



# Management of congenital ichthyoses: European guidelines of care, part two\*

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## Summary

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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

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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.

#### 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.

Congenital ichthyoses (CIs) 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.<sup>1,2</sup> 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 CIs 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 nonsyndromic ichthyoses [including common ichthyosis, autosomal recessive congenital ichthyosis (ARCI), keratinopathic ichthyosis and other forms] and syndromic ichthyoses<sup>3</sup> (see part one).<sup>4</sup>

The CIs usually have a major effect on quality of life 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 two sections. Part two covers the management of complications and the particularities of CI. The first part covered topical therapies, systemic therapies, psychosocial management, communicating the diagnosis, and genetic counselling. The methodology of the guidelines is detailed in part one.<sup>4</sup>

### Complications

Several complications of CI require specific management. Their prevalence is not well known and they are detailed in Table S1 (see Supporting Information). Although these complications are rarely assessed in clinical practice or studies,<sup>5</sup> they significantly affect quality of life.<sup>6,7</sup> Pain was one of the most important factors. Pruritus, ocular complications and alopecia were some of the 10 most important clinical concerns of the patients according to a study on therapeutic

difficulties.<sup>8</sup> The recommendations with their level of evidence (LoE) and grade of recommendation (GoR) are presented in Table S2 (see Supporting Information) and mentioned in the text.

#### Ophthalmic complications

The primary aim of ophthalmic management is to maintain normal visual development and protect the ocular surface integrity while minimizing the risk of corneal epithelial defects.<sup>9–23</sup>

We recommend regular ophthalmic examination, which 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.<sup>24–26</sup> Examples of lubricants include carboxymethylcellulose 0.5–1%, carmellose sodium, or hyaluronic acid and petrolatum ointment at night if nocturnal lagophthalmos exists.<sup>27–31</sup> Lipid-containing eye drops are effective in improving symptoms and signs of dry eye and are particularly recommended in the presence of meibomian gland dysfunction.<sup>27,32</sup> Frequency of use may vary from once or twice daily to half hourly in extremely severe cases.

Ectropion predisposes 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 shows that eyelid emollients and massage (vertical lid massage and stretching) can improve lagophthalmos and ectropion (LoE 3, GoR D).<sup>33–36</sup> Other topical agents may be helpful (LoE 3, GoR B), but may induce irritation. These

include urea or lactic acid, N-acetylcysteine [efficacy of a 5–10% concentration in urea 5% reported in a few cases of children with lamellar ichthyosis (LI) who were also treated by emollients or acitretin]<sup>37–39</sup> and tazarotene (efficacy reported in an adult with ARCI<sup>40</sup> and in five children or neonates with LI).<sup>41</sup>

Evidence on the effectiveness of oral retinoid therapy to improve ectropion is very limited.<sup>42–44</sup> In clinical practice retinoids 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).<sup>4</sup>

Eyelid skin grafting is a third-line therapy that may be considered only 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 relapse, which may occur rapidly,<sup>45</sup> 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 has also been reported.<sup>46</sup> Harvest sites for full-thickness grafts are varied.<sup>47–52</sup> Oral buccal mucosa may be considered in preference to skin for grafts where skin is unavailable.<sup>53–55</sup> A recent case report suggested the combination of inverting sutures in addition to systemic retinoids and lubrication.<sup>56</sup> 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 inhibition of tumour necrosis factor (TNF)- $\alpha$ ] minimized the recurrence of eyelid ectropion after 26 months of follow-up, but no criteria evaluating the effect were provided.<sup>57</sup>

The efficacy and safety of repeated hyaluronic acid gel filler injections were reported in a small series of three infants with severe LI or harlequin ichthyosis (HI).<sup>58</sup> 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

Hearing loss is the main issue in ear complications and may interfere with the development of language and communication.<sup>59–61</sup> It is commonly due to build-up of scales and blockage of the external auditory canal,<sup>61</sup> and is aggravated in young children by the small size of the ear canal.<sup>62</sup>

We recommend hearing evaluations at least every 6 months for children younger than 6 years (LoE 4, GoR D). Referral to ear nose and throat (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 and treat ear canal occlusion.<sup>63,64</sup> Different ear drops may be used.<sup>65</sup> According to one randomized controlled study on patients with cerumen, docusate sodium solution was a more effective ceruminolytic than

trietanolamine polypeptide.<sup>66</sup> Many patients can control blockage of ear canals by simple measures such as applying oil regularly. Mechanical techniques performed by ENT are commonly used (microsuctioning, debridement and curettage) and may be highly effective and safe.<sup>59,60</sup> The frequency usually varies from once to four times a year (LoE 3, GoR D). Oral retinoids are not considered a primary treatment to avoid ear canal blockage.<sup>61</sup> 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 to 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.<sup>67</sup> Regular topical skincare, such as wet wrappings with emollients, helps to reduce itch,<sup>68–71</sup> via a cooling effect. Antihistamines or other systemic therapies (antidepressants)<sup>72</sup> used in other skin diseases with pruritus are often ineffective or have little effect. An antipruritic effect of oral retinoids (see part one)<sup>4</sup> has been described;<sup>73</sup> others report itch as a side-effect.<sup>43,74–77</sup>

We primarily recommend regular topical skincare (see part one)<sup>4</sup> 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

The symptom of pain 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).<sup>4</sup> In the absence of specific recommendations, guidelines established for treating pain in epidermolysis bullosa or other dermatological diseases<sup>78–80</sup> or pain in general may be used (LoE 4, GoR D).<sup>81</sup>

### Cutaneous infections

So far there are no publications on the microbiome of CI. Clinical experiences suggest that the impaired epidermal barrier significantly modifies bacterial or 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.<sup>82</sup> The occurrence of methicillin-resistant *S. aureus* colonization is possible but is not well documented.<sup>83</sup> The exact frequency of bacterial colonization or infection is not known. Some forms of CI seem to be more prone to develop recurrent skin infections, including ARCIs, notably HI,<sup>84</sup> epidermolytic ichthyosis (EI), Netherton syndrome (NS)<sup>85–89</sup> and keratitis–

ichthyosis–deafness (KID) syndrome.<sup>90</sup> Many patients with ARClS<sup>91–97</sup> or KID syndrome<sup>98,99</sup> experience 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.<sup>100,101</sup> Human papillomavirus infections have often been described in patients with NS (see the specific section below). Scabies may be difficult to diagnose in ichthyotic skin and usually manifests 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).<sup>4</sup> Clinically obvious skin infections require therapy with topical (if limited involved areas) or additional oral antibiotics (if large areas or in children with comorbidities) (LoE 4, GoR D). Although retapamulin, mupirocin and fusidic acid are effective against *S. aureus* and group A streptococci, resistance has recently been identified in nearly 10% of analysed strains from children with skin infections.<sup>103</sup> In these cases, topical ozenoxacin and topical antiseptics represent comparably effective treatments.<sup>104</sup> It is important to take into consideration the increased risk of systemic absorption of local therapy in CI (see part one).<sup>4</sup> Bacteriophage therapy was reported as an alternative therapy in a young patient with NS complicated by resistant chronic *S. aureus* skin infection and allergy to multiple antibiotics.<sup>105</sup> 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.<sup>106</sup> Increased epidermal turnover, chronic skin inflammation and cutaneous protein loss, especially in patients with highly inflammatory ichthyoses such as NS, may contribute to extreme resting energy expenditure in CI.<sup>107,108</sup>

After the neonatal period, we recommend that growth parameters be 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 the 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 endocrinological abnormalities (LoE 4, GoR D).<sup>106</sup> Successful treatments with growth hormone have been demonstrated in patients with NS.<sup>109</sup> 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.<sup>110</sup>

### Vitamin D deficiency

The risk for 25-hydroxyvitamin D deficiency in CI is well established, especially in children, with many case reports in the literature. These include four small retrospective series of five to 15 patients with keratinization disorders, including CI,<sup>111–114</sup> and three prospective studies of 45–119 patients with CI.<sup>115–117</sup> The underlying mechanism of vitamin D deficiency in CI remains unclear. The presence of scales increases the thickness of the skin and probably reduces the ultraviolet (UV)B penetration in the skin. The intrinsic barrier defect of ichthyosis could also disturb previtamin D synthesis in the skin.<sup>117</sup> This deficiency may be severe and associated with clinical and radiological evidence of rickets. Vitamin D deficiency was reported for many forms of CI, but ARCl and EI could be associated with a higher risk.<sup>117</sup> Pigmented skin, severity of disease and winter or spring season were reported as risk factors.<sup>111,115,116</sup> Oral retinoids have also been implicated in the occurrence of vitamin D deficiency, but no conclusion can be made without baseline measurements for comparison.<sup>118</sup>

We recommend checking vitamin D in CI, yearly or twice yearly if risk factors are present (LoE 2++, GoR B). The optimal vitamin D status is not universally agreed, but experts recommend a level of at least 30 ng mL<sup>-1</sup> (75 nmol L<sup>-1</sup>) for adults<sup>119</sup> and 20 or 30 ng mL<sup>-1</sup> (50 or 75 nmol L<sup>-1</sup>) for children.<sup>120</sup> In case of severe deficiency (< 10 ng mL<sup>-1</sup>, 25 nmol L<sup>-1</sup>), 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<sup>121</sup> and children<sup>120</sup> (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 vitamin D supplementation was reported in five children with ARCl associated with vitamin D deficiency. Nevertheless, none had a follow-up, one patient developed hypercalcaemia and this regimen was not effective for two patients with EI.<sup>114</sup>

### 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).<sup>4</sup> 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,<sup>122</sup> suggesting the existence of additional functional defects

of the sweat glands. The effects of local and systemic therapy are not well known. Topical therapy may help to reduce the hyperkeratotic plugging of sweat glands. Of note, hypohidrosis in CI has essentially been measured in only one case report, showing a positive effect of systemic retinoid therapy.<sup>123</sup>

We recommend avoiding extreme temperatures and outdoor activities during the hottest periods of the day (LoE 4, GoR D). Patients should wear adequate clothing. In a hot climate, cold water or packs (regular water spraying, bathtubs, showers) and cooling devices (air conditioning, fans) can help to cool the skin. We recommend regular topical skincare (LoE 4, GoR D) (see part one).<sup>4</sup> In cases with severe thermoregulation, 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).<sup>4</sup>

### Particularities of congenital ichthyosis

There are some particularities of the management of CI that are related either to the age of the patient or to the form of ichthyosis. Recommendations with level of evidence and grade are presented in Table S3 (see Supporting Information).

#### Particularities of management in the neonatal period

Clinical presentations at birth necessitating special care include collodion baby, neonates with HI, congenital ichthyosiform erythroderma, NS, EI and ichthyosis prematurity syndrome (IPS). Neonatal presentation increases the risk of complications that are associated with an impaired barrier function, such as increased transepidermal water loss (TEWL).<sup>124</sup> Infections, electrolyte imbalance, disrupted thermoregulation and/or metabolic wasting and respiratory distress (in IPS) can be life threatening. Some forms of CI are also associated with prematurity.

#### Management of collodion baby and harlequin ichthyosis (LoE 3, GoR D)

Clinical presentations and complications are described in Table S4 (see Supporting Information). A list of CIs with a collodion membrane at birth is presented in Table S5 (see Supporting Information). Evidence about management is limited as there are only six retrospective descriptive series including 17–32 collodion babies<sup>125–128</sup> or 16–45 patients with HI,<sup>84,129</sup> as well as some case reports.<sup>124,130–133</sup> There are also some review papers describing disease management.<sup>134–142</sup>

**Neonatal intensive care unit** Newborns must be admitted to a neonatal intensive care unit and require an interdisciplinary

approach. This involves 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).<sup>4</sup>

**Incubator** Collodion babies and neonates with 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.<sup>126</sup> 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 adequate caloric intake and appropriate weight gain.

**Nutrition and electrolyte balance** Bodyweight is one of the best clinical indicators of sufficient nutrient 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.<sup>133</sup>

**Topical therapy** Emollients decrease TEWL and are recommended three to eight times a day.<sup>143</sup> 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.<sup>127,144</sup> 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.<sup>145–149</sup> An absolute contraindication is the use of salicylic acid.<sup>150–152</sup> Daily bathing is advisable before ointment application.

**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.<sup>62</sup>

**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%).<sup>145</sup> Antifungal creams may be used on areas of macerated skin in order to avoid fungal infection. Prophylactic antibiotic treatment is not recommended in collodion babies, but may be an option in HI.

**Invasive procedures in neonates** Invasive procedures should be avoided as they are a 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 ischaemia** Massages using ointments (simple emollient or 10% urea in limited areas) may be helpful for prevention. Digital ischaemia has been reported to respond to topical tazarotene 0.1%.<sup>153,154</sup> Oral retinoids may be highly efficient.<sup>155</sup> Surgery (linear band incisions) may also be considered.<sup>156</sup>

**Oral retinoids in the neonatal period** In collodion babies, 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 *et al.*,<sup>84</sup> 83% of patients with HI receiving systemic retinoids survived, whereas long-term survival was only 24% in neonates who did not undergo retinoid treatment. It is unknown whether 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.<sup>157</sup> Although isotretinoin has been occasionally used in the neonatal period,<sup>158</sup> when oral retinoids become necessary we recommend acitretin.<sup>154,159</sup>

**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.<sup>160</sup> Analgesics before bathing and skincare may be necessary and may facilitate respiration. Nonpharmacological interventions (i.e. non-nutritive sucking) and/or various drugs may be used.<sup>160</sup> Soft bedding or a waterbed may also be useful.

### Management of congenital ichthyoses with other neonatal presentations (LoE 3, GoR D)

Congenital ichthyosiform erythroderma and NS present at birth with erythroderma and peeling. EI presents at birth with blistering and areas of denuded skin.<sup>141,161</sup> Patients may be admitted to a neonatal intensive care unit, placed in an incubator and monitored closely; they require adapted skincare 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<sup>162–164</sup> (avoidance of adhesives and high temperatures that may induce blisters).<sup>136</sup> The most important issues are regular antibacterial wound management, management of pain and dehydration, and nutrition.<sup>165</sup> Babies with IPS are prone to complications related to the prematurity and life-threatening neonatal asphyxia caused by aspiration of corneocyte-containing amniotic fluid.<sup>166–168</sup> They need immediate oropharyngeal suction with or without initial ventilation and intubation. Some babies with recessive X-linked ichthyosis may also show cutaneous manifestations at birth, with red skin and peeling or 'collodion-like' presentation.

### Particularities of management related to other forms of congenital ichthyosis

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 S3.

#### Management of skin inflammation and eczema lesions

**Topical steroids** Topical steroids (e.g. class I–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<sup>169</sup> and severe skin atrophy.

**Topical calcineurin inhibitors** Topical tacrolimus ointment (0.03% or 0.1%) and pimecrolimus cream (1%) (available only in some European countries) have been used in a limited number of patients with NS: one prospective series of three patients,<sup>170</sup> four retrospective series of two to four patients<sup>171–174</sup> and four case reports.<sup>89,175–177</sup> All but one patient reported efficacy. The main concern is related to systemic absorption, which has been reported in many cases, especially for tacrolimus ointment and even for application to limited body surface areas. Therefore, we recommend their use only for short-term management of flares on limited areas (LoE 3, GoR D). Otherwise, monitoring of serum or plasma drug levels is necessary.

**Phototherapy** The efficacy of phototherapy was reported in a few case reports, in four children treated with narrowband UVB<sup>178–181</sup> and in two adults treated with psoralen–UVA (PUVA)<sup>182</sup> or UVA-1.<sup>183</sup> Short-term efficacy was reported in all but one.<sup>182</sup> We do not recommend PUVA therapy (LoE 3, GoR D). Narrowband 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 immunoglobulins** The use of ciclosporin A has been reported as ineffective in two patients.<sup>182,184</sup> Given the risk of skin cancer associated with both NS and ciclosporin A,<sup>185</sup> we do not recommend using it (LoE 3, GoR D). Systemic immunoglobulins have been reported as safe and effective in five patients,<sup>86,186,187</sup> 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 two patients with NS.<sup>188,189</sup> We cannot recommend such therapy (LoE 3, GoR D), based on the following arguments: paucity of data about TNF- $\alpha$  inhibitors in NS, skin cancers (see below) and recurrent infections reported in NS, significantly increased risk of infections and nonmelanoma skin cancers for patients treated with TNF- $\alpha$  inhibitors<sup>190,191</sup> and some cancers being aggressive.<sup>192,193</sup> Omalizumab was

reported to decrease allergic skin symptoms in one patient with NS.<sup>194</sup>

**Future treatments** In the future, targeted therapy will probably be available.<sup>67,195</sup>

### Risk of skin cancers

Patients with NS have been reported to be at risk for several types of skin cancer. Patients may present with squamous and basal cell carcinomas with or without papillomavirus (more than 15 case reports).<sup>182,196–203</sup> 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) in case of a failure of all medical treatments.<sup>204,205</sup>

### Other forms of congenital ichthyosis 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 S3.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Table S1** Complications of congenital ichthyosis.

**Table S2** Management of complications of congenital ichthyosis: recommendations with level of evidence and grade.

**Table S3** Management of the particularities of congenital ichthyosis related either to the age of the patient or to the form of ichthyosis: recommendations with level of evidence and grade.

**Table S4** Clinical presentation and complications of collodion baby and harlequin ichthyosis in the neonatal period.

**Table S5** Ichthyosis forms that may present with collodion membranes at birth.