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


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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. These guidelines 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 two, covering the management of complications and the particularities of some forms of congenital ichthyosis.
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). Complications include ophthalmic and ear complications, pain and pruritus, cutaneous infections, growth failure, vitamin D deficiency, hair and nail anomalies, excessive reactions to hot or cold climates and physical limitations. 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) (See Part One (S1)). The 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. We have developed European guidelines following a systematic review of the current literature, a guideline conference and a consensus on the discussions. The recommendations are divided into 2 sections. Part two covers the management of complications and the particularities of CI. The first part has covered topical therapies, systemic therapies, psychosocial management, communicating the diagnosis and genetic counselling. The methodology of the guidelines is detailed in Part one.
COMPLICATIONS

Several complications of CI require specific management. Their prevalence is not well known and they are detailed in Table 1. Although these complications are rarely assessed in clinical practice or studies (5), they significantly affect QOL (6,7). Pain was one of the most important factors. Pruritus, ocular complications and alopecia were some of the ten most important clinical concerns of the patients according to a study on therapeutic difficulties (8). The recommendations with their level of evidence (LoE) and grade of recommendations (GoR) are presented in Table 2 and mentioned in the text.

Ophthalmic complications (9–23)

The primary aim of ophthalmic management is to maintain normal visual development and protect the ocular surface integrity whilst minimizing the risk of corneal epithelial defects.

We recommend regular ophthalmic examination that should ideally include age-appropriate vision-assessment and either slit lamp or alternative portable assessment of the ocular surface. Cycloplegic refraction should be undertaken to exclude any significant, correctable refractive error. The frequency may vary from monthly to once or twice a year (LoE 4, GoR D).

If lagophthalmos is present, even during blink, then ocular lubrication is essential and should be maintained long term (LoE 4, GoR D). Based on several studies on dry eye, preservative-free topical lubrication is strongly recommended for patients who require long term eye drop administration (24–26). Examples of lubricants include 0.5–1% carboxymethylcellulose, carmellose-sodium or hyaluronic acid (HA) and
petrolatum ointment at night if nocturnal lagophthalmos exists (27–31). Lipid-containing eye drops are effective in improving symptoms and signs of dry eye and particularly recommended in the presence of meibomian gland dysfunction (27,32). Frequency of instillation may vary from once or twice daily to half-hourly in extremely severe cases.

Ectropion pre-disposes to lagophthalmos and therefore frequent ocular lubricants as a first-line treatment are highly recommended for all patients (LoE 4, GoR D). Evidence from case reports show that eyelid emollients and massage (vertical lid massage and stretching) can improve lagophthalmos and ectropion (LoE 3, GoR D) (33–36). Other topical agents may be helpful (LoE 3, GoR B) but may induce irritation: urea or lactic acid, N-acetylcysteine (efficacy of 5% to 10% concentration in urea 5% reported in a few cases of children with LI who were also treated by emollients or acitretin) (37–39) or tazarotene (efficacy reported in an adult with autosomal recessive congenital ichthyosis (ARCI) (40) and in 5 children or neonates with lamellar ichthyosis (LI) (41)).

Evidence on the effectiveness of oral retinoid therapy to improve ectropion is very limited (42–44). In clinical practice, they are recommended as a second line therapy in combination with topical agents, in order to reduce moderate to severe ectropion and prevent further worsening (LoE 3, GoR B). However, oral retinoids may induce ophthalmic side-effects such as dry eyes (see Part One).

Eyelid skin grafting is a third line therapy that may only be considered when symptomatic corneal exposure or epiphora persists despite adequate conservative treatments (LoE 3, GoR B). It should ideally be undertaken before keratinization of the palpebral conjunctiva occurs. The main issue is the relapse that may occur rapidly (45) and subsequent topical therapy remains necessary. Autologous skin
grafts are the most commonly reported surgical interventions. The successful use of both full-thickness and split-thickness autologous skin grafts have also been reported (46). Harvest sites for full-thickness grafts are varied (47–52). Oral buccal mucosa may be considered in preference to skin for grafts where skin is unavailable (53–55). A recent case report suggested the combination of inverting sutures in addition to systemic retinoids and lubrication (56). A patient with LI associated with severe ectropion underwent surgery and was then started on apremilast for concomitant psoriasis. The author considered that apremilast (possibly via an inhibition of the tumor necrosis factor-α) minimized the recurrence of eyelid ectropion after 26 months of follow up but no criteria evaluating the effect were provided (57).

Efficacy and safety of repeated hyaluronic acid gel filler injections was reported in a small series of 3 infants suffering from severe LI or harlequin ichthyosis (HI) (58). This treatment could help to delay invasive surgical procedures, but larger studies are necessary to recommend this method. It should only be performed by experienced ophthalmologists (LoE 3, GoR B).

**Ear complications** (59–61)

Hearing loss is the main issue and may interfere with the development of language and communication. It is commonly due to build-up of scales and blockage of the external auditory canal (61) and is aggravated in young children by the small size of the ear canal (62).

*We recommend hearing evaluations at least every six months for children younger than six years (LoE 4, GoR D). Referral to ENT should also be performed in cases of pruritus or pain in the ear, ear discharge, a feeling of clogged ears or hearing loss (LoE 4, GoR D). Various methods are available to remove earwax/cerumen and treat*
ear canal occlusion (63,64). Different ear drops may be used (65). According to one randomized controlled study on patients with cerumen, docusate sodium solution was a more effective ceruminolytic than triethanolamine polypeptide (66). Many patients can control blockage of ear canals by simple measures such as applying oil regularly. Mechanical techniques performed by ENT are commonly used (micro suctioning, debridement and curettage) and may be highly effective and safe (59,60). Frequency usually varies from to once to four times a year (LoE 3, GoR D). Oral retinoids are not considered a primary treatment to avoid ear canal blockage (61). In cases of external otitis, once the cleansing and debridement measures have been completed, it is recommended to use topical medication (drops with antibiotics, e. g. ciprofloxacin, with or without corticosteroids) and protect the external auditory canal using oils (LoE 4, GoR D).

Pruritus

The specific pathophysiology of itch in CI has not been systematically studied and may be related to skin inflammation (67). Regular topical skin care helps to reduce itch (68–71), e. g. wet-wrappings with emollients via a cooling effect. Antihistamines or other systemic therapies (antidepressants) (72) used in other skin diseases with pruritus are often ineffective or have little effect. An antipruritic effect of oral retinoids (see Part One) has been described (73), others report itch as a side-effect (43,74–77).

We primarily recommend regular topical skin care (see Part One) with emollients and exclusion of skin infections (LoE 4, GoR D). In cases with persistent pruritus, antihistamines or oral retinoids can be tried (LoE 4, GoR D).
Pain

This symptom should be part of the patient’s evaluation. Topical and systemic therapy are recommended and may help to reduce skin pain (LoE 4, GoR D) (see Part One). In the absence of specific recommendations, guidelines established for treating pain in epidermolysis bullosa or other dermatological diseases (78–80) or pain in general may be used (LoE 4, GoR D). (http://apps.who.int/iris/bitstream/10665/44540/1/9789241548120_Guidelines.pdf).

Cutaneous infections

So far there are no publications on the microbiome of CI. Clinical experiences suggest that the impaired epidermal barrier significantly modifies bacterial/fungal skin colonization. These changes are illustrated for many forms of CI, in which patients develop a characteristic and sometimes unpleasant smell. Bacterial cutaneous infections may also appear, with different pathogenic agents identified, including Staphylococcus aureus and group A streptococci (81). The occurrence of methicillin-resistant Staphylococcus aureus colonization is possible but is not well documented (82). The exact frequency of bacterial colonization or infection is not known. Some forms of CI seem to be more prone to develop recurrent skins infections, including autosomal recessive congenital ichthyosis (ARCI), notably HI (83), epidermolytic ichthyosis (EI), Netherton syndrome (NS) (84–88) and Keratitis-Ichthyosis-Deafness (KID) syndrome (89). Many patients with ARCI (90–96) or KID syndrome (97,98) suffer from recurrent dermatophytosis (e. g. from Trichophyton rubrum). This may be easily overlooked on ichthyotic scaly skin. Patients often complain of increased itching. Moreover, patients with KID syndrome may present with mucocutaneous candidiasis (99–101). Human papillomavirus infections have often been described in
patients with NS (see specific paragraph). Scabies may be difficult to diagnose in ichthyotic skin and usually manifest as increased pruritus with a deterioration in abnormal skin.

The paucity of reliable data does not allow for universal recommendations. We advise to perform a thorough physical examination for signs of infections at regular intervals. Microbiological samplings should be performed if an infection is suspected (LoE 4, GoR D). Increasing risk of infections requires antiseptics and bathing on a daily basis (see Part One) (LoE 4, GoR D). Clinically obvious skin infections require therapy with topical (if limited involved areas) or additional oral antibiotics (if large areas or children with comorbidities) (LoE 4, GoR D). Although retapamulin, mupirocin and fusidic acid are effective against *Staphylococcus aureus* and group A streptococci, resistance has recently been identified in nearly 10% of analyzed strains from children with skin infections (102). In these cases, topical ozenoxacin, and topical antiseptics represent comparably effective treatments (103). It is important to take into consideration the increased risk of systemic absorption of local therapy in CI (see Part One). Bacteriophage therapy was reported as an alternative therapy in a young patient with NS complicated by resistant chronic *Staphylococcus aureus* skin infection and allergy to multiple antibiotics (104). Widespread tinea confirmed by specific culture requires systemic antifungal therapy (LoE 4, GoR D).

**Growth failure and nutritional deficiency**

Growth failure affects children with a number of chronic diseases (105). Increased epidermal turnover, chronic skin inflammation and cutaneous protein loss, especially
in patients with very inflammatory ichthyoses ie NS, may contribute to extreme resting energy expenditure in CI (106,107).

After the neonatal period, we recommend that growth parameters are recorded in height-for-age and weight-for-age percentiles at regular intervals, the frequency of check-ups being inversely proportional to the patient’s age and dependent on prior results and practices of the country of origin (LoE 4, GoR D). In case of growth delay, a paediatric endocrinologist and/or nutritionist must be involved in order to check and correct any metabolic, nutritional or endocrinologic abnormalities (LoE 4, GoR D) (105). Successful treatments with growth hormone have been demonstrated in patients with NS (108). 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 (109).

**Vitamin D deficiency**

The risk for 25-hydroxyvitamin D (VitD) deficiency in CI is well established, especially in children, with many case reports in the literature, 4 small retrospective series of 5 to 15 patients with keratinization disorders, including CI (110–113) and 3 prospective studies of 45 to 119 CI (114–116). The underlying mechanism of VitD deficiency in CI remains unclear. The presence of scales increases the thickness of the skin and probably reduces the UV B penetration in the skin. The intrinsic barrier defect of ichthyosis could also disturb previtamin D synthesis in the skin (115). This deficiency may be severe and associated with clinical and radiological evidence of rickets. VitD deficiency was reported for many forms of CI but ARCI and EI could be associated with a higher risk (116). Pigmented skin, severity of disease and winter/spring season were reported as risk factors (110,114,115). Oral retinoids have
also been implicated in the occurrence of vitD deficiency but no conclusion can be made without baseline measurements for comparison (117).

We recommend checking VitD in CI, yearly or twice yearly if risk factors are present (LoE2++, GoR B). The optimal Vit D status is not universally agreed, but experts recommend a level of at least 30 ng/mL (75nmol/L) for adults (118) and 20 or 30 ng/mL (50 or 75 nmol/L) for children (119). In case of severe deficiency (less than 10 ng/ml (25 nmol/L), serum parathyroid hormone, calcium and phosphorus should also be measured (LoE 3, GoR D. Radiological examination is mandatory (bone mineral density and X-rays) if skeletal symptoms are present. Supplementation methods are not defined in CI. Therefore, we recommend following the general international recommendations for adults (120) and children (119) (LoE 4, GoR D). Maintenance therapy has to be considered due to the chronicity of CI. A clinical improvement in CI after short-term high-dose vitD supplementation was reported in 5 children with ARCI associated with vitD deficiency. Nevertheless, none had a follow-up, one patient developed hypercalcemia and this regimen was not effective for 2 EI (113).

**Hair and nail anomalies**

Aggravating factors may be checked (iron deficiency, thyroid dysfunction, drugs) (LoE 4, GoR D). Topical and/or systemic therapies are useful in case of adherent thick scalp scales (see Part One). The benefit of intensive management of scalp desquamation 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

Hypohidrosis probably results from plugging of the sweat ducts by hyperkeratosis but is also seen in mild forms of CI (121), suggesting the existence of additional functional defects of the sweat glands. The effect of local and systemic therapy is not well known. Topical therapy may help to reduce the hyperkeratotic plugging of sweat glands. Of note, hypohidrosis in CI has only been really measured in one case report showing a positive effect of systemic retinoid therapy (122).

We recommend avoiding extreme temperatures and outdoor activities during the hottest periods of the day (LoE 4, GoR D). The patients should wear adequate clothing. In a hot climate, cold water/packs (regular water spraying, bathbubs, showers) and cooling devices (air conditioning, fans) can help to cool the skin. We recommend regular topical skin care (LoE 4, GoR D) (see Part One). In cases with severe thermodyisregulation, oral retinoids can be tried (LoE 4, GoR D).

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 local therapy and oral retinoids (LoE 4, GoR D) (see Part One).

PARTICULARITIES OF CONGENITAL ichthyosis

There are some particularities of the management of CI that are either related to the age of the patient or to the form of ichthyosis. Recommendations with level of evidence and grade are presented in Table 3.
Particularities of management in the neonatal period

Clinical presentations at birth necessitating special care include collodion baby (CB), neonates with HI, congenital ichthyosiform erythroderma (CIE), NS, EI and ichthyosis prematurity syndrome (IPS). Neonatal presentation increases the risk of complications that are associated with an impaired barrier function, e.g. increased transepidermal water loss (TEWL) (123). Infections, electrolyte imbalance, disrupted thermoregulation and/or metabolic wasting and respiratory distress (IPS) can be life-threatening. Some forms of CI are also associated with prematurity.

Management of CB and HI (LoE 3, GoR D).

Clinical presentations and complications are described in Table 4. The list of CI with a collodion membrane at birth is presented as a supplement (S1). Evidence about management is limited since there are only 6 retrospective descriptive series including 17 to 32 CB (124–127) or 16 to 45 HI (83, 128) as well as some case reports (123,129–132). There are also some review papers describing the management (133–141).

Neonatal intensive care unit

Newborns must be admitted to a neonatal intensive care unit and require 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 (see Part One).
**Incubator**

CB and HI must be placed in a high humidity incubator that decreases TEWL. It is recommended to start with 60-80% humidity and decrease every 3-4 days to reach normal conditions (125). Higher humidity may promote the growth of bacteria such as Pseudomonas or fungal infections (candidiasis). The optimal temperature is 32-34°C. Close monitoring of body temperature is necessary to avoid hypothermia or overheating. The infant may be transferred to an open crib when there is an adequate caloric intake and an appropriate weight gain.

**Nutrition and electrolyte balance**

Body weight is one of the best clinical indicators of sufficient nutrients and fluid intake. It should be checked daily, together with an accurate calculation of intake and output. Nutritional assessment and support through an oro- or nasogastric tube is often necessary because of poor sucking due to eclabium and increased metabolic demands (132).

**Topical therapy**

Emollients decrease TEWL and are recommended 3 to 8 times a day (142). Sterile occlusive ointments such as white petrolatum are commonly used but some authors consider that they may increase the risk of cutaneous infections and impair sweating (126,143). Water-in-oil emollients may therefore be an alternative. The application technique should avoid contamination (latex-free gloves, single use packets). It is also important to keep in mind the risk of percutaneous absorption* and therefore active substances like urea, lactic acid or silver sulfadiazine must be avoided (144–148). An absolute contraindication is the use of salicylic acid (149–151). Daily bathing is advisable before ointment application.

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Eye and ear care

Neonates require close evaluation of the eyes and ears. Skin debris from the auditory canal may be removed on a regular basis (62).

Neonatal infections

Monitoring for signs of cutaneous or systemic infection and standard precautions are necessary. Regular bacterial swabs (twice a week) should be performed, especially from the flexures, eyes and intravenous line sites. Antiseptics may be used on erosive lesions (e.g. aqueous chlorhexidine (0.05%)) (144). Antifungal cream may be used on areas of macerated skin in order to avoid fungal infection. Prophylactic antibiotic treatment is not recommended in CB, but may be an option in HI.

Invasive procedures in neonates

Invasive procedures should be avoided (source of infection). Nevertheless, endotracheal intubation may be required, especially in restricted pulmonary ventilation or nasal occlusion. If peripheral access is impossible, an umbilical venous line may be used for a limited period.

Constriction bands and distal limb ischemia

Massages using ointment (simple emollient or 10% urea in limited areas) may be helpful for prevention. Digital ischemia has been reported to respond to topical tazarotene 0.1% (153,154). Oral retinoids may be highly efficient (155). Surgery (linear band incisions) may also be considered (156).
Oral retinoids in the neonatal period

In CB, the membrane usually sheds spontaneously within a few weeks and therefore oral retinoids are usually not necessary. For HI, their real value is controversial. In the retrospective review by Rajpopat (83), 83% of HI receiving systemic retinoids survived, whereas long term survival was only 24% in neonates who did not undergo retinoid treatment. It is unknown if the improved neonatal survival of babies with HI was due to improved neonatal management or to systemic retinoids. Moreover, the genetic diversity of ABCA12 mutations itself has a large influence on the outcome (157). Although isotretinoin has been occasionally used in the neonatal period (158), when oral retinoids become necessary, we recommend acitretin (154,159).

Analgesia for neonates

Fissured skin and digital constrictions are likely to cause considerable pain. Adapted pain assessment tools may be used for routine pain assessment (160). Analgesics before bathing and skin care may be necessary and may facilitate respiration. Non-pharmacological interventions (i. e. non-nutritive sucking) and/or various drugs may be used (160). Soft bedding or a waterbed may also be useful.

Management of CI with other neonatal presentations (LoE 3, GoR D)

CIE and NS present at birth with erythroderma and peeling. EI presents at birth with blistering and areas of denuded skin (140,161). They may be admitted to a neonatal intensive care unit, placed in an incubator, monitored closely and require adapted skin care such as bathing (including antiseptics) and emollients. Neonates with EI have fragile skin and need medical care similar to that of neonates with epidermolysis bullosa (162–164) (avoidance of adhesives and high temperatures that may induce blisters) (135). The most important issues are regular antibacterial wound
management, management of pain, dehydration and nutrition (165). Babies with IPS are prone to complications related to the prematurity and life-threatening neonatal asphyxia caused by aspiration of corneocyte-containing amniotic fluid (166–168). They need immediate oropharyngeal suction with or without initial ventilation and intubation. Some babies with RXLI may also show cutaneous manifestations at birth, with red skin and peeling or “collodion-like” presentation.

**Particularities of management related to other forms of CI**

**Netherton syndrome (NS)**

Patients with NS present with severe skin inflammation and eczema lesions that necessitate specific therapy. They are also prone to develop skin cancers. Other particularities of management of NS are detailed in Table 3.

*Management of skin inflammation and eczema lesions*

- **Topical steroids**

  Topical steroids (e.g. class I to II) may be used for a limited period of time for eczema lesions (LoE 3, GoR D), bearing in mind the risk of iatrogenic Cushing syndrome (169) and severe skin atrophy.

- **Topical calcineurin inhibitors**

  Topical tacrolimus ointment (0.03% or 0.1%) and pimecrolimus cream (1%) (only available in some European countries) have been used in a limited number of patients with NS (1 prospective series of 3 patients (170), 4 retrospective series of 2 to 4 patients (171–174) and 4 case reports (88,175–177). All but one patient reported
efficacy. The main concern is related to systemic absorption that has been reported in many cases, especially for tacrolimus ointment, even for limited body surface area application. Therefore, we recommend their use only for short-term management of flares on limited areas (LoE 3, GoR D). Otherwise, monitoring of serum/plasma drug levels is necessary.

- Phototherapy

Efficacy of phototherapy was reported in a few case reports (4 children treated with narrow band ultraviolet B (UVB) (178–181) and 2 adult treated with PUVA (182) or UVA-1 (183). Short term efficacy was reported in all but one (182). We do not recommend PUVA therapy (LoE 3, GoR D). 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 in NS (see below).

- Immunosuppressive drugs and intravenous immune globulins

The use of ciclosporin A has been reported as ineffective in 2 patients (182,184). Given the risk of skin cancer associated with both NS and ciclosporin A (185), we do not recommend using it (LoE 3, GoR D). Systemic immune globulins have been reported as safe and effective in 5 patients (85,186,187), but there is limited evidence to recommend them for long term treatment (LoE 3, GoR D).
- **Biologics**

Infliximab was reported as improving skin inflammation in 2 patients with NS (188,189). We cannot recommend such therapy (LoE 3, GoR D) based on the followings arguments: paucity of data about TNFα inhibitors in NS, skin cancers (see below) and recurrent infections reported in NS, significantly increased risk of infections and non-melanoma skin cancers for patients treated with TNFα inhibitors (190,191), some cancers being aggressive (192,193). Omalizumab was reported to decrease allergic skin symptoms in one patient with NS (194).

- **Future treatments**

In the future, targeted therapy will probably be available (67,195).

*Risk of skin cancers*

Several type of skin cancers have been reported for NS. Patients may present with squamous and basal cell carcinomas with or without papillomavirus (more than 15 case reports) (182,196–203). Patients may also present with large perineal flexural exophytic tumours corresponding to epidermal hyperplasia without evidence of malignancy. We recommend regular dermatological check-ups. Skin cancers may necessitate surgery (LoE 3, GoR D) because of a failure of all medical treatments (204,205).
Other forms of CI necessitating some particularities of management

EI, CI with prominent erythroderma or CI with severe scales present some particularities of management, the recommendations (LoE 3, GoR D) are presented in Table 3.

Table 1: Complications of congenital ichthyosis (*See part One)

<table>
<thead>
<tr>
<th>Type of complications</th>
<th>References</th>
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<tbody>
<tr>
<td><strong>Ophthalmic complications</strong></td>
<td>(9–23)</td>
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<tr>
<td><strong>Eyelids</strong></td>
<td>(9–11,13–16)</td>
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<tr>
<td>- Ichthyosis of the lids</td>
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<tr>
<td>- Scales on the lashes</td>
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<tr>
<td>- Madarosis (loss of eyelashes and sometimes eyebrows)</td>
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<tr>
<td>- Eyelid retraction and cicatricial ectropion:</td>
<td>(11,13,16)</td>
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<tr>
<td>More common in severe inherited ichthyosis such as lamellar ichthyosis and harlequin ichthyosis</td>
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<tr>
<td>May result in:</td>
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<tr>
<td>- Lagophthalmos</td>
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<tr>
<td>- Chronic ocular surface exposure</td>
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<tr>
<td>- Superficial keratopathy, thinning, scarring, bacterial keratitis and even corneal perforation</td>
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<tr>
<td>- Epiphora (excessive watering of the eye)</td>
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<tr>
<td>- Photophobia</td>
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<tr>
<td>- Loss of vision</td>
<td></td>
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<tr>
<td>- Keratinization of the palpebral conjunctiva</td>
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Meibomian gland dysfunction
- Contributes to dry eyes
- Reported in
  - Keratitis-Ichthyosis-Deafness (KID) syndrome
  - Ichthyosis Follicularis, Alopecia and Photophobia syndrome
  - Lamellar ichthyosis
- Dry eyes caused by oral retinoids*

**Conjunctiva and cornea**

- Deep corneal stromal opacities
- Do not impair vision, reported in
  - X-linked recessive ichthyosis
  - Lamellar ichthyosis (occasionally)
- Corneal scarring and vascularization
  - In Keratitis-Ichthyosis-Deafness (KID) syndrome
  - In IFAP syndrome
- Corneal perforation as a result of ectropion

**Ear complications**

- Sensorineural deafness in some syndromic forms of ichthyosis such as Keratitis-Ichthyosis-Deafness (KID) syndrome
- Conductive hearing loss due to build-up of scales and blockage of the external auditory canal
- Ear pruritus
- Ear pain
- Recurrent external otitis with risk of cholesteatoma

**Pruritus**
- Characteristic finding of several specific forms, e. g. Sjögren Larsson syndrome, Netherton syndrome
- Can be severe in peeling skin disease

### Pain
- Due to fissuring of the thickened skin, especially soles, erosions with skin fragility or blisters (epidermolytic ichthyosis, areas of inflamed skin or skin infections)
- May be responsible for impaired mobility

### Cutaneous infections
- Bacterial \( (81-88) \)
- Fungal \( (90-95,97,98) \)
- Viral

### Growth failure
- More frequent in some forms such as Netherton syndrome and harlequin ichthyosis \( (83-87) \)

### Vitamin D deficiency
- \( (110-116) \)

### Hair and nails anomalies

#### Hair anomalies
- Desquamation of the scalp, sometimes with adherent thick scales and/or skin inflammation
- Alopecia without hair dysplasia
- Alopecia due to specific hair dysplasia (Netherton syndrome, trichothiodystrophy, ichthyosis follicularis alopecia and photophobia) \( (209) \)
Hair changes caused by oral retinoids
- Reversible telogen effluvium
- Alteration of hair texture (curly hair) that may be permanent

Nails anomalies
- Nails anomalies in some forms of ichthyosis
- Nails changes caused by oral retinoids
- Fragility with onychorrhexis and onychoschizia (most common findings)
- Nail shedding
- Onycholysis
- Transverse leuconychia
- Median canaliform dystrophy
- Painful paronychia
- Onychomycosis

Reactions to hot or cold climates
- Less resistance to cold temperature (especially if erythroderma)
- Hypohidrosis, sensitivity to hot temperatures, heat intolerance and overheating
- Heat also worsens skin findings in bathing suit ichthyosis (temperature sensitive TGM1 mutation)
- Hypohidrosis is also a feature of the ichthyosis-hypotrichosis syndrome

Physical limitations
- The thickening/hyperkeratosis of the skin may limit the normal
range of motion of many joints.
In severe forms (lamellar ichthyosis, harlequin ichthyosis, epidermolytic ichthyosis)
- Palmoplantar keratoderma may limit walking distance and fine motor skills.
- More frequent in some forms such as severe lamellar ichthyosis, harlequin ichthyosis, epidermolytic ichthyosis

**Table 2: Management of complications of congenital ichthyosis: recommendations with level of evidence and grade (*See Part One*)**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Level of evidence</th>
<th>Grade</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Regular monitoring</td>
<td>4</td>
<td>D</td>
<td>(9,11)</td>
</tr>
<tr>
<td>from monthly to once or twice a year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ocular lubrication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Regular and long term ocular lubrication with preservative-free topical medication if lagophthalmos (from once daily to half-hourly)</td>
<td>4</td>
<td>D</td>
<td>(9,11)</td>
</tr>
<tr>
<td><strong>Ectropion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* First-line treatment for all patients : ocular lubrication</td>
<td>3</td>
<td>B</td>
<td>(37,41)</td>
</tr>
<tr>
<td>* Emollients and massage of the eyelid</td>
<td>3</td>
<td>B</td>
<td>(44)</td>
</tr>
<tr>
<td>* Other topical agents* (urea or N-acetylcysteine or topical tazarotene) applied on the eyelid may be helpful</td>
<td>3</td>
<td>B</td>
<td>(45)</td>
</tr>
<tr>
<td>* Oral retinoids* : second line therapy in case of moderate to severe ectropion help to reduce moderate to severe ectropion and prevent worsening</td>
<td>3</td>
<td>B</td>
<td>(58)</td>
</tr>
<tr>
<td>*Eyelid skin grafting: third line therapy, may only be considered when symptomatic corneal exposure or epiphora persists despite adequate conservative treatments.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hyaluronic acid gel fillers' injections may be beneficial. They should be only undertaken by experienced ophthalmologists.

**Ear complications**
- Regular hearing evaluations (every 6 months for children younger than 6 years).
- ENT referral in case of pruritus or pain of the ear, ear discharge, feeling of clogged ears or hearing loss.
- Removal of earwax/cerumen by using ear drops, oil and mechanical techniques once to four times a year.
- External otitis: cleansing and debridement measures associated with drops with antibiotics and protection of the external auditory canal using oils.

<table>
<thead>
<tr>
<th>Pruritus</th>
<th>4</th>
<th>D</th>
<th>(59–61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Topical skin care*</td>
<td>4</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>- Antihistamines, oral retinoids* can be tried</td>
<td>4</td>
<td>D</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain</th>
<th>4</th>
<th>D</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Topical skin care*</td>
<td>4</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>- Oral retinoids*</td>
<td>4</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>- Analgesics used for treating pain in other dermatological diseases</td>
<td>4</td>
<td>D</td>
<td>(79)</td>
</tr>
</tbody>
</table>

**Cutaneous infections**
- Microbiological samplings if an infection is suspected.
- Antiseptics and bathing* if increased risk of skin infections.
- In case of skin infections: topical antibiotics (if limited involved areas) or additional oral antibiotics (if large areas or children with comorbidities).
- Antifungal systemic therapy if widespread fungal infection.

<table>
<thead>
<tr>
<th>Growth failure</th>
<th>4</th>
<th>D</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Growth parameters must be recorded periodically, frequency depending on prior results and failure of growth milestones</td>
<td>4</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>- Referral to a paediatrician in case of growth delay, in</td>
<td>4</td>
<td>D</td>
<td>-</td>
</tr>
</tbody>
</table>
order to check and correct any metabolic, nutritional or endocrinologic abnormalities

<table>
<thead>
<tr>
<th>Vitamin D</th>
<th>Level</th>
<th>Grade</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Checking of 25-hydroxyvitamin D in all forms, yearly or twice yearly if risk factors</td>
<td>2++</td>
<td>B</td>
<td>(114–116)</td>
</tr>
<tr>
<td>- In case of severe deficiency, checking of parathyroid hormone, calcium, phosphorus, bone mineral density and X-rays (if skeletal symptoms)</td>
<td>3</td>
<td>D</td>
<td>(114–116)</td>
</tr>
<tr>
<td>- Supplementation methods following the general recommendations for adults and children</td>
<td>4</td>
<td>D</td>
<td>(119,120)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hair and nails</th>
<th>Level</th>
<th>Grade</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Aggravating factors may be checked (iron deficiency, thyroid dysfunction, drugs).</td>
<td>4</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>- Adherent thick scalp scales : topical* and/or systemic therapies*</td>
<td>4</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>- Nails: no available therapy</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reactions to hot or cold atmospheres</th>
<th>Level</th>
<th>Grade</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Avoidance of extreme temperatures, adequate clothing and limitation of outdoors activities during the hottest parts of the day, cold water and cooling devices</td>
<td>4</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>- Topical therapy*</td>
<td>4</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>- Oral retinoids* may be considered if severe thermodynamics</td>
<td>4</td>
<td>D</td>
<td>(122)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical limitations</th>
<th>Level</th>
<th>Grade</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Physical therapy in combination to topical* and systemic* therapies</td>
<td>4</td>
<td>D</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 3**: Management of the particularities of congenital ichthyosis either related to the age of the patient or to the form of ichthyosis: recommendations with level of evidence and grade

*See part One
**See specific paragraph of Part Two
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Level of evidence</th>
<th>Grade</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neonatal period</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Management of Collodion baby (CB) and harlequin ichthyosis (HI)</td>
<td>3</td>
<td>D</td>
<td>(83,124–128,133–141)</td>
</tr>
<tr>
<td>Admission to neonatal intensive care unit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Interdisciplinary approach and joint care with neonatologists</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Highly humidified incubator (&gt;60%) with monitoring of body temperature, weight, water and electrolyte balance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Nutritional support: regular assessment and caloric supplementation, oro or nasogastric tube if necessary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Topical therapy: bathing, emollient 3 to 8 times a day, avoid other topical medication, use of antiseptics in erosive lesions and antifungal cream in macerated areas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Infections: monitoring, standard precautions, regular bacteriological samplings. No prophylactic antibiotic treatment for CB, it may be an option in HI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Eye regular evaluations, bland eye ointments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ear: removal of ear scales</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Constriction bands: massages for preventative massage, surgery if ischemia, oral retinoids to be considered.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Oral retinoids: may be used in HI, not in CB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Invasive procedures: avoid them</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pain: regular assessment, use of analgesics when required</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Psychological support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newborns with erythroderma</td>
<td>3</td>
<td>D</td>
<td>(140,161)</td>
</tr>
<tr>
<td>- Neonatal intensive care unit, incubator, close monitoring, bathing including antiseptics and emollients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermolytic ichthyosis</td>
<td>3</td>
<td>D</td>
<td>(140,161)</td>
</tr>
<tr>
<td>Intensive care unit, incubator, avoidance of adhesives, regular antibacterial wound management, management of pain, dehydration and nutrition</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Ichthyosis prematurity syndrome**
Immediate oropharyngeal suction with or without initial ventilation and intubation. Neonatal intensive care unit

<table>
<thead>
<tr>
<th>Particularities of some forms of congenital ichthyosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Netherton syndrome</strong></td>
</tr>
<tr>
<td>- Skin care* : preference for hypoallergenic emollients, no keratolytics</td>
</tr>
<tr>
<td>- Complications</td>
</tr>
<tr>
<td>* Growth failure**</td>
</tr>
<tr>
<td>* Food allergies: allergy testing and specific diet</td>
</tr>
<tr>
<td>* Risk of allergic contact dermatitis</td>
</tr>
<tr>
<td>* High risk of cutaneous infections: regular use of antiseptics**</td>
</tr>
<tr>
<td>* Vitamin D deficiency **</td>
</tr>
<tr>
<td>* Hair**: gentle care, wig</td>
</tr>
<tr>
<td>* Skin cancers : regular dermatological check-ups, surgery</td>
</tr>
<tr>
<td>- Skin inflammation and eczema lesions</td>
</tr>
<tr>
<td>*Topical steroids may be applied to eczema lesions for a limited period of time</td>
</tr>
<tr>
<td>*Topical calcineurin inhibitors may be applied on eczema lesions for a limited period of time and on limited areas</td>
</tr>
<tr>
<td>*PUVA or long term UVB phototherapy : not recommended</td>
</tr>
<tr>
<td>*Immunosuppressive drugs : not recommended</td>
</tr>
<tr>
<td>*Systemic immune globulins : limited evidence to recommend</td>
</tr>
<tr>
<td>*Biologics : not recommended</td>
</tr>
<tr>
<td>- Oral retinoids* : acitretin is usually not recommended or may be used with caution at a low dosage, altretinoin may reduce erythema</td>
</tr>
</tbody>
</table>

**Epidermolytic ichthyosis**
- Neontal period**: skin fragility and erosions | 3 | D | (140,161) |
- Bacterial colonization responsible for bad odour : regular use of antiseptics during bathing* | 3 | D | - |
- Frequent cutaneous infections** | 3 | D | - |
- Hyperkeratosis and palmoplantar keratoderma | | | |
| *Oral retinoids* with caution and at low dosage (risk of exacerbation of blistering) | 3 | D | (229) |
| *High concentration keratolytics* | 3 | D | - |

**Ichthyosis with prominent erythroderma**

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Ichthyosis with prominent and severe scales
- Keratolytics*
- Oral retinoids*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating</th>
<th>Effect</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No keratolytics*</td>
<td>3</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>Oral retinoids* may be used but with caution and at a low dosage. Alitretinoin may reduce erythema</td>
<td>3</td>
<td>D</td>
<td>(227)</td>
</tr>
</tbody>
</table>

* indicates medications may be effective but require careful monitoring and low dosages.
Table 4: Clinical presentation and complications of collodion baby and harlequin ichthyosis in the neonatal period (133–141)
(CB: collodion baby, HI: harlequin ichthyosis)

<table>
<thead>
<tr>
<th>Clinical presentation:</th>
<th>Complications (more severe for HI):</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Abnormal skin</td>
<td>- Electrolyte imbalance, dehydration</td>
</tr>
<tr>
<td>- CB: parchment-like membrane covering the body surface</td>
<td>- Disrupted thermoregulation</td>
</tr>
<tr>
<td>- HI: massive armour-like hyperkeratosis with fissuring, severe erythroderma</td>
<td>- Pain</td>
</tr>
<tr>
<td>- Ectropion (extreme for HI)</td>
<td>- Caloric malnutrition and weight loss (poor feeding and sucking)</td>
</tr>
<tr>
<td>- Eclabium (extreme for HI)</td>
<td>- Infections</td>
</tr>
<tr>
<td></td>
<td>- CB: parchment-like membrane covering the body surface</td>
</tr>
<tr>
<td></td>
<td>- HI: massive armour-like hyperkeratosis with fissuring, severe erythroderma</td>
</tr>
<tr>
<td></td>
<td>- Ectropion (extreme for HI)</td>
</tr>
<tr>
<td></td>
<td>- Eclabium (extreme for HI)</td>
</tr>
<tr>
<td></td>
<td>- Cutaneous:</td>
</tr>
<tr>
<td></td>
<td>- Bacteria (including methicillin-resistant Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa and Klebsiella)</td>
</tr>
<tr>
<td></td>
<td>- Fungal infections (Candida albicans)</td>
</tr>
<tr>
<td></td>
<td>- Systemic (e.g. pneumonia)</td>
</tr>
<tr>
<td></td>
<td>- Percutaneous toxicity (highly disturbed epidermal barrier)</td>
</tr>
<tr>
<td></td>
<td>- Mechanical compression due to constricting bands, distal limb ischemia</td>
</tr>
<tr>
<td></td>
<td>- Conjunctivitis and keratitis</td>
</tr>
<tr>
<td></td>
<td>- Obstruction of external ear canal</td>
</tr>
<tr>
<td></td>
<td>- Respiratory distress</td>
</tr>
</tbody>
</table>
REFERENCES


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172. Shah KN, Yan AC. Low but detectable serum levels of tacrolimus seen with the use of very dilute, extemporaneously compounded formulations of tacrolimus ointment in the treatment of patients with netherton syndrome. Arch Dermatol 2006;142:1362-3.

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