Management of congenital ichthyoses

This text was adapted from the original guidelines published in the British Journal of Dermatology ***in 2019*** *(Part I and Part II) (references below) by Pr. Juliette Mazereeuw-Hautier and the subgroup ichthyosis of the ERN-Skin network, and patients' support groups. These guidelines were built with the aim of harmonising practices among European centers. An update in planed every 5 years since knowledge is growing rapidly.*

This is a simpler version for the use of patients. This text could help patients to better understand the management of the disease. Patients must be aware that every patiens is different and may requiere a different management that must be supervised by a physician.

The text contains some abbreviations and technical words that are explained in the glossary.*

References of the original guidelines

- Management of congenital ichthyoses: European guidelines of care, ***part one.*** *Mazereeuw-Hautier J, Vahlquist A, Traupe H, Bygum A, Amaro C, Aldwin M, Audouze A, Bodemer C, Bourrat E, Diociaiuti A, Dolenc-Voljc M, Dreyfus I, El Hachem M, Fischer J, Gånemo A, Gouveia C, Gruber R, Hadj-Rabia S, Hohl D, Jonca N, Ezzedine K, Maier D, Malhotra R, Rodriguez M, Ott H, Paige DG, Pietrzak A, Poot F, Schmuth M, Sitek JC, Steijlen P, Wehr G, Moreen M, O'Toole EA, Oji V, Hernandez-Martin A. Br J Dermatol. 2019 Feb;180(2):272-281*

- Management of congenital ichthyoses: European guidelines of care, ***part two****. Mazereeuw-Hautier J, Hernández-Martín A, O'Toole EA, Bygum A, Amaro C, Aldwin M, Audouze A, Bodemer C, Bourrat E, Diociaiuti A, Dolenc-Voljč M, Dreyfus I, El Hachem M, Fischer J, Ganemo A, Gouveia C, Gruber R, Hadj-Rabia S, Hohl D, Jonca N, Ezzedine K, Maier D, Malhotra R, Rodriguez M, Ott H, Paige DG, Pietrzak*

A, Poot F, Schmuth M, Sitek JC, Steijlen P, Wehr G, Moreen M, Vahlquist A, Traupe H, Oji V. Br J Dermatol. 2019 Mar;180(3):484-495.

PLAN

1- INTRODUCTION

Congenital Ichthyoses (CI) represent a group of diseases characterized by scaling and/or hyperkeratosis*, often associated with erythroderma*. CIs often affect the entire skin (or most of the skin surface) and usually start at birth or in early infancy. CIs are genetic diseases caused by mutation of a single gene (more than 50 genes identified to date). These mutations are responsible for a defective skin barrier*.

They are different forms of CI, the classification being based on the clinical presentation. This classification basically distinguishes non-syndromic ichthyoses (including common ichthyosis, autosomal recessive congenital ichthyosis (ARCI), keratinopathic ichthyosis and other forms) and syndromic ichthyoses*.

CIs usually have a major effect on the quality of life (QoL).

So far ichthyoses cannot be “cured”, but various effective symptomatic treatment options exist.

2- METHODS

In 2015, a European expert multidisciplinary group was constituted, including 25 dermatologists, one paediatrician, one ENT, one ophthalmologist, one clinical geneticist, one psychologist, one pharmacist, one dermato-epidemiologist and one nurse. Patients and families were also involved with the participation of the 3 representatives from patient support groups.

3- TOPICAL AND SYSTEMIC THERAPIES

There are different therapeutic options that are described below. The choice of treatment depends on the clinical aspect of the skin, the symptoms, the disease severity and the age of the patient.

Topical therapy

Topical agents represent the first-line treatment, they are considered to be essential and used by almost all patients. They are also recommended by all experts. They help to reduce scales, skin discomfort, itching, and may improve the general appearance of the skin. A variety of topical agents are available (see below). They can be used alone or in combination with systemic therapy (see further paragraph). The choice of a specific topical agent is based on various parameters: availability, formulation and texture, possibilities for reimbursement and cost. Unpleasant smell or a very greasy consistency of ointments should be avoided. Finally, application of topical therapies being time consuming, the willingness of the patient to follow the therapy is an essential requirement for a satisfying therapeutic result. Therefore, preferences of the patients are decisive in the choice of topical agents.

Topical agents used in CI

Urea (<5%) Propyleneglycol (<20%) Dexpanthenol Macrogol 400 Glycerol (i.e. glycerine)
Petrolatum/vaseline Paraffin
Urea (≥ 10 %), up to 40% (must be used with caution in children) Propylene glycol (>20%) (must be used with caution in children) Alpha hydroxy acids (lactic acid, glycolic acid) (5-12%) (must be used with caution in children) Salicylic acid (2-5%), up to 25% (must be used with caution in children, not allowed in children less than 2 years)
Topical retinoids (tazarotene, adapalene)
Calcipotriol (Vitamin D analogue) N-acetylcysteine (the addition of fragrances may partially lessen the strong odor).

Emollients*

Many emollients* are available and their properties vary according to their composition and the ratio between greasy elements and water. There are no studies

comparing different emollients* and in clinical practice, the preferred emollient* varies among patients. Application of emollients* is recommended for all ichthyosis, as often as necessary, at least twice a day and ideally after bathing to improve skin hydration. Emollients* are safe. Rarely they may induce minor symptoms such as itching or a burning sensation. Since they may not be well tolerated, emollients* containing urea are not recommended on inflamed skin, flexural areas* or wounds.
Increased skin permeability due to skin barrier defect may increase the risk of allergic contact dermatitis. Furthermore, extensive applications of occlusive pure ointments (creams impermeable to air) are not recommended since they may further reduce heat tolerance, promote maceration of the skin and induce infections, particularly in hotter climates.
For patients with thick scaling/hyperkeratosis, addition of other agents is often necessary.

Keratolytics

Their superiority over emollients* in removing scales/hyperkeratosis was demonstrated. They include urea (more than 10% in the final product), alpha hydroxyl acids (5 to 12%), propylene glycol (more than 20%), salicylic acid (more than 2%), alone or as a combination. All are effective and 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. Keratolytics are usually applied once or twice daily and can be reduced depending on the response. Side-effects include itching, burning sensation and irritation. Application on the face, flexural areas* and areas of skin wounds are not recommended since they may induce irritation. Absorption into the organism leading to toxicity must be taken into account considering the reduced barrier effect of the ichthyotic skin, especially in children. Therefore, all keratolytics must be avoided in newborns and young infants, the exact age limit not being well defined. The use of salicylic acid is not allowed for children under the age of 2, and may be restricted to once daily application to limited areas for older children (risk of skin absorption and serious side-effects). Urea (at or over 10% concentration) is not recommended before the age of 1, excepted once daily on limited areas such as palms and soles.

Topical retinoids

They are currently no more marketed in Europe.

Other topical agents

Calcipotriol, a vitamin D derivative that has demonstrated efficacy in adults but limited by a maximum weekly dose of 100 g. N-acetylcysteine showed efficacy in a small study. Nevertheless, the sulphuric smell may be very unpleasant. The addition of fragrances may partially lessen the strong odour but may also expose to the risk of sensitization.

Bathing

Cleaning of the skin is important to remove scaling and residual emolients*, to reduce discomfort and for hygiene. Most patients use bathing, which might be more effective in removing scales, others prefer showers. We can recommend the following modalities. Mild soap or soap-free cleansing base may be used. Daily lukewarm baths (30 min or more at a moderate temperature) are recommended. In case of thick scales, they can be removed by gently rubbing (e.g. with sponges, microfiber cloths or pumice stone). Moisturizing additives (hydratants), colloidal preparations, baking soda (3-6g/1L) or saltwater baths can provide additional benefits. Antiseptics should not be used routinely, except in CI with recurrent skin infections. In those patients, they can be used 2-3 times a week. Several antiseptics may be used: biocides as triclosan, chlorhexidine or diluted bleach baths (0.005% solution). 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, as they have shown benefits in a single uncontrolled study. Daily steam baths need to be tested individually.

Treatment of the scalp

Most patients present with scales on the scalp, sometimes severe and adherent thick. 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 frequency. Application under occlusion (using a plastic kitchen film) enhance efficacy, but also increase the absorption of active substances (caution in children). After shampooing, scales must be gently removed with a comb. Some centres use a professional hair steamer to better remove adherent scales with hot steam. In CI with fragile skin, more gentle procedures are recommended.

Treatment of palmoplantar keratoderma (PPK)

In cases of moderate to severe PPK, high concentrations of keratolytics in ointment formulations may be used. In practice, salicylic acid (up to 25%) or urea (up to 40%) for a limited period and only for adults seem to be the most effective keratolytic agents. We can recommend to use them once or twice daily after protection of fissures/wounds and surrounding skin (for instance using petroleum jelly), with or without a plastic film (with caution) in order to improve effectiveness and with manual removal of excess callus (operation that may involve podiatrists).

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. Systemic therapy in CI is mainly based on oral retinoids (analogues of vitamin A that limit the production of excessive scales). Three systemic retinoids are available in most European countries: isotretinoin, alitretinoin, acitretin (etretinate is no longer available).

Acitretin

Efficacy and therapeutic indications

Acitretin is the drug of choice: it is the main retinoid used in Europe and is the only one approved by the European Medical Agency (EMA) for treating CI. Acitretin is effective in removing scales and thinning the hyperkeratosis. Other effects include: improvement of hypohidrosis*, hair regrowth, improvement of ectropion* and eclabion*, improvement of hearing and shortening of the daily time spent on skin

care. Acitretin is especially relevant for patients with thick scales but also for milder forms. Some ichthyosis may worsen on oral retinoids.

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. The optimal dosage of acitretin varies between patients and depends on the type of CI and patient's weight. 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. The maximum dosage approved by the EMA is 75 mg/day. Patients with marked erythroderma* should be treated with caution and with low retinoid dose (less than 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/day 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. A too rapid dose escalation may increase the risk for side-effects. After stabilization of the desired effects, the dosage may be reduced to the lowest effective dose. 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.

Specific situation of children

There is no minimum age for the use of retinoids but the treatment should be prescribed in collaboration with a paediatrician or a dermatologist specialized in paediatric dermatology. 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.

It is recommended to reserve oral retinoids for severe cases and in presence of functional impairment (ie. eye or ear problems, reduced mobility and contractures). 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.

Adverse effects

Teratogenesis* is the main adverse effect. Pregnancy prevention must be performed carefully in all women of childbearing potential (according to current regulations in your country).

The other adverse effects of oral retinoids vary in frequency and severity and are dose-dependent (the higher dose and duration of use, the more frequent and/or severe the adverse effects). Common reversible effects include mucosal dryness, blood abnormalities (e.g. abnormal lipids or liver tests) and hair loss.

Long-term adverse effects to muscles, bones and joints are the main source of concern. In adults, hyperostosis* of the spine and calcifications of tendons and ligaments can occur in case of a very high cumulative dose of retinoids, previous treatment with etretinate and old age. The risk of osteoporosis* is controversial.

In children, various skeletal anomalies including premature closure of the epiphyses* have been reported, but only in case of association with high dosages of etretinate (up to 2.5 mg/kg/day).

In summary, risk-benefit analysis of acitretin is considered very favourable, even though potential adverse effects necessitate a monitoring.

Monitoring

Regular monitoring is necessary and recommended by the EMA. Your physician can read the original text of the guidelines in order to get all the details of the monitoring.

Other retinoids (alitretinoin and isotretinoin)

Alitretinoin and isotretinoin have the advantage of a shorter period of teratogeneicity*.

Alitretinoin has been reported as effective for patients with erythema and thin scales (effect on thick scales would necessitate too high dose). Side-effects are similar but may also include headache and hypothyroidism*.

Isotretinoin may be used but higher doses of isotretinoin are necessary to be effective and the safety profile is poorer than acitretin, especially for bone toxicity.

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 some retinoids, alitretinoin or isotretinoin should be used.

Specific situation of syndromic ichthyosis

Patients suffering from syndromic ichthyosis may be candidates for oral retinoids, even in cases of liver involvement or eye symptoms. However, they must be monitored more closely for adverse effects.

4- PSYCHO SOCIAL MANAGEMENT, COMMUNICATING THE DIAGNOSIS, GENETIC COUNSELLING

CI may have a profound impact on quality of life (QoL) from childhood to adult age, for the patients and their family. The identified factors influencing QoL are related to physical health, daily life, relations with others or oneself. 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 (females have a worse QoL). It was demonstrated that the burden of the disease is related to domestic life (skin care, housework, clothing), educational or professional lives (rejection and bullying by other children at school, workplace discrimination, social and sexual life) and leisure/sports activities. The patient's economic resources are constrained and consumed 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. Living with a child with CI may also be a difficult situation for parents due to time spent for skin care and because ichthyosis is a rare and not well-known skin disease whose consequences are often underestimated by the medical professionals and the general public. Therefore, it is recommended to assess QoL and burden using ichthyosis specific questionnaires. Due to the impact on QoL and on daily life, psychological support is strongly recommended and is an important part of ichthyosis care. 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 expectations. This 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 addressed, not only during a life-threatening situation, but also for mating and sexuality during puberty and later on.

Support of affected individuals or parents may prevent or alleviate psychological trauma and allow an appropriate response to hurtful comments. During the neonatal period it is very important to permit maternal-infant attachment facilitating close physical contact between the baby and the parents and supporting the parents in the understanding of the child's condition. This mother-child contact and even more the experience of the following cutaneous separation from the mother is particularly important for the child's psychological development.

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. 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. 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. Nevertheless, formal and structured multidisciplinary educational programs have been established in only a few European countries. 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. Healthcare providers should inform patients/families about the patient support groups and/or give their contact details (see http://www.ichthyose.eu/).

Communication of the diagnosis to the family should be offered as soon as the diagnosis is known. Explaining a diagnosis of severe ichthyosis is a delicate situation, as it will shape the family's life from then on, 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. 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.

5- COMPLICATIONS

Several complications of CI significantly affect QoL and require specific management.

Ophthalmic complications

The primary aim of management of the eye condition is to maintain normal visual development and protect the ocular surface integrity whilst minimizing the risk of defects of the cornea. We recommend regular ophthalmic examination ideally including age-appropriate vision assessment. The frequency may vary from monthly to once or twice a year

If the patient is unable to completely close the eyelid, even during blink or in case of ectropion*, ocular lubrication with eye drops is essential as a first line therapy. It should be maintained on a regular basis and the frequency of instillation may vary from once or twice daily to half-hourly in extremely severe cases. Massages (vertical lid massage and stretching) can also be useful.

As a second line therapy, in combination with eye drops, oral retinoids are recommended even if they may induce side-effects such as dry eyes.

The third line therapy is eyelid skin grafting that may only be considered when constant exposure of the cornea or persistent lacrimation remains evident. The main issue is the relapse that may occur rapidly and subsequent topical therapy remains necessary.

Ear complications

Hearing loss is the main issue and may interfere with the development of language and communication, especially in children. It is commonly due to build-up of scales and blockage of the external auditory canal and is aggravated in young children by the small size of the ear canal.

We recommend hearing evaluations at least every six months for children younger than six years. Referral to ENT should also be performed in cases of itching or pain in the ear, ear discharge, a feeling of clogged ears or hearing loss. Various methods are available to remove earwax/cerumen and treat ear canal occlusion and different

ear drops may be used. Frequency usually varies from once to four times a year. Oral retinoids are not considered a primary treatment to avoid ear canal blockage. In cases of external otitis, once the cleansing and debridement (the medical removal of dead, damaged, or infected tissue) measures have been completed, it is recommended to use topical medication (drops with antibiotics) and protect the external auditory canal using oils.

Itching

Regular topical skin care helps to reduce itch. Antihistamines or other systemic therapies (as antidepressants) used in other skin diseases with pruritus* have little or no effect. An antipruritic effect of oral retinoids has been described, others report itch as a side-effect, so there is no consensus on their usefulness against itching.

We primarily recommend regular topical skin care with emollients* and exclusion of skin infections. In cases of persistent itching*, antihistamines or oral retinoids can be tried.

Pain

This symptom should be part of the patient's evaluation. Topical and systemic therapy are recommended and may help to reduce skin pain. In the absence of specific recommendations, guidelines established for treating pain with non specific analgesics* in other dermatological diseases or pain in general may be used.

Cutaneous infections

Some forms of CI, seem to be more prone to develop recurrent bacterial, viral or fungal skin infections that can be overlooked on ichthyotic scaly skin. Patients often complain of increased itching. Scabies* may be difficult to diagnose in ichthyotic skin and usually manifest as increased itching with a deterioration in abnormal skin.

We advise to perform a thorough physical examination for signs of infections at regular intervals. Samplings should be performed at the laboratory if an infection is suspected. An increased risk of infections requires antiseptics and bathing on a daily basis, while clinically obvious skin infections require therapy with topical (if limited

involved areas) or additional oral antibiotics (if large areas or in children with other health issues). It is important to take into consideration the increased risk of systemic absorption of local therapy in CI.

Growth failure and nutritional deficiency

Growth failure affects children with a number of chronic diseases including ichthyosis, especially in case of very inflammatory skin.

After the neonatal period, we recommend that growth parameters are recorded at regular intervals, the check-ups being more frequent at a young age. In case of growth delay, a paediatric endocrinologist and/or nutritionist must be involved. Successful treatments with growth hormone have been demonstrated in patients with Netherton syndrome. In adolescents, special attention should be paid to signs of delayed puberty. Severely affected children with failure to thrive, as a result of chronic disease, had improved growth after starting retinoids.

Vitamin D deficiency

The risk for vitamin D deficiency in CI is well established, especially in children. This deficiency may be severe and associated with clinical and radiological evidence of rickets. Pigmented skin, severity of ichthyosis and winter/spring season were reported as risk factors.

We recommend checking Vitamin D in CI, yearly or twice yearly if risk factors are present. In case of severe deficiency, other investigations (biological or radiological) must be performed. Supplementation methods are not well defined in CI, therefore, we recommend following the general international recommendations for adults and children. Maintenance therapy has to be considered due to the chronicity of CI.

Hair and nail anomalies

Additionnal causes of hair and nail anomalies must be checked (iron deficiency, thyroid dysfunction, drugs). The benefit of intensive management of scalp scaling to

prevent alopecia* is unknown. Patients with pronounced alopecia* should be offered a wig. There is no available therapy for nail anomalies.

Reactions to a hot or cold climate

Topical therapy may help to reduce the hypohidrosis*. The effect of oral retinoids is not established.

We recommend avoiding extreme temperatures (too hot or too cold) and outdoor activities during the hottest periods of the day. In a hot climate, cold water/packs (regular water spraying, bathtubs, showers) and cooling devices (air conditioning, fans, cooling vests) can help to cool the skin.

We recommend regular topical skin care. In cases with severe anomalies, oral retinoids can be tried.

Physical limitations

Patients may require physical therapy (splinting at night) and occupational therapy devices (e. g. special large handled cutlery or pens or devices to help with opening jars), combined with local therapy and oral retinoids.

6- PARTICULARITIES OF CONGENITAL ICHTHYOSIS

Particularities of management in the neonatal period

In the neonatal period there is an increased risk of complications due to the impaired barrier function* of the skin, mainly with increased water loss through the skin. Babies are prone to various complications that can be life-threatening. Some forms of CI are also associated with prematurity.

At birth, babies may present with erythroderma* and scaling. They can also present with blisters and erosions or as a collodion baby* or harlequin foetus*. The 2 latest are 2 severe and transient presentation of ichthyosis. Their management is complex and require an admission to a neonatal intensive care unit for an interdisciplinary

approach involving a multidisciplinary team (including dermatologists, neonatologists, ophthalmologists, ENT, plastic surgeons, dieticians, psychologists and nursing staff). Parental involvement in care of the baby must be encouraged. Babies must be placed in a high humidity incubator with a close monitoring.

Emollients* are recommended 3 to 8 times a day, ideally using sterile occlusive ointments such as white petrolatum. It is also important to keep in mind the risk of an increased absorption of ointments through the skin and therefore active substances that must be avoided. An absolute contraindication is the use of salicylic acid. Daily bathing is advisable before ointment application.

Neonates require close evaluation of the eyes and ears. Skin debris from the auditory canal may be removed on a regular basis.

Monitoring for signs of cutaneous or systemic infection and standard precautions are necessary. Prophylactic antibiotic treatment is usually not recommended.

Invasive procedures should be avoided as they represent a possible source of infection.

In case of hand constriction bands, massages using ointment may be helpful for prevention. Surgery may be necessary.

The use of oral retinoids are usually not necessary.

Pain assessment is necessary and analgesics before bathing and skin care may be necessary. Non-pharmacological interventions (i. e. sugar sucking) and/or various drugs may be used.

Particularities of management related to some forms of CI

Netherton syndrome (NS)

Patients with NS present (with) severe skin inflammation and eczema lesions that necessitate specific therapy.

Management of skin inflammation and eczema lesions

- Topical steroids (corticoids)

Topical steroids may be used for a limited period of time for eczema lesions, bearing in mind the risk of adverse effects due to steroid local and systemic toxicity.

- Topical calcineurin inhibitors

Systemic absorption has been reported in many cases, even for limited body surface area application. Therefore, we recommend their use only for short-term management of flares on limited areas. Otherwise, monitoring of serum/plasma drug levels is necessary.

- Phototherapy

Narrow band UVB therapy may provide relief in the short term, but long-term UVB therapy is not safe because of increased susceptibility to skin cancers. Other phototherapies are not recommended.

- Immunosuppressive drugs and intravenous immune globulins: not recommended, especially due to limited evidence.

- Biologics*

Not recommended due to the scarcity of data available, the risk of skin cancers and recurrent infections reported in NS.

- Risk of skin cancers

Several type of skin cancers have been reported for NS and therefore we recommend regular dermatological check-ups.

- Other particularities are as follows:

Skin care : preference for hypoallergenic emollients*, no keratolytics
Complications

* Growth failure
* Food allergies: allergy testing and specific diet
* Risk of allergic contact dermatitis
* High risk of cutaneous infections: regular use of antiseptics
* Vitamin D deficiency
* Hair: gentle care, wig