Dermatology Part 2: Ichthyoses and Psoriasis

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Abstract

Acute and chronic inflammatory skin diseases are frequent in childhood and may be hereditary or acquired. In this context, ichthyosis is rather a symptom than a defined disease as scaling is accompanying a number of disorders and is mostly consequence of a disrupted skin barrier. Ichthyosis is the basic pathogenic trait of atopic dermatitis but on the other side describes a group of rare hereditary diseases. These may only affect the skin or comprise several internal symptoms as well. Psoriasis is another scaling inflammatory skin disease with classical sharply demarcated erythematosquamous plaques and with a distinct immunogenetic background. It comprises several clinical subsets, some of which are characteristic for children and demanding in both diagnostics and therapy. Comorbid diseases point towards a systemic inflammatory response and require ample, often systemic treatment. Both ichthyosis and psoriasis may be topically treated including emollients with and without humectants as well as active agents like corticosteroids, vitamin D derivatives, and calcineurin inhibitors. In moderate to severe diseases, systemic treatment should be applied using methotrexate, ciclosporin, fumarates, or biologics. Their use should be critically discussed yet if necessary and indicated be applied to avoid chronic physical and psychological damage to the affected children.

Keywords

Ichthyosis · Psoriasis · Systemic therapy · Topical therapy · UV-therapy

1 Introduction

Chronic inflammatory skin diseases pose major therapeutic challenges, especially when present in children and adolescents. Apart from aspects like reduction of quality of life and a major influence on physical and emotional development of the affected children, only few therapeutic agents are evaluated and even fewer licensed for use in this delicate age period. Many skin diseases may be treated by external or topical agents only, yet more severe and chronic disease is often better treated systemically. With the advent of novel, well-tolerated, and effective systemic agents, the use of topical therapy has diminished. However, in many cases it is still needed to increase clinical effectivity and to treat residual or undulating limited skin manifestations.

2 Ichthyoses

Ichthyoses represent a group of very heterogeneous skin diseases with a distinct genetic background which are characterized by increased and mostly disseminated scaling (Yoneda 2016; Takeichi and Akiyama 2016). Quite a few are already present at birth (congenital) and perpetuate through childhood or even adulthood. Clinical

manifestations vary from mild to severe or even life-threatening. Apart from skin involvement, internal manifestations and malformations may be associated.

Four groups of ichthyoses are differentiated: (1) isolated, that is, skin-restricted, noncongenital ichthyoses, (2) associated congenital ichthyoses, (3) isolated congenital ichthyoses, and (4) associated non-congenital ichthyoses. Among these, autosomal dominant *ichthyosis vulgaris* is the most common disease with a prevalence of 1:250. It is related to a mutation at 1q21 which codes for the structural protein filaggrin. Grayish scaling is found on the trunk and extensor surfaces of extremities sparing the folds of arms and legs. The handlines are often prominent. Around half of the cases are associated with atopic diseases (atopic dermatitis and other forms of eczema, rhinoconjunctivitis, and asthma bronchiale). *X-chromosomal recessive ichthyosis* has an incidence of 1:2,000 among boys with an underlying genetic deficit of steroid sulfatase. A fine scaling can be seen immediately after birth. After vanishing until the age of 3–4 months, dark brown rhomboid scales remain to be seen on extremities and trunk, often suggesting lack of hygiene to the patient's surrounding. Palms and soles are always spared, but folds may be involved. Among *associated noncongenital ichthyoses*, Refsum syndrome and multiple sulfatase deficiency show only mild scaling, but associated internal organ, ophthalmological and neurological symptoms have to be excluded.

In contrast, *isolated congenital ichthyoses*, comprising lamellar and epidermolytic ichthyoses, are present at birth already, with distinct scaling, some accompanied by erythroderma which may fade in early childhood. The genetic background is not known for all disease subsets. *Epidermolytic ichthyoses* are very rare with a prevalence of less than 1:100,000 and comprise bullous ichthyosiform erythroderma Brocq and ichthyosis bullosa Siemens, both associated with specific keratin-mutations (Peter Rout et al. 2019). Clinically *Brocq-type ichthyosis* shows both erythroderma and massive bullous manifestations, which regress in early childhood and evolve into spinular keratoses. In contrast, *Siemens type ichthyosis* lacks erythroderma, but shows formation of bullae after even minor trauma as well as circumscribed keratoses, mainly on the limbs sparing the trunk except the umbilical area.

Associated congenital ichthyoses comprise among others Sjögren-Larsson and Tay as well as Netherton syndrome, again associated with ichthyosiform erythroderma at birth. Other clinical associations include mental retardation (Sjögren-Larsson), increased rate of skin cancer (Tay and other trichothiodystrophy syndromes) and atopic diseases as well as immune defects (Netherton syndrome) which have to be included into therapeutic decisions.

Apart from intensive and regular topical rehydrating and keratolytic treatment for all ichthyoses, systemic retinoids are efficient and should individually be discussed for congenital ichthyoses (Mazereeuw-Hautier et al. 2019a, b; Cortés et al. 2019). Systemic corticosteroids and immunomodulatory agents should not be used, however, if indicated topical or systemic antibiotic treatment in addition to ample skin dressings for erosions and bullous manifestations.

3 Psoriasis

Psoriasis is one of the most common human inflammatory skin diseases afflicting 1.5–2% of the Caucasian population (Lowes et al. 2007). Epidemiologically, two peaks of incidence have been described, one in the third decade of life with a distinct hereditary, familial background, and a more severe course and a second peak in the fourth to fifth decade with a variable clinical course (Swanbeck et al. 1995). However, 20 percent of all psoriasis patients have the first manifestation of their diseases before the twentieth birthday with obvious consequences on their physical, emotional, and socioeconomic development (Augustin et al. 2010). At the same time, therapeutic approaches in childhood and adolescence are limited, and only few agents are licensed for this age.

The disease spectrum may grossly be divided into plaque and pustular psoriasis. Around 80% of all cases in adulthood present as *plaque psoriasis or psoriasis vulgaris* apparently with a similar percentage in childhood based on comparably limited epidemiological data available for this age (Benoit and Hamm 2007; Augustin et al. 2010; Chiam et al. 2011; Svendsen et al. 2016). Psoriasis plaques are sharply demarcated, distinctly red, and covered by medium-sized to coarse scales. Predilections sites are the extensor surfaces of extremities, the scalp and external meatus of the ear, as well as behind the auricle, at the umbilicus and at the rima ani. This is quite in contrast to atopic dermatitis which is diffusely demarcated, of pale red color, and covered by fine scaling. The synonymous term flexural dermatitis for AD is misleading as this location is mainly found in school age, whereas young children and adolescents show extensor surfaces predominantly involved. Similarly, napkin psoriasis is sharply demarcated and more common than napkin AD. Facial and palmar manifestations are rare in adult psoriasis, but characteristic for childhood. *Nail involvement* with nail pitting, salmon patches, and onycholysis is found in about 30% of juvenile patients and may indicate psoriasis arthritis where severe nail involvement is common (80%) but may also be present as minimal and only manifestation in familial, otherwise noninvolved cases (Pourchot et al. 2017).

A specific subtype in childhood is *guttate psoriasis* with oval, slightly elevated plaques of around 10 millimeter diameter, of yellow-reddish color, and covered by only mild scaling (Svendsen et al. 2016). They appear as an exanthema mainly on the trunk 1–2 weeks after viral or bacterial infections, characteristically after streptococcal tonsillitis and will vanish within the course of several weeks or few months (Thorleifsdottir et al. 2016, 2017; Rachakonda et al. 2015). The effects of tonsillectomy are discussed controversially, but surgical indication should be liberal. Oral antibiotic treatment may be advisable in acute cases, and for a limited period, effects of long-term antibiotic treatment are, however, much debated (Dogan et al. 2008; Owen et al. 2001; Horton et al. 2016).

In addition, vaccinations have been suspected to initiate or exacerbate skin manifestations (Gunes et al. 2015; Kokolakis et al. 2010). All recommended childhood vaccinations can and should be administered as long as there is no active skin disease (Groot et al. 2015; Heijstek et al. 2011). Ongoing and well-tolerated topical and systemic therapy do not pose a contraindication. However, any live vaccines should be administered before starting systemic immunomodulatory treatment or only after interrupting therapy for an interval depending on the agent used.

Guttate psoriasis may present as a single bout of disease, recidivate after further infections, may persist or even evolve into classical plaque psoriasis either in childhood or later life especially when the family history for psoriasis is positive. Many cases of childhood psoriasis may not be diagnosed at all, but treated as atopic dermatitis and mycosis, the classical and much more frequent differential diagnoses.

Twenty percent of psoriasis patients show *pustular psoriasis* with the most common subtype of *pustulosis palmoplantaris (PPP)* on palms and soles which is sharply demarcated at the edges of hand and feet where palmar borders dorsal skin. The simultaneous presentation of pain, erythema, and sterile pustules turning yellowish-brown when drying and coarse, partly circular scaling is characteristic. Classical plaque psoriasis may be present at other body sites in rare cases. Despite the circumscribed area involved, ample use of hands and feet in everyday life is severely hampered and demands efficient treatment. *Generalized pustular psoriasis* (GPP) is rare (2% of all adult cases), yet a severe disease with fever and a distinct reduction of general condition (Liao et al. 2002; de Oliveira et al. 2010). Differential diagnosis should include other pustular exanthemas due to infections or drug reactions. *Acrodermatitis continua suppurativa Hallopeau* with acral and periungual pustules and redness is often associated with acral bone erosions and arthritis.

Psoriasis arthritis (PsA) of childhood is included in the group of juvenile idiopathic arthritis (JIA) and covers classical peripheral as well as axial arthritis. In contrast to adult psoriasis where PsA presents after around 10 years of skin involvement in 75% of cases, the majority of childhood cases present before and even without any distinct skin manifestations. PsA is found in 30% of adult cases; comparable data for childhood psoriasis are hardly available. Details of this disease subset are covered in other chapters of this book but need to be addressed here as concomitant PsA distinctly influences therapeutic decisions on psoriatic skin disease (Cellucci et al. 2016; Ringold et al. 2013).

Similarly, *comorbid diseases* as found and extensively studied in adult psoriasis are relevant in childhood and have obvious impact on disease severity and therapeutic choices. Metabolic (diabetes mellitus, dyslipidemia, increased body weight) and cardiovascular diseases (esp. arterial hypertension) are more prevalent in childhood compared to healthy, age-related controls (Skinner et al. 2015; Tollefson et al. 2018; Kara et al. 2019; Osier et al. 2017). In adult disease, a two- to fivefold increase of comorbidities could be shown in different ethnic populations. If both psoriasis and comorbidities are mutually influencing each other or are results of shared, yet independent or parallel pathogenic pathways is still a matter of debate.

Disease severity is well defined in adult psoriasis, and several instruments for physician- and patient-based quantification are available, some validated or consented. A widely accepted approach to quantify disease severity and to monitor effective treatment is the psoriasis area and severity index (PASI) which summarizes redness, infiltration, scaling, and distribution on the skin surface in a numerical scale between zero (no skin manifestations) and 72 (maximal disease severity) (Fredriksson and Pettersson 1978; Langley and Ellis 2004; van Geel et al. 2017; Finlay 2005). Alternatively the percentage of affected body surface area (BSA) can be used. For life quality aspects, the dermatological life quality index (DLQI) is well-established and – though not psoriasis-specific – most widely used (Finlay and Khan

1994; Lewis-Jones and Finlay 1995; Beattie and Lewis-Jones 2006). PASI and BSA have not been validated for children: however, an adaptation of DLQI for ages 4–16 years is available (CDLQI) (Lewis-Jones and Finlay 1995).

Moreover, patient perception of disease severity, its impact on every day aspects as well as patient expectations towards therapy and its appreciation are currently discussed intensively for adults. A number of patient related outcomes (PRO) have become available recently for practical use. For adult treatment decisions, a PASI and/or BSA and DLQI above ten have been consented to discriminate between mild and moderate/severe disease defining the need for systemic treatment. In addition, distinct manifestations at visible (scalp, face, nails) or delicate sites (intertriginous, anogenital) are a criterion for disease severity as is the number and severity of comorbid diseases. In most cases, PsA will demand systemic treatment.

Treatment goals regarding efficacy in induction therapy have been consented for adults with a reduction of initial PASI after 12–16 weeks by at least 75% (PASI75) or a PASI 50–75 and DLQI $\leq$5 (Mrowietz et al. 2011). These may be adapted to children by using the CDLQI.

Psoriasis treatment options can be separated into three groups, (1) topical treatment, (2) treatment with ultraviolet (UV) light, and (3) systemic treatment (Peter Rout et al. 2019) (Table 1). Many of them may be combined to increase efficacy; some should not be combined which in many cases demands broad dermatological expertise (Bruner et al. 2003; van de Kerkhof 2015; van Geel et al. 2015). Therefore it is the decision of both patient/parents and physician based on individual parameters which treatment and when to initiate and how long to use. German and European guidelines for adult psoriasis and recently for juvenile psoriasis are available which critically cover the different treatment options (Nast et al. 2015, 2018; Eisert et al. 2019a, b). Decisions depend on the severity of the disease as described above, response to previous treatments, duration of disease-free state off treatment, expectations towards time to response and extent of response (disease-free state, minimal disease, or distinct improvement). Long-term response and tolerability have to be taken into account when treating a chronic inflammatory skin disease. In children and adolescents, such considerations have to be done even more critically than compared to adult patients (Sticherling et al. 2011; Ståhle et al. 2010; de Jager et al. 2010).

Table 1 The three main therapeutic approaches to psoriasis

Topical	UV	Systemic
Salicylic acid	Narrow band UV-B (311 nm)	Fumarates
Urea	Broad spectrum UV-B	Methotrexate
Corticosteroids	Photochemo-therapy (PUVA)	Ciclosporin
Vitamin D3 analogues	Balneophototherapy Bath-PUVA	Retinoids
Vitamin A analogues (Tazaroten)	Balneophototherapy Salt solution baths + UV-B	Apremilast
Dithranol		Biologics
Tar		

Currently there is no cure for psoriasis, yet available options allow at least distinct improvement of psoriasis manifestations and long-term suppression of exacerbation. This will differentially be discussed with the individual agents and approaches below; however when doing so, off-label status and local or national health imbursement regulations have to be taken into account.

4 Topical Therapy

Topical treatment, also referred to as local or external, plays an important role even with very effective and well-tolerated systemic treatments currently available and even more so in childhood psoriasis (Brune et al. 2003; Albrecht et al. 2011; Fluhr et al. 2000; Mason et al. 2013; van de Kerkhof 2015; Stein Gold 2016). It may be used as monotherapy in limited disease, in combination with systemic treatment or UV light to improve or accelerate clinical responses or when other modalities are contraindicated. Topical products usually contain (1) emollients as basic formulation, (2) humectants, (3) keratoplastic/keratolytic agents, and (4) active agents. In the following, the various therapeutic agents are differentially discussed for use in ichthyoses and psoriasis.

4.1 Emollients

Apart from active ingredients, the appropriate emollient is of prime importance for the efficacy of topical therapy as the penetration of agents through stratum corneum and epidermis is not only facilitated but enhanced by appropriate base composition. As an example, the same steroid compound may clinically be differently resorbed and thus differently potent depending on the formulation of emollient. Most commonly used emollients are white soft paraffin (petrolatum) apart from liquid paraffin, lanolin, castor oil, cetyl and stearyl alcohols, silicone oils, cocoa and shea butter, isopropyl myristate and palmitate, as well as polyethylene glycols. Special care is advised for juvenile patients by avoiding fragrances, artificial colors, and chemical conservation.

Numerous vehicles are available from creams to lotions, ointments, gels, foams, sprays, and shampoos. Young patients and their parents should be educated in the correct application of topical agents with respect to the frequency and duration of daily application and the maximal body surface area to be treated. A “fingertip unit” is easy to communicate and defines the optimal 500 mg of topical that should be applied to one hand size area of skin which in turn is equivalent to about 1% of adolescent or adult body surface area.

Based on the activity of skin inflammation (water in oil for subacute and chronic, oil in water base for acute disease), the affected body site (face versus extremities, skin folds versus free integument), and skin type (dry, oily, mixed skin) as well as season of the year (oil in water base in summer, water in oil in winter), galenic formulations have to be individually adapted.

4.2 Humectants

The skin barrier function is impaired in both psoriasis and ichthyosis resulting in increased transepidermal water loss and epidermal hyperproliferation and dyskeratosis. Therefore skin moisturization is of prime importance in addition to active anti-inflammatory agents. Humectants are often added to increase or maintain moisture in skin, most popular among them glycerol, sorbitol, polyethylene glycols, and urea (Gelmetti 2009; Lindh and Bradley 2015). Urea is a low molecular weight organic compound which is used in concentrations from 2 to 10% for rehydration of skin as well as for increasing the penetration of active agents like corticosteroids (Celleno 2018; Pan et al. 2013; Friedman et al. 2016; Fluhr et al. 2000). Mild skin irritation, especially at sensitive sites like face and folds, is the major unwanted effects and is especially relevant in children. Therefore concentrations below 2% should be used or glycerol as an alternative humectant.

4.3 Keratolytic/Keratoplastic Agents

Epidermal hyperproliferation and dyskeratosis are characteristic for psoriasis and ichthyoses. Therefore, initially excessive scaling material should be removed to enable penetration of active agents. The most common agent is salicylic acid which shows keratinolytic activity at concentrations above 5%, whereas lower concentrations are antiseptic (Madan and Lewitt 2014). Salicylic acid should, however, not be used in children younger than 12 years because of possible relevant resorption and intoxication. Similarly, modern topical combinations, with corticosteroids to increase their penetration into the skin, are only evaluated in adults and should be used cautiously in childhood. Alternative keratolytic agents are propylene glycol and dimethicon. The keratolytic activity of urea is only found well above a concentration of 5% which restrict its use in children (Eisert et al. 2019a, b).

4.4 Active Topical Agents

Most of the currently available topical agents are very effective and their clinical use is well-established; however, their evidence levels regarding efficacy and tolerability in childhood are limited (Table 2). Long-term topical treatment of larger skin areas will challenge the compliance of young patients, especially in adolescence as it takes time to apply in addition to tolerate greasiness and stickiness, skin irritation, as well as odor and the risk of contact sensitization. Continuous and widespread use of topical agents like corticosteroids and vitamin D derivatives may result in relevant systemic resorption which can be overcome by de-escalation and proactive treatment protocols as outlined below or by combination with other topical agents, with UV light or systemic treatment.

Table 2 Topical and systemic therapy for ichthyoses and psoriasis

	Plaque psoriasis	Guttate psoriasis	Pustular psoriasis	Ichthyosis vulgaris	X-chrom. recessive ichthyosis	Epidermolytic ichthyosis	Associated congenital ichthyosis
Topical							
Emollients	++	++	+	++	++	++	++
Topical GCS	++	++	+	–	–	–	–
Topical Calcineurin-inhibitors	+	+	–	–	–	–	–
Topical vitamin D	++	+	–	–	–	–	–
Topical vitamin A	(+)	–	(+)	–	–	–	–
Dithranol	+	++	–	–	–	–	–
Tars	(+)	–	–	(+)	(+)	–	–
Systemic							
Systemic GCS	(+)	–	+	–	–	–	–
Fumarate	–	–	–	–	–	–	–
Methotrexate (MTX)	+	(+)	++	–	–	–	–
Ciclosporin	+	(+)	+		–	–	–
Acitretin	+	(+)	+	(+)	–	+	+
Biologics					–	–	–
Adalimumab	++	–	(+)	–	–	–	–
Etanercept	+	–	(+)	–	–	–	–
Biosimilars	(+)	–		–	–	–	–

–not recommended (+) may be used, no evidence + recommendation ++ high recommendation

5 Topical Corticosteroids

Corticosteroids (CS) are until today the most effective and reliable anti-inflammatory agents available in medicine. Their clinical effects are mediated by intracellular corticoid receptors resulting in altered levels of inflammatory cytokines, adhesion molecules, and lipid mediators. The potency of topical corticosteroids has been classified into three to seven classes, numbered by decreasing potency in the USA, by increasing potency in Europe (Table 3).

With regard to their long-term local and systemic side effects, they should, however, very cautiously be used in chronic, recidivating inflammatory diseases like psoriasis and atopic dermatitis and for no longer than 4–8 weeks (Eisert et al. 2019a, b; Sticherling et al. 2011; Ståhle et al. 2010; de Jager et al. 2010). Especially childhood skin is prone to local side effects even after short-term use and with regard to the special relation of body surface to body volume of children which will result in relevant systemic resorption (Kragballe et al. 1991; Ruiz-Maldonado et al. 1982; van de Kerkhof 2015). Topical steroids should be used for induction therapy only and be slowly tapered by decreasing the application frequency upon improvement ("de-escalation"). Continued use over weeks or months twice a week at the sites which were originally involved ("proactive treatment") may spare steroid dose as well as reduce the number and severity of flares.

Topical corticosteroids have been pharmacologically improved over the years by increasing their lipophilicity through esterification, thus limiting their activity to the skin organ by inactivation within the epidermis. This holds true especially for mometasone and methylprednisolone aceponate or the development of novel formulations like sprays or foams. Hydrocortisone may be used in early childhood and delicate locations like the face and groin; otherwise class two agents are to be preferred. Prednisone is not topically effective. Corticosteroids are available in diverse vehicles which allows their appropriate use at any body site including sensitive areas like the face and folds as well as in a sensitive patient group like children.

Table 3 Topical corticosteroids listed by potency in Europe and the USA

Europe	USA		Corticosteroid compound (examples)
I	VII	Mildest	Hydrocortisone
	VI	Mild	Prednicarbate
II	V	Medium	Methylprednisolone aceponate Betamethasone valerate Triamcinolone acetonide
III	IV	Potent	Betamethasone dipropionate
	III	Very potent	Mometasone furoate
	II	Super potent	Halobetasol propionate
IV	I	Super high	Clobetasol proprionate

6 Vitamin D Analogues

Synthetic topical vitamin D-analogues are able to modulate keratinocyte proliferation and differentiation as well as inflammatory processes by intracellular receptor-driven mechanisms directly regulating pertinent genes. Calcipotriene (USA), called calcipotriol in Europe and Canada, is probably one of the best studied topical agents by GCP-criteria (Guenther et al. 2002; Kragballe et al. 2006; Park et al. 1999; van de Kerkhof et al. 2002). Available data for children are, however, limited (Eisert et al. 2019a, b). Clinical application may often have to be discontinued especially in children due to frequent skin irritation. Otherwise contact sensitization is rare and cancerogenic properties absent. Three different agents (calcipotriol, tacalcitol, calcitriol) are available as solution, cream, and ointment (Guenther et al. 2002; Weindl et al. 2006). Because of systemic resorption with hypercalcemia and hypercalciuria, vitamin D analogues should only be used on less than 30% of the body surface for maximally 8 weeks. Their efficacy can be increased by combination with UV light; however, simultaneous use of lactic and salicylic acid should be avoided as vitamin D analogues destabilize in their presence.

7 Topical Vitamin A Analogues

The acetylene retinoid tazarotene is a third-generation topical retinoid licensed for psoriasis in adults aged above 18 years in the USA and acne vulgaris in patients above the age of 12 (Weinstein et al. 2003; Weindl et al. 2006). However, tazarotene is currently not available in many countries. The agent binds to the retinoic acid receptors ß and gamma with a resulting decrease of epidermal proliferation and de-differentiation. Skin irritation is often limiting its clinical use. No more than 10–20% of body surfaces should be treated at a time. Altogether systemic retinoids like acitretin are more effective in chronic and hyperproliferative (scaling) skin manifestations and should be considered in chronic and widespread disease. Their effects in ichthyoses are not evaluated.

8 Topical Calcineurin-Inhibitors

Calcineurin inhibitors downregulate intracellular calcineurin resulting in a decreased production of interferon gamma, IL-2, and IL-4 by T-lymphocytes. Two topical macrolide calcineurin inhibitors, pimecrolimus and tacrolimus, are licensed for atopic dermatitis only (Steele et al. 2005); however, good clinical effects were seen for plaque psoriasis as well as in inverse locations of psoriasis in a number of case compilations and controlled studies (Brune et al. 2007; Castellsague et al. 2018; Eichenfield et al. 2002; Malecic and Young 2016). Initial burning sensations and pruritus may subside under continuous treatment. Long-term date does not support a black box warning on the risk of lymphoma following prolonged use of topical calcineurin inhibitors (Paghdal and Schwartz 2009). Topical calcineurin inhibitors may represent an alternative to corticosteroids at sensitive sites and in sensitive populations like children.

9 Dithranol

Dithranol (anthralin, cignolin) is a synthetic derivative of a natural mixture of plant ingredients, which has been used in medicine for centuries (Eisert et al. 2019b; Körber et al. 2019; Saraswat et al. 2007). Neither is it resorbed, mutagenic, and cancerogenic nor does it cause contact sensitization. Short *contact therapy* at increasing concentrations of 0.1–3% is applied over weeks starting with a few minutes to be subsequently rinsed off (Eisert et al. 2019a). In contrast *long-contact therapy* is started at lower concentrations of 0.01% and left on for 8–12 h. Mild skin irritation is intended but may limit its use with children where on the other side guttate psoriasis responds exceptionally well. Major additional disadvantages are reversible dark discoloration of the skin, hair, and nails and washable discoloration of clothing as well as sanitary fittings. As for conservation reasons, 1% salicylic acid is regularly added to the ointment; combination with vitamin D analogues should therefore be avoided. Dithranol is mainly used in a hospital setting for induction therapy of mild to moderate psoriasis (Eisert et al. 2019a). However, dithranol appears to have the longest disease-free interval among all other psoriasis treatments.

10 Tars

The various tar preparations (coal, wood tar) show (Sekhon et al. 2018) anti-inflammatory, antipruritic, and antiproliferative as well as antibacterial and antifungal activity (Paghdal and Schwartz 2009). Coal tar is available as crude tar or liquor carbonis detergens (LCD) and mostly sold over the counter. The *World Health Organization's List of Essential Medicines* rates tars among the most effective and safe medicines. A reduction of DNA synthesis as well as mitotic activity may normalize epidermal keratinization with positive clinical results on psoriasis and other epidermal hyperkeratotic diseases. In the USA crude coal tar (2–4% in petrolatum) is combined with artificial ultraviolet radiation (either broad or narrowband UVB) for the treatment of psoriasis as described by the American dermatologist William H. Goeckerman (1884–1954) and is regarded as safe and efficacious (Zhu et al. 2016; Kortuem et al. 2010). (Mild) irritation at the sites of application, folliculitis, and photosensitivity in addition to smell and discoloration of the skin and clothing limit its use especially in children. Conflicting data are available on carcinogenesis which is not relevant in short-term use (Eisert et al. 2019a; Paghdal and Schwartz 2009). In children, tars should be used with special care and only in cases when topical alternatives are neither available nor applicable (Eisert et al. 2019a).

11 Novel Topical Agents and Skin Delivery Systems

Progress in the development of topical agents has been limited over the last decade (Eisert et al. 2019a; Körber et al. 2019). New galenic formulations or penetration promotors may improve local treatment in the future. Novel agents currently in

phase 2 and 3 studies include Janus and tyrosine kinase (JAK and TYK inhibitors) as well as phosphodiesterase 4 (PDE4) inhibitors (Svendsen et al. 2016) with good therapeutic responses together with good to fair tolerability. Oral counterparts have already been licensed for rheumatoid and psoriasis arthritis.

12 Treatment with Ultraviolet Light

Ultraviolet light (UV) belongs to the broad spectrum of light emitted by the sun with wave lengths from 180 to 400 nm (Table 4). It comprises UVC (180–280 nm), UVB (280–320 nm), and UVA (320–400 nm) (Table 5). Belonging to electromagnetic radiation, the wavelength correlates to the depth of invasion into material or tissues. UVC is therefore efficiently filtered by the upper atmosphere and ozone layer, whereas UVB and A reach the Earth's surface and unprotected human skin. UVB is penetrating to the epidermal-dermal layer and UVA down to the middle dermis. Similarly, UVA light may penetrate glass panes and will be present until dawn, whereas UVB light will maximally reach the Earth's surface at midday. Around 11 o'clock in the morning and 3 o'clock in the afternoon, maximal UV irradiation is seen, and both adults and especially children should avoid direct sun exposure at that time. UV protection can be achieved by just staying out of the sun in the shade, by protective clothes, and by using chemical or physical UV protection, the latter recommended for children.

Biologically, UV light was shown to exert distinct immunological reactions on all resident and migratory cells of the skin (keratinocytes, endothelial cells, fibroblasts, Langerhans cells, T-cells) mostly resulting in a localized and temporary downregulation of immune mechanisms. Therefore the human skin exploits UV light to counteract constantly ongoing allergic and autoimmune processes. At least four different skin types are differentiated according to the color of the skin, hair, and eyes, erythema time and the degree of tanning after UV exposure. The most frequent skin types II and III in North Europe show an erythema time of unprotected skin of around 30 min. The skin is, however, able to counteract UV exposure to some extent

Table 4 Wave lengths of total sun light

Sun light	Wavelength (nm)
Ultraviolet light	180–400
Visible light	400–800
Infrared light	800–3,000

Table 5 Distribution of wave lengths within the ultraviolet spectrum

Ultraviolet light	Wavelength (nm)
UV-C	180–280
UV-B	280–320
UV-A	320–400
UV-A2	320–340
UV-A1	340–400

through production of melanin by melanocytes, by thickening of the epidermis and especially stratum corneum as well as active repair of UV-induced cell and DNA damage. With overdrive of these protective or reparative mechanisms, acute and chronic UV effects have to be anticipated. Sunburn is probably the most frequent human skin disease and may comprise a clinical range of mild erythema to blister formation. Repetitive sunburns in childhood are related to the incidence of malignant melanoma. Chronic and repetitive UV exposure will result in earlier and more pronounced skin aging as well as a higher rate of skin cancer, predominantly basal cell carcinoma, and squamous cell carcinoma. Though these tumors are very rare in children, they can be expected under massive immunosuppression or defective UV repair as in xeroderma pigmentosum.

Apart from casual UV-exposure through sunlight, UV is therapeutically used to treat inflammatory and neoplastic skin diseases like psoriasis and atopic dermatitis or cutaneous T-cell lymphoma. It can be produced by artificial lamps or ample filters and usually needs regular and repetitive visits (3–5 per week, 20–30 treatments) of practice rooms to apply (Zamberk et al. 2010). UVB narrowband (311 nm) is recommended as it represents the biologically active wave length of UVB avoiding unwanted effects of neighboring wave lengths. UVB may be used in adolescents, but should be very critically used in children (Nguyen et al. 2009). UVA monotherapy will only show minor anti-inflammatory effects but will accelerate skin aging as well as induce skin malignancy. Combination with psoralen either orally or in bath water or cream to increase the UV sensibility (PUVA) is regularly and successfully used in adults but should be avoided in children and adolescents (Eisert et al. 2019b).

13 Systemic Treatment

Effective and well-tolerated systemic treatment for chronic skin diseases is increasingly available and used in adults (Nast et al. 2015, 2018). Limited evidence for children and adolescents, however, will result in critical individual discussion of therapeutic options on one side, should, however, on the other not withhold ample and effective treatment of those affected (Eisert et al. 2019b; Posso-De Los Rios et al. 2014; van Geel et al. 2015; Napolitano et al. 2016). Whereas treatment goals and algorithms for psoriasis have been defined for adults and may cautiously be transferred to children, they are missing for other chronic inflammatory skin disorders. Recently, a German S2k guideline was published on the therapy of psoriasis in children and adolescents, the first one available on this issue (Eisert et al. 2019a, b). While summarizing the relevant systemic treatment options in the following chapter, local and national regulations regarding reimbursement, licensing, and drug monitoring as well as other recommendations and guidelines should be taken into account.

14 Systemic Corticosteroids

Though systemic corticosteroids are still widely used for the treatment of plaque psoriasis, general expert consensus is that they should be avoided for skin manifestations (Nast et al. 2018; Eisert et al. 2019b). Despite their immediate, reliable, and effective responses, continued and repetitive use will result in a number of severe unwanted effects which are especially relevant for children. Systemic corticosteroids may in single cases be used short-term for highly inflammatory skin manifestations, for acute arthritis or generalized pustular psoriasis and should be rapidly substituted by other immunomodulatory agents. Initial doses should be 0.5–1 mg/kg body weight prednisolone or equivalent. If administered for a few days, no tapering will be necessary.

15 Methotrexate

Methotrexate (MTX) is probably the most frequently used immunomodulatory agent in childhood (Eisert et al. 2019b; Posso-De Los Rios et al. 2014). As folic acid antagonist is exerts immunomodulatory activity on T-cells and cells of innate immunity. It is generally well-tolerated in childhood as limiting effects of lifestyle drugs relevant for adults (e.g. alcohol) as well as concomitant medication are mostly absent. Nevertheless, there is no official label for MTX use in children. It may be used for psoriasis arthritis, pustular psoriasis, severe manifestations of plaque psoriasis and guttate psoriasis. Maximal clinical effects may take up to 3 months to appear. Therefore, initial dosing should be 10–15 mg per square meter body surface once per week and may be increased every 4–8 weeks by 2.5 mg. With respect to gastrointestinal tolerance, the oral dose may be divided into a morning and evening dose; alternatively subcutaneous application should be used. The following day, 5 mg of folic acid should be administered to improve tolerability. After maximal clinical improvement, MTX doses should be slowly decreased again by 2.5 mg every 4–8 weeks; long-term and continuous application is reasonable and often necessary in individual cases. Blood count, liver enzymes, and renal parameters, preferentially creatinine, should be controlled after 1 and 6 weeks, thereafter every 6–12 weeks.

16 Ciclosporin

Ciclosporin (CSA) is an inhibitor of intracellular calcineurin resulting in the downregulation of various inflammatory cytokines, especially IL-2 by T-cells. Compared to methotrexate, clinical effects are evident after 4–8 weeks already; on the other side, continuous use longer than 6 months is critical with regard to nephrotoxic symptoms and possible arterial hypertension (Eisert et al. 2019b; Di Lernia et al. 2016; Pereira et al. 2006). Dosing ranges between 2.5 and 5 mg/kg body weight divided in two daily doses. It may be started with 2.5–3 mg, and

increased when clinical effects are small or missing, or alternatively started with 4–5 mg/kg body weight for severe disease. After clinical improvement, daily dosing can be reduced by 0.5 mg/kg body weight every month. Blood monitoring should include blood count, liver enzymes, serum electrolytes, and creatinine before treatment, after 4, 8, and 12 weeks, and every 3 months thereafter. CSA may be combined with any topical treatment, not, however, with UV treatment.

17 Fumarates

Fumaric acid esters or fumarates are a mixture of three compounds that have been licensed in Germany for the treatment of adult plaque psoriasis since 1994, the single substance dimethyl fumarate (DMF) in Europe since 2017. Available data from case reports, retrospective studies, and a controlled study not published yet suggest both good efficacy and tolerability in children and adolescents (Reich et al. 2016; Balak et al. 2013; van Geel et al. 2016; Eisert et al. 2019b). Dosing is increased over weeks similar to adult dosing, and efficacy is monitored by month 3. Full clinical effects may take more than 3 to 6 months to appear. Monitoring should include blood count, liver enzymes, and creatinine before treatment, initially every 4 weeks and from month 4 on every 8 weeks.

18 Retinoids

Vitamin A derivatives have been used over decades for hyperkeratotic diseases and diseases of sebaceous glands. Currently acitretin and isotretinoin are available (Kopp et al. 2004). The latter is preferably used for acne in adolescents and is less effective in hyperkeratosis yet better tolerated and less critical with respect to pregnancy: both agents need a monthly negative pregnancy test to start and continue, yet women should not become pregnant at least 3 years after stopping acitretin but only 4–12 weeks after stopping isotretinoin. This aspect becomes relevant for adolescent girls. Though no clinical studies on acitretin are available for childhood, numerous case reports and retrospective chart reviews suggest good effectivity and tolerance especially for pustular psoriasis and erythroderma, however, with relapses after stopping the treatment. Reassuring data on long-term efficacy and tolerability are available for various forms of ichthyosis. Combination with narrowband UVB may increase clinical improvement in psoriasis which usually takes 2–3 months. No effects are seen on psoriasis arthritis. Initial dosing should be 0.3–0.5 mg/kg body weight and may be increased stepwise up to 1 mg/kg body weight. Upon improvement, the doses should be slowly tapered to around 0.2 mg/kg body weight. The German guideline recommends acitretin for moderate to severe pustular psoriasis of girls and boys before puberty and for male adolescents (Eisert et al. 2019b; Guenther et al. 2017; Chen et al. 2018). Unwanted effects are dryness of skin and mucous membranes which may limit the treatment in childhood, alopecia, and bone as well as muscle pain. Effects on bone development of spine and long bones should

be clinically monitored and evaluated by X-ray if necessary. Laboratory monitoring includes blood count, liver enzymes, triglycerides, cholesterol and HDL, creatinine, and urea before treatment, initially every 4 weeks and every 12 weeks from month three on. A monthly negative pregnancy test is mandatory if relevant.

19 Biologics

Biologics have dramatically changed our therapeutic options of adult psoriasis in the last decades. These fusion proteins or monoclonal antibodies specifically inhibit the pathogenetically relevant inflammatory cytokines tumor necrosis factor alpha (TNFα), IL-12/IL-23, IL-17, and IL-23 with very good efficacy and tolerability. Using the recently licensed anti-IL-23 agents, PASI 90 improvements of more than 70% can be achieved. However, only few of these agents are evaluated and licensed for childhood psoriasis. A number of case reports on the use of biologics in childhood psoriasis are available, including pustular disease (Eisert et al. 2019b; Wright et al. 2010; Saikaly and Mattes 2016).

20 TNF-Blockers

Two TNF-blockers are available for subcutaneous application in children, the fusion protein etanercept from the age of 6 years and the monoclonal antibody adalimumab for children from 4 years and older.

21 Adalimumab

The monoclonal anti-TNF antibody was licensed in 2008 for children above the age of 4 suffering from severe plaque psoriasis who have responded insufficiently to topical and UV therapy (Braun et al. 2018; Wright et al. 2010). The German guideline recommends adalimumab for moderate to severe psoriasis in childhood with a 71% consensus (Eisert et al. 2019b). Five of seven experts preferred methotrexate. There is no license for juvenile psoriasis arthritis nor axial or ankylosing spondylarthritis. At a body weight up to 30 kg, adalimumab is started with 20 mg once a week for 2 weeks, thereafter 20 mg every 2 weeks, similarly at a body weight above 30 kg with 40 mg. Clinical evaluation and decision for continued treatment should be done at week 16. Initial laboratory monitoring includes differential blood count, liver enzymes, hepatitis B/C, and HIV serology with differential blood count and liver enzymes after 4 and 12 weeks, thereafter every 3 months. The German guideline recommends initial tuberculin skin test in children younger and quantiferon test in children older than 5 years. Chest X-ray should only be done with clear clinical suspicion. Annual Tb screening is not necessary with low Tb risk and initially negative Tb tests.

22 Etanercept

Etanercept is licensed for chronic severe psoriasis in children from 6 years and older who have not responded to or have not tolerated at least one conventional systemic agent or UV therapy, in addition to psoriasis arthritis above the age of 12 in children who have not responded to or not tolerated methotrexate. The German guideline recommends etanercept only when adalimumab or methotrexate failed. The dosing is individually adapted to body weight, with 0.8 mg/kg up to 50 mg per doses, above the weight of 62.5 kg with 50 mg as prefilled syringe or pen. Clinical evaluation and decision for continued treatment should be done at week 12. The initial and continuous laboratory monitoring including Tb screening is identical to adalimumab.

23 IL-12/IL-23 Blocker Ustekinumab

The monoclonal antibody ustekinumab is directed against the p40 unit shared by IL-12 and IL-23 and is licensed for children from the age of 12. It is applied at weeks 0 and 4 and every 3 months thereafter. Dosing is 40 mg at a body weight between 60 and 100 kg, 90 mg above 100 kg. Below 60 kg the recommended dose is 0.75 mg/kg body weight which can be drawn individually from a 45 mg glass vial. Clinical evaluation and decision for continued treatment should be done at week 28. Initial and continuous laboratory monitoring including Tb screening is identical to adalimumab.

24 Biosimilars

Biosimilars have become available after patent expired for adalimumab and etanercept. Regulations demand comparability to the original agents with respect to efficacy and safety which have to be proven in a least one licensed adult indication. Transfer of such data to children is critical, and biosimilar effects should be examined in juvenile patients in well-controlled clinical studies. Therefore, the use of both agents as biosimilars in children should be individually decided (Nast et al. 2018; Braun et al. 2018; Eisert et al. 2019b).

25 Novel Agents

The oral phosphodiesterase 4 (PDE-4) inhibitor apremilast has been licensed for adult plaque psoriasis and psoriasis arthritis in the USA in 2014 and in EU and Switzerland in 2015. Controlled clinical studies in children are ongoing and licensing for children may be expected soon. Several other clinical phase 2 and 3 studies are ongoing for adult psoriasis including novel monoclonal antibodies and oral inhibitors of Janus kinase (JAK) and phosphodiesterase 4 (PDE-4). Current regulatory procedures demand early initiation of clinical studies in juvenile patients.

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