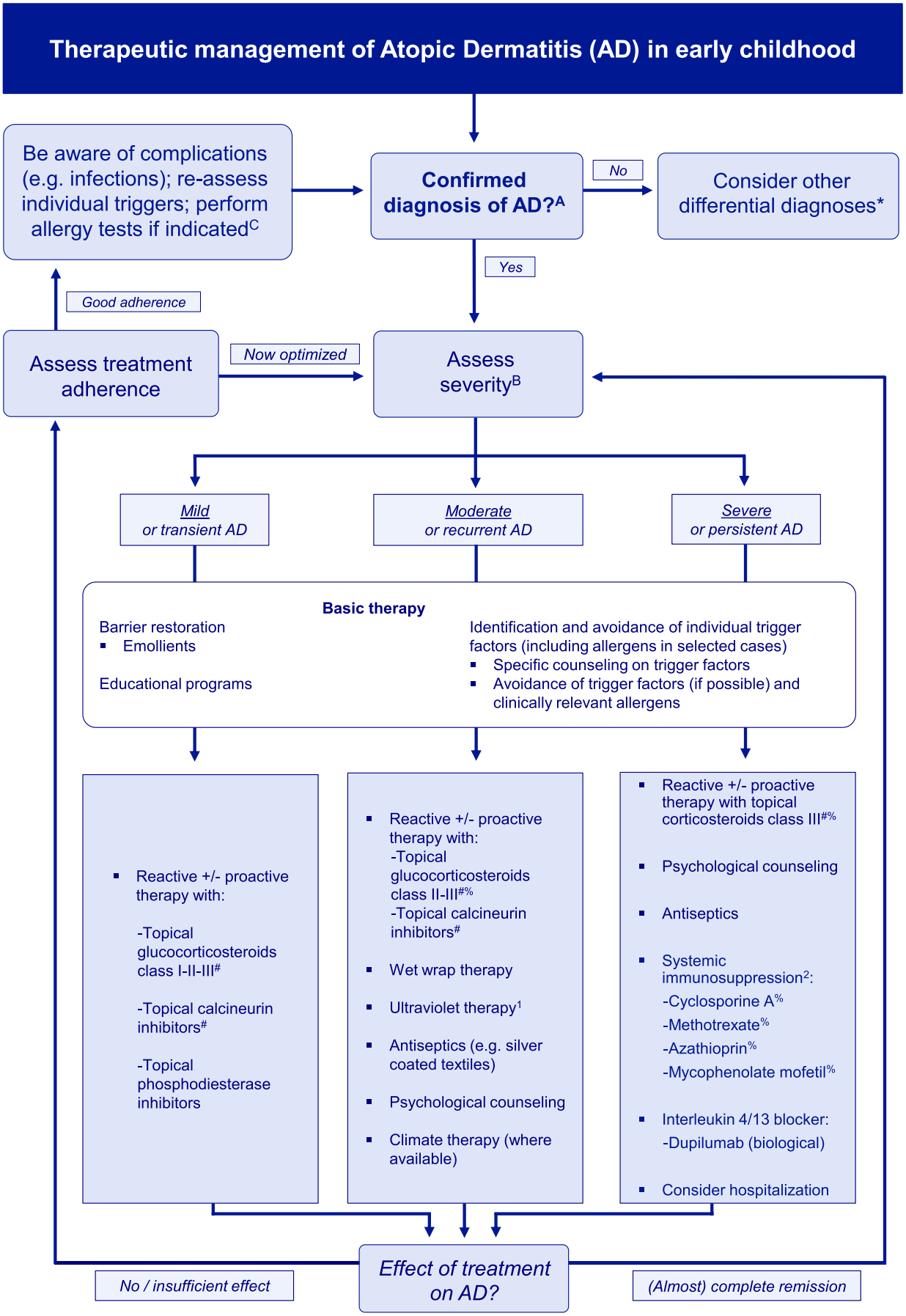

only be used systemically in cases of superinfection and not for the treatment of *S aureus* colonization. Long-term daily use of sedating antihistamines in childhood may affect sleep quality and is not recommended. In some countries, melatonin is used to improve sleep quality. A therapeutic algorithm is presented in Figure 1.

The algorithms (part I and part II) summarize the current standards for diagnosis and therapy of AD; however, the landscape is changing rapidly, especially for new therapeutic options. Dupilumab is currently the only biological approved for ages ≥12 years, with trials in younger children underway. Also, other drug classes are currently under investigation (eg, Janus-kinase and phosphodiesterase inhibitors for topical and systemic use). Given the special pace of innovation in AD treatment, the future is bright for young children with severe atopic dermatitis!

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CONFLICTS OF INTEREST

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