Management of congenital ichthyoses

European guidelines of care, part one


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Management of congenital ichthyoses: European guidelines of care: Part One

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What's already known about this topic? Various symptomatic treatment options exist for congenital ichthyoses but there are no European guidelines.

What does this study add? These European guidelines for the management of congenital ichthyosis may help to improve outcomes and quality of life for patients.
ABSTRACT

These guidelines for the management of congenital ichthyoses have been developed by a multidisciplinary group of European experts following a systematic review of the current literature, an expert conference held in Toulouse in 2016, and a consensus on the discussions. They summarize evidence and expert-based recommendations and intend to help clinicians with the management of these rare and often complex diseases. These guidelines comprise two sections. This is Part one, covering topical therapies, systemic therapies, psychosocial management, communicating the diagnosis and genetic counselling.

INTRODUCTION

Congenital ichthyoses (CI) comprise a heterogeneous group of genetic diseases usually present at birth or appearing early in life. They affect the entire skin and are characterized by hyperkeratosis and scaling, often associated with skin inflammation (1,2). The CI are primarily monogenic diseases with more than 50 genes identified to date, leading to a defective skin barrier. The classification is based on the clinical presentation and distinguishes basically between non-syndromic (including common ichthyosis, autosomal recessive congenital ichthyosis (ARCI), keratinopathic ichthyosis and other forms) and syndromic ichthyoses (3) (S1). CI usually have a major effect on the quality of life (QOL) and therefore require lifelong treatment. So far, there are no curative therapies, but various symptomatic treatment options exist. The only available guidelines for the management of CI are national guidelines from Germany (4). We have developed European guidelines following a systematic review of the current literature, a guidelines conference and a consensus on the discussions. The recommendations are divided into 2 sections. Part one, covers topical therapies, systemic therapies, psychosocial management, communicating the diagnosis and genetic counselling. The second part will cover the management of complications and the particularities of some forms of CI.
AIM

These guidelines provide recommendations for the therapeutic management of CI. It may help to improve outcomes and QOL for patients.

USERS

Dermatologists and other health professionals including paediatricians, general practitioners, otolaryngologists (ENT), ophthalmologists, clinical geneticists, pharmacists, nurses, psychologists and podiatrists; patient support groups and patients with CI.

TARGET GROUP

These guidelines are aimed at the management of adults and children with CI.

DISCLAIMERS AND LIMITATIONS

Therapeutic strategies need to be adapted depending on the health care system and local conditions. Moreover, readers are advised to keep up to date with newly published data.

METHODS

In 2015, a European (16 countries) expert multidisciplinary group (involved in the ichthyoses sub-thematic group of the European Reference Network for rare and undiagnosed skin disorders (ERN-Skin)) was constituted, including 25 dermatologists, one paediatrician, one otorhinolaryngologist, one ophthalmologist, one clinical geneticist, one psychologist, one pharmacist, one dermato-epidemiologist and one nurse. Patients and families were also
strongly involved with the participation of the 3 representatives from patient support groups: one suffering from CI, 2 having affected children. The AGREE II instrument (23-item tool comprising 6 quality-related domains) (5) was used to develop these guidelines. Literature searches and the methodology of the conference are detailed in S2. Levels of evidence (LoE) and grades of recommendation (GoR) were evaluated using the Scottish Intercollegiate Network guidelines (S3). Our review of the literature revealed a very low number of randomized controlled trials including small heterogeneous groups of patients without standardization of outcome measures (6). Most articles were case reports or small series. For some topics, there were no data in the literature. Therefore, the level of evidence was often restricted to the categories 3 to 4 (expert opinion). These recommendations are presented in Table 1 and mentioned in the text.

PLANS FOR UPDATING THE GUIDELINES

An update of these guidelines and literature search will be necessary every 5 years after the publication. For future updates we will stick to a formal and consistent wording of recommendations. To ensure their availability and dissemination, the guidelines and their revisions will be disseminated via the European Reference Network for rare skin diseases as well as the patient support groups (www.ichthyose.eu).

TOPICAL AND SYSTEMIC THERAPIES

The different therapeutic options are described below. The choice of treatment depends on the morphology (i.e. scaling, hyperkeratosis), the disease distribution, the presence/absence of inflammation or erosions, the disease severity and the age of the patient.
Topical therapy

Topical agents represent the first-line treatment. They help to reduce scales, skin discomfort, pruritus, and may improve the general appearance of the skin. Their effect on barrier dysfunction is variable (7). Topical agents are considered to be essential and used by almost all patients. They are recommended by all experts (8–10), even though evidence from the literature is weak. Clinical studies have evaluated the effects of topical agents on scaling (and sometimes erythema and pruritus) on the body but not specifically on the scalp or palmoplantar skin. A variety of topical agents are available (Table 2). They can be used as monotherapy or in combination with oral retinoids. The choice of a specific agent is based on the various parameters described above (LoE 4, GoR D): availability, formulation and texture, possibilities for reimbursement and costs. Unpleasant smell or a very greasy consistency of ointments needs to be avoided. Finally, the preferences of the patients are decisive considering that the therapeutic outcome is largely dependent on therapy compliance, as application of topical therapies is time consuming and demanding (11).

Emollients

Emollients act via skin hydration, lubrication and occlusion (12). Many emollients are available and their properties vary according to formulation and lipid-to-water ratio content. There are no studies comparing different emollients. In clinical practice, the preferred emollient varies among patients. Application of emollients is recommended for all ichthyosis (LoE 1, GoR B), as often as necessary, at least twice a day and ideally after bathing to improve skin hydration (LoE 3, GoR D) (9). Except for transient minor symptoms such as itching or a burning sensation, moisturizers are safe (8,13,14). Since they may not be well tolerated, emollients containing urea are
not recommended on inflamed skin, flexural areas or erosions (LoE 3, GoR D) (1).

Increased skin permeability may increase the risk of allergic contact dermatitis (15). Large applications of occlusive pure ointments are not recommended since they may further impair heat tolerance, promote maceration and infections, particularly in hotter climates (LoE 4, GoR D) (9). For patients with thick scaling/hyperkeratosis, we suggest addition of other agents (LoE 1, GoR B).

Keratolytics

Their superiority over emollients in removing scales/hyperkeratosis was demonstrated in a few studies (13,16–21). These studies included urea (≥10%), alpha hydroxyl acids (5 to 12 %), propylene glycol (>20%), salicylic acid (>2%), alone or as a combination. There is no evidence to conclude which is the best keratolytic agent or which is the best combination. In clinical practice, urea is the most frequently used agent; its concentration may be increased up to 20%, even 40% in localized area of thick scale or hyperkeratosis. Keratolytics are usually applied once or twice daily and can be tapered depending on the response (LoE 1, GoR B). Side-effects include itching, burning sensation and irritation. Application on the face, flexures and areas of fissuring are not recommended since they may induce irritation (LoE 1, GoR B) (8). Systemic absorption and toxicity must be taken into account considering the epidermal barrier defect (22), especially in children. Therefore, all keratolytics must be avoided in newborns and young infants (LoE 3, GoR D), the exact age limit not being well defined. We recommend to strictly contraindicate salicylic acid for children under the age of 2, and to restrict the application once daily to limited areas for older children (23-27). Urea (≥10%) is not recommended before the age of 1, except once daily on limited areas such as the palms and soles.
Topical retinoids

Topical tazarotene has demonstrated efficacy in a small open study of 12 patients with CI (28) and one patient with severe X-linked recessive ichthyosis (XLRI) (29); adapalene was used in a patient with epidermolytic ichthyosis (El) (30). Topical tazarotene may also be used for ectropion (see Part Two). Although a meta-analysis including pregnant women who were exposed to topical retinoids was reassuring (31) and repeated topical administration on limited areas are unlikely to induce systemic effects (32), the use of topical retinoids is contraindicated during pregnancy (LoE 1, GoR B).

Other topical agents

Other topical agents may be useful (LoE 3, GoR B). Calcipotriol, a vitamin D derivative has demonstrated efficacy in adults (33) but limited by a maximum weekly dose of 100 g. N-acetylcysteine, a thiol derivative used as a mucolytic agent showed efficacy in a small case series (34). Nevertheless, the sulphuric smell may be very unpleasant. The addition of fragrances may partially lessen the strong odor but may also expose to the risk of sensitization.

Targeted topical therapy

There is now evidence that topical therapy can be designed to specifically address disease pathogenesis. For example, in CHILD syndrome, the understanding of the pathophysiology of the skin manifestations (two major mechanisms: deficiency of cholesterol and toxic accumulation of aberrant steroid precursors) enabled to use the combination of topical cholesterol with a topical statin to reverse the ichthyotic phenotype (35–37).
Bathing

Cleaning of the skin is of utmost importance to remove scaling and residual ointments, to lessen discomfort and for hygiene. Most patients use bathing, which may be more effective in removing scale, others prefer showers. We can recommend the following modalities (LoE 4, GoR 4). Mild soaps or soap-free cleansing base may be used. Daily lukewarm baths (30 min or more) are recommended (8,10). Scales may then be removed by gently rubbing (e.g. with sponges, microfiber cloths or pumice stone) (10). Moisturizing additives, colloidal preparations, baking soda (3-6g/1L) or saltwater baths (normal saline 0.9%) can provide additional benefits (10,38–40). Antiseptics should not be used routinely, except in CI with recurrent skin infections such as Keratitis-Ichthyosis-Deafness (KID) syndrome or Netherton syndrome (NS). In those patients, they can be used 2-3 times a week (LoE 4, GoR D). Several antiseptics may be used: biocides as chlorhexidine (dilution 5/1,000-5/10000), octenidine 0.1%, polihexanide 0.1%, potassium permanganate (dilution 1/10000) or diluted bleach baths (0.005% solution) (9,10). Iodine based antiseptics are not recommended (risk of thyroid dysfunction). Antiseptics should be rinsed to avoid irritation. Balneotherapy and hydrotherapy with thermal waters may be useful (LoE 2+, GoR C), they have shown benefits in a single uncontrolled study (41). Studies are needed to test the benefits of steam baths.

Treatment of the scalp

Most patients present with scalp desquamation, sometimes with adherent thick scales requiring treatment. Foams, solutions and shampoos are cosmetically more acceptable than gels and ointments but may be less effective. The application of a layer of emollient or keratolytic (washable preparation) may be necessary (for a few hours or overnight), with variable weekly periodicity (LoE 4, GoR D). (10). Plastic occlusion may enhance efficacy, but transfollicular penetration of active substances is much higher than elsewhere and must be taken into account, particularly in children (42,43). After shampooing, scales must be gently
removed with combs (44). Some centers use a professional hair steamer to better remove adherent scales with hot steam. In CI with fragile skin or brittle hairs, e. g. NS or trichothiodystrophy, more gentle procedures are recommended.

_Treatment of palmoplantar keratoderma_

Some patients present with disabling palmoplantar keratoderma (PPK), predisposing to fissuring and pain. In cases of moderate to severe PPK in adults, high concentrations of keratolytics in ointment formulations may be used for a limited period (salicylic acid (up to 25%) or urea (up to 40%) (9). For children : see precautions in the paragraph on keratolytics). We can recommend to use them once or twice daily after protection of fissures and surrounding skin (i.e. using petroleum jelly), with or without a plastic film (with caution) in order to improve effectiveness and with manual removal of excess callus (9) (that may involve podiatrists) (LoE 4, GoR D). In cases of milder forms, topical tazarotene may be used (LoE 4, GoR D).

_Systemic therapy_

Systemic therapy may be considered in addition to topical therapies, in case they are insufficiently effective or patients need respite from excessive topical treatment (LoE 2, GoR D) (8,10,45,46). Systemic therapy in CI is mainly based on oral retinoids. Other types of systemic therapy, i.e. ciclosporin (47), have been tried, but can not be recommended. Novel therapies targeting skin inflammation could be candidates for future clinical studies, especially for CI with severe inflamed skin such as NS (see Part Two). Retinoids are analogues of vitamin A that principally act via an “anti-keratinising” effect (48,49) (S4). Four systemic retinoids can be considered for treatment of CI: isotretinoin, alitretinoin, etretinate (no longer available in Europe) and acitretin. Moreover, retinoid acid metabolism blocking agents were effective in clinical studies on CI, but did not progress to marketing (50,51).
Acitretin

Efficacy and therapeutic indications

Retinoids revolutionized the lives of many patients with severe CI, especially harlequin ichthyosis (HI) and lamellar ichthyosis (LI). Evidence of retinoid efficacy came from old trials with etretinate, before the introduction of acitretin. Acitretin is the drug of choice (LoE 2, GoR D): it is the main retinoid used in Europe and is the only one approved by the European Medical Agency (EMA) for treating CI (52). Efficacy of acitretin was demonstrated in a few pilot studies and from numerous case series (53–63). Acitretin is effective in removing scales and thinning the hyperkeratosis. Other effects include: improvement of hypohidrosis (64), hair regrowth, improvement of ectropion and eclebion, improvement of hearing and shortening of the daily time spent on skin care (8,10,45,46). Acitretin is especially relevant for patients with thick scales (i.e. LI and HI), but also for milder forms such as severe XLRI (50,65). In EI, the results are much better for patient with KRT10 mutations than KRT1 mutations who may even deteriorate on retinoids (57) (S5).

Dosage and scheduling

Acitretin is administrated orally (10 or 25 mg capsules) once daily and should be prescribed only by dermatologists experienced in its management (LoE 2, GoR D). The optimal dosage of acitretin varies between patients and depends on the type of CI (LoE 2, GoR D). Most patients do not require more than 0.5 mg/kg per day and may be maintained on doses as low as 10-25 mg/day. Higher doses of up to 1 mg/kg/day may be needed in adults with very severe ichthyosis, e. g. LI. The maximum dosage approved by the EMA is 75 mg/day. Of note, patients with marked erythroderma, e. g. EI (S5) and NS, should be treated with caution. They may only need a low retinoid dose (<25-30 mg/day in adults), otherwise skin irritation fragility or blistering may occur. Patients may start with a low dose (i.e. 10 mg for adults) once daily or every second day. The effect should be evaluated after a few weeks
and the dosage may be gradually increased until there is sufficient improvement with tolerable side-effects (LoE 2, GoR D). A too rapid dose escalation may increase the risk for side-effects, making the patient negative towards continued acitretin therapy. After stabilization of the desired effects, the dosage may be tapered to the lowest effective dose (55). Therapeutic effects of acitretin persist only for a short time after discontinuation of the medication. Long term therapy may be interrupted during humid and hot weather (LoE 4, GoR D).

Specific situation of children

There is no minimum age for the use of retinoids (for neonatal period: see Part two). The treatment should be prescribed in collaboration with a paediatrician or a dermatologist specialized in pediatric dermatology (LoE 2, GoR D). In most countries, there are no paediatric formulations, but the appropriate dosage can be prepared by the pharmacist. Since acitretin is light sensitive, capsules should be opened away from daylight or added to breast milk in a bottle protected by an aluminium foil. Efficacy of acitretin in children is documented in a few small case series of various disorders of keratinisation, essentially in LI, CIE (53,60–63) or HI (67–74). It is recommended to reserve retinoids for those with a severe phenotype and functional impairment. The daily dose should be kept as low as possible, less than 1 mg/kg/day, ideally close to 0.5 mg/kg/day, in order to limit the potential adverse effects (LoE 2, GoR D).

Adverse effects

Teratogenesis is the main adverse effect (75–77). Pregnancy prevention must be performed carefully in all women of child-bearing potential (LoE 2, GoR D) (S6). Many decades of treatment experience exist, and adverse effects of retinoids are well-known (Table 3). They vary in frequency and severity and are dose-dependent. Common reversible effects include
mucosal dryness, blood abnormalities (e.g., lipids or liver tests) and hair loss. Long-term musculoskeletal adverse effects are the main source of concern. In adults, spinal and extraspinal hyperostosis and calcifications of tendons and ligaments were reported but cannot be differentiated from age-induced bone changes. The majority of patients were on retinoids for many years or had taken etretinate previously (53,78–92). The risk for skeletal anomalies seems to be higher if a high cumulative dose of retinoids, previous treatment with etretinate (longer half-life and prolonged bone exposure) and old age are present. The risk of osteoporosis is controversial. It was reported after long-term therapy with etretinate (92,93). A short term prospective study with acitretin (94) and a retrospective study of 23 patients treated with acitretin or etretinate for various disorders of keratinization and followed over a long period (53) did not reveal osteoporosis. Osteoporosis in CI may be due to vitamin D deficiency (95) which is often associated with ichthyosis (see Part Two) (96).

In children, various skeletal anomalies including premature closure of the epiphyses were reported in association with high dosages of etretinate (up to 2.5 mg/kg/day) (97–101). Nevertheless, no baseline studies were available. Such anomalies were not found in two series of children on long-term etretinate therapy (102,103) or both etretinate and acitretin (53,62). No growth delay was reported on retinoids. Rather, severely affected children with failure to thrive as a result of chronic disease, had improved growth after starting retinoids (98). In summary, risk-benefit analysis of acitretin is considered as favourable, even though potential adverse effects may be problematic.

**Monitoring**

Regular monitoring is necessary and recommended by the EMA (LoE 2, GoR D) (Table 3).
Interactions and contraindications

Interactions of acitretin with other drugs and contraindications are presented as a supplement (S7).

Other retinoids (alitretinoin and isotretinoin)

Alitretinoin and isotretinoin have the advantage of a more rapid clearance than acitretin. There is no proper comparative study with acitretin. Alitretinoin has been reported as effective in reducing erythema in a small series of CI (104) and some case reports (105,106). Efficacy on scaling was reported for a few patients at high dose (107). Side-effects include headache, benign intracranial hypertension and hypothyroidism. The effectiveness of isotretinoin in LI and EI has been demonstrated in an open label study (108) and case reports including HI (72,109,110). High doses of isotretinoin are necessary (108) and the safety profile seems to be poorer than acitretin, with a well-established risk for intracranial hypertension, myalgia, muscle stiffness and tenderness (111). The main concern is related to skeletal toxicity that, in contrast to acitretin, is clearly reported for isotretinoin (112–114). Isotretinoin was also reported to be associated with a possible exacerbation of corneal neovascularization in KID syndrome (115).

Therefore, we recommend the choice of acitretin for long-term therapy, due to its approval by the EMA, its efficacy and its safety profile. In case of female patients considering a future pregnancy or in the rare event of hypersensitivity to aromatic retinoids (116), alitretinoin or isotretinoin should be preferred (LoE 2, GoR D).

Specific situation of syndromic ichthyosis

Patients suffering from syndromic ichthyosis may be candidates for oral retinoids (LoE 2, GoR D) (S8), even in cases of liver involvement (Chanarin-Dorfman syndrome (117,118), or
eye symptoms (KID syndrome) (119–125). However, they should be monitored for side effects more closely.

**PSYCHO SOCIAL MANAGEMENT / COMMUNICATING THE DIAGNOSIS / GENETIC COUNSELLING**

The CI may have a profound impact on QOL from childhood to adult age, for the patient and his family (126–132). The identified factors influencing QOL are related to physical health, daily life, relations with others or oneself (127). The importance of each individual parameter varies among patients with CI, but cutaneous pain emerged as the most significant factor influencing QOL, followed by skin scaling and gender (female) (131). It was demonstrated that the burden of the disease was related to domestic life (skin care, housework, clothing), educational/professional lives (rejection and bullying by other children at school, workplace discrimination) and for leisure/sports activities. The patient's economic resources were constrained by ichthyosis. The expenses that can be covered by national health systems and disability allowances are very variable among European countries but expense of moisturizing creams are often the main contributor to the financial impact of the disease (11,133). Living with a child with CI may also be a difficult situation for parents because ichthyosis is a rare and not well-known skin disease whose consequences are often underestimated by the medical profession and the general public. Therefore, we recommend to assess QOL and burden (LoE 3, GoR D) using ichthyosis specific questionnaires (132,134) (if available in the appropriate language) or dermatology QOL questionnaires such as DLQI/CDLQI (135). Due to the effect on QOL and daily life, psychological support is strongly recommended and is an important part of ichthyosis care, although the effects of psychosocial interventions on ichthyosis outcomes have not been tested. Ideally, psychosocial management should be offered as soon as possible, then throughout life, for children, adults and families; and should be adapted to their needs and
Psychosocial support should be provided by a psychologist but may involve other healthcare providers involved in patient's care, such as dermatologists, social workers or specialist nurses. Relevant complications should be honestly addressed, not only during a life-threatening situation such as HI at birth, but also for mating and sexuality during puberty and later on. Support of affected individuals or parents may prevent/alleviate psychological trauma and allow an appropriate response to hurtful comments. During the neonatal period it is very important to permit maternal-infant attachment with facilitating close physical contact between the baby and the parents (136–138) (LoE 4, GoR D). This mother-child contact and even more, the experience of the following cutaneous separation from the mother is particularly important for the child to recognize itself as « me » and to develop its « skin ego ». Family therapy may be useful if feelings of guilt or reproach are shown by parents. The situation of siblings must be taken into account since they may feel abandoned (LoE 4, GoR D). It may be very useful to provide patient or family group interviews. Due to the financial burden, it is necessary to inform families about reimbursement opportunities, ideally via the involvement of a social worker (LoE 4, GoR D). The physician in charge and the social worker could also work together to provide evidence that CI can be a disability and help with appropriate professional orientation.

Educational interventions (“ichthyosis schools”) may be very useful to improve treatment adherence and lessen fears and misconceptions (139) (LoE 3, GoR D). Nevertheless, formal and structured multidisciplinary educational programs have been established in a minority of European countries and there are very few data evaluating their impact (140). Patients must be informed about National patient support groups that exist in many European countries and allow support from other families and sharing of individual experiences (LoE 4, GoR D). Healthcare providers should inform patients/families about the patient support groups and/or give their contact details (http://www.ichthyose.eu/).
Communication of the diagnosis to the family should be offered as soon as the diagnosis is known (LoE 4, GoR D). Explaining a diagnosis of severe ichthyosis is a delicate situation and therefore may be best performed in a multidisciplinary consultation, ideally involving a psychologist. Genetic counselling must be offered to family/patient by the clinical geneticist (LoE 4, GoR D). The role of the clinical geneticist is to calculate the risk for other family members or the expected child to be affected or not, and to answer questions concerning prenatal testing or predictive or preimplantation diagnosis if convenient and available (141).
Table 1: Use of topical and systemic therapies / psychosocial management / communicating the diagnosis / genetic counselling: recommendations with level of evidence and grade.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Level of evidence</th>
<th>Grade</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- The choice of the topical agent is based on several parameters: severity and form of ichthyosis, location of the lesions, availability in the country, formulation and texture, reimbursement and cost, personal experience of the clinician and patient preferences.</td>
<td>4</td>
<td>D</td>
<td>(2,4,8,10)</td>
</tr>
<tr>
<td><strong>Emollients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Emollients should be used in all types of ichthyosis.</td>
<td>1</td>
<td>B</td>
<td>(9,12,14)</td>
</tr>
<tr>
<td>- Emollients should be applied several times a day (at least twice) and ideally after bathing.</td>
<td>3</td>
<td>D</td>
<td>(41)</td>
</tr>
<tr>
<td>- Occlusive moisturizers are unsuitable for hot climates.</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>- Emollients containing urea are unsuitable for inflamed or eroded skin, on flexural areas.</td>
<td>4</td>
<td>D</td>
<td>(9)</td>
</tr>
<tr>
<td><strong>Keratolytics / topical retinoids / others topical agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Thickened/hyperkeratotic skin requires keratolytics, topical retinoids or other topical agents</td>
<td>3</td>
<td>D</td>
<td>(1)</td>
</tr>
<tr>
<td>- Keratolytics may be applied once or twice daily and can be tapered depending on the response and</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Keratolytics should be avoided in case of inflamed or eroded skin, on the flexures and face.
- All keratolytics should be used in caution in newborns and young infants, in particular salicylic acid (risk of absorption).
- Topical retinoids are contraindicated during pregnancy.
- Calcipotriol or N-acetylcysteine may be useful.

**Bathing**
- Bathing once or twice a day with mild soap is recommended.
- Additives and mechanical removal of scales may be used.
- Routine use of antiseptics is not recommended. If recurrent infections, they can be used 2-3 times a week.
- Thermal therapy may be useful.

**Scalp**

**Palmoplantar keratoderma**
- In case of disabling lesions in adults, manual removal of excess callus after application for a limited period, under a plastic film, of high concentrations of keratolytics in ointment formulations after protection of fissures and surrounding skin.
- In cases of milder forms, topical tazarotene may be used
Oral retinoids

- Oral retinoids may be considered in addition to topical therapy when topical therapy is insufficient to reduce the scaling or hyperkeratosis.
- Acitretin is the drug of choice (better efficacy and safety profile).
- The prescriber should be experienced in the management of retinoids.
- In children, collaboration with a paediatrician or a dermatologist specialized in paediatric dermatology is required. The daily dose should be kept as low as possible.
- It is recommended to start acitretin at low dose, then gradually increase until the improvement is satisfactory and finally gradually reduce to the minimally effective dose.
- The optimal dosage of acitretin varies between patients and depends on the type of CI. Most patients do not require more than 0.5 mg/kg/d. Higher doses of up to 1 mg/kg/d may be necessary in patients...
with very severe ichthyosis (75 mg/day : maximum dosage approved by the EMA), low dose (<25-30 mg/day in adults) if marked erythroderma.

- Long term oral retinoid therapy is often required but some patients find it possible to interrupt the treatment during warmer weather.

- The pregnancy prevention program must be performed carefully in women of child-bearing potential.

- The monitoring of adverse effects is necessary during retinoid therapy, including the skeletal system in case of long-term therapy.

- Isotretinoin or alitretinoin should be preferred for female patients considering a future pregnancy (shorter half-life) or in case of a previous allergy to acitretin.

- Patients suffering from syndromic ichthyosis may be candidates for oral retinoids if side effects are monitored more closely.

<table>
<thead>
<tr>
<th>2</th>
<th>D</th>
<th>(75–77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>D</td>
<td>(104,105,107)</td>
</tr>
<tr>
<td>2</td>
<td>D</td>
<td>(117–125)</td>
</tr>
</tbody>
</table>

**Psychosocial management / delivery of diagnosis / genetic counselling**

- Quality of life and burden must be assessed.

<table>
<thead>
<tr>
<th>3</th>
<th>D</th>
<th>(11,126–132,134)</th>
</tr>
</thead>
</table>

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- Psychosocial management should be offered as soon as and throughout life.
- During the neonatal period, close physical contact between the baby and the parents must be encouraged.
- Family therapy can be useful and the situation of siblings must be taken into account.
- Ideally with the aid of a social worker, families must be informed about the opportunities related to reimbursement, school facilities and professional help available.
- If available, ichthyosis education must be offered to patients and family.
- Families must be informed about patient support groups.
- Communication of the diagnosis to the family should be offered as soon as the diagnosis is known.
- Genetic counselling must be offered to family/patient.

<table>
<thead>
<tr>
<th>Action</th>
<th>Grade</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Close physical contact</td>
<td>4</td>
<td>(136–138)</td>
</tr>
<tr>
<td>Family therapy</td>
<td>4</td>
<td>(11,133)</td>
</tr>
<tr>
<td>Inform about reimbursement, school facilities, professional help available</td>
<td>4</td>
<td>(140)</td>
</tr>
<tr>
<td>Offer ichthyosis education</td>
<td>4</td>
<td>(141)</td>
</tr>
<tr>
<td>Offer patient support groups</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Offer genetic counselling</td>
<td>4</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 2: Topical agents used in congenital ichthyoses

<table>
<thead>
<tr>
<th>Hydrating agents</th>
<th>Urea (&lt;5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Propylenglycol (&lt;20%)</td>
</tr>
<tr>
<td></td>
<td>Dexpanthenol</td>
</tr>
<tr>
<td></td>
<td>Macrogol 400</td>
</tr>
<tr>
<td></td>
<td>Glycerol (i.e. glycerine)</td>
</tr>
<tr>
<td>Lubricating agents</td>
<td>Petrolatum/vaseline</td>
</tr>
<tr>
<td></td>
<td>Paraffin</td>
</tr>
<tr>
<td>Keratolytic agents*</td>
<td>Urea (≥ 10 %), up to 40%</td>
</tr>
<tr>
<td></td>
<td>Propylene glycol (&gt;20%)</td>
</tr>
<tr>
<td></td>
<td>Alpha hydroxy acids (lactic acid, glycolic acid) (5-12%)</td>
</tr>
<tr>
<td></td>
<td>Salicylic acid (2-5%), up to 25%</td>
</tr>
<tr>
<td>Topical retinoids</td>
<td>Topical retinoids (tazarotene, adapalene)</td>
</tr>
<tr>
<td>Other topical agents</td>
<td>Calcipotriol (Vitamin D analogue)</td>
</tr>
<tr>
<td></td>
<td>N-acetylcysteine ***</td>
</tr>
</tbody>
</table>

* All keratolytics must be used with caution in children (risk of absorption).

**The addition of fragrances may partially lessen the strong odor.
Table 3: Main adverse effects of acitretin, precautions and monitoring
(B: Before, C: common, D: During, LT: Long term, ND: Not determined, R: Rare, ST: Short term).

<table>
<thead>
<tr>
<th>Involved organ</th>
<th>Adverse effects</th>
<th>Short term (ST)</th>
<th>Long term (LT)</th>
<th>Dose Dependent</th>
<th>Reversible</th>
<th>Precautions</th>
<th>Monitoring:</th>
<th>Principal references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Cheilitis (C)</td>
<td>ST</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>(45,49,52)</td>
</tr>
<tr>
<td></td>
<td>Skin dryness and peeling (C)</td>
<td>ST</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thinning and skin fragility (C)</td>
<td>ST</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fissuring of the finger tips (C)</td>
<td>ST</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pruritus (C)</td>
<td>ST</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Redness (C)</td>
<td>ST</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Photosensitivity (C)</td>
<td>ST</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucous membranes</td>
<td>Dry mouth (C)</td>
<td>ST</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>Mucous examination</td>
<td>(45,49,52)</td>
</tr>
<tr>
<td></td>
<td>Dry nose (C)</td>
<td>ST</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nose bleeding (R)</td>
<td>ST</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stomatitis, gingivitis, taste</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>Oral care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disturbance</td>
<td>Eye</td>
<td>Hair</td>
<td>Nails</td>
<td>Liver</td>
<td>Lipids</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Dry eyes and irritation (C)</td>
<td>Telogen effluvium (C)</td>
<td>Fragility, nails dystrophy (C)</td>
<td>Elevation of liver enzymes (C)</td>
<td>Elevated triglycerides (C)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Blepharitis, conjunctivitis (C)</td>
<td>Alteration in texture, curly hairs (R)</td>
<td>Paronychia-like periungual granulation (R)</td>
<td>Cholestatic hepatitis (R)</td>
<td>Hypercholesterolemia (C)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Intolerance of contact lenses (C)</td>
<td></td>
<td></td>
<td>Liver cirrhosis (R)</td>
<td>Decreased HDL levels (C)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Photophobia (R)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Poor night vision (R)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Glare sensitivity, changes in color perception (R)</td>
<td></td>
<td></td>
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<tr>
<td>ST</td>
<td>ST</td>
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<td>ST</td>
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<td>ST</td>
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<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systematic use of eye drops</td>
<td>Eye examination</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoidance of contact lenses</td>
<td>Liver tests**</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low fat diet</td>
<td>Lipid tests***</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>System</th>
<th>Condition</th>
<th>ST</th>
<th>ND</th>
<th>+/−</th>
<th>Avoidance of concurrent treatment with cyclines</th>
<th>Neurological evaluation</th>
<th>+/−</th>
<th>(Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Benign intracranial hypertension (R)</td>
<td>ST</td>
<td>ND</td>
<td>+</td>
<td>Avoidance of concurrent treatment with cyclines</td>
<td>Neurological evaluation</td>
<td>+</td>
<td>(111,145)</td>
</tr>
<tr>
<td>Peripheral nerves</td>
<td>Peripheral sensory neuropathy (R)</td>
<td>ST</td>
<td>ND</td>
<td>+</td>
<td>Nerve examination</td>
<td>+</td>
<td>+</td>
<td>(111,146)</td>
</tr>
<tr>
<td>Muscle</td>
<td>Myalgia, Muscle stiffness (R)</td>
<td>ST</td>
<td>ND</td>
<td>+</td>
<td>Avoid intense physical exercise</td>
<td>Muscle examination</td>
<td>+</td>
<td>(53,111)</td>
</tr>
<tr>
<td>Bones</td>
<td>Spinal- and extraspinal hyperostosis (DISH) (R)</td>
<td>LT</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>Growth (children)</td>
<td>+</td>
<td>(53,62,78,7</td>
</tr>
<tr>
<td></td>
<td>Calcifications of tendons and ligaments (R)</td>
<td>LT</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>Pain, restriction</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Slender long bones (R)</td>
<td>LT</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>Radiological screening</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Premature closure of epiphyses in children (R)</td>
<td>LT</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>- X-rays ****</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Osteoporosis, Osteopenia (R)</td>
<td>LT</td>
<td>ND</td>
<td>ND</td>
<td>−</td>
<td>- Bone density******</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitamin D deficiency (R)</td>
<td>ST</td>
<td>ND</td>
<td>+</td>
<td>Supplementation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Other blood tests to be performed before starting: complete blood count, electrolytes, fasting glucose, urea, creatinine.
** Alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, alkaline phosphatase, bilirubin. Every 2-4 weeks during the first 2 months, every 3 months during the first year, two times yearly the second year and then once a year.

Other risk factors for liver toxicity should be avoided.

Frequency must be increased in cases of comorbidities (ie. alcohol misuse, obesity) or in patients on high dose.

Transaminases more than three times the upper normal range should lead to discontinuation of retinoid therapy.

***Triglycerides, cholesterol: Every month during the first 2 months, every 3 months during the first year, two times yearly the second year and then once a year.

Frequency must be increased in cases of comorbidities (hyperlipidaemia, alcohol misuse, obesity) or in patients on high dose.

In hypertriglyceridemia approaching or above 10 mmol/l, discontinuation of acitretin is needed (risk of pancreatitis).

****Once during follow-up.

*****X-rays of all four limbs and lateral spine (plus targeted x-rays if skeletal pain). During follow-up only if previous anomalies or symptoms.

******Follow-up restricted to those with previous anomalies or additional risk factors (i.e. vitamin D deficiency, familial history).

The monitoring of the pregnancy tests, according to the pregnancy prevention program, is detailed in S6.
REFERENCES


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