Inherited ichthyoses: emergency treatment card

Inherited ichthyoses - definition and general information:

Inherited ichthyoses are a group of diseases caused by mutations of the genes involved in the development of the skin barrier, resulting in a deficiency of the latter.
Inherited ichthyoses are classified into two groups: non-syndromic and syndromic. Syndromic forms can affect organs other than the skin (abnormalities of the nervous system, liver, etc.).
Inherited ichthyosis begins mostly from birth or more rarely in childhood or even as a young adult. Patients present with squama (scales) that cover their whole body and which may be associated with erythroderma (generalised erythema). Progression is chronic with periods of exacerbation and improvement. The condition often has a significant impact on the quality of life of patients.
The many complications include: ophthalmological and ENT abnormalities, functional limitation (fine motor skills), stunted growth in children, pruritus, painful skin, heat intolerance/discomfort, vitamin D deficiency and skin infections.
Treatment aims to improve the condition of the skin and relies on topical care (emollients, keratolytic agents). In severe forms, systemic treatment with oral retinoids is sometimes required. Potential secondary complications should also be prevented and treated.

In all cases, it is important to listen carefully to patients and their entourage, as they are experts about their condition and are usually the first ones to spot an unusual symptom that should reported and taken into consideration.

Patients concerned
Children (except during the neonatal period) and adults.
All forms of moderate to severe ichthyosis (excluding mild ichthyosis vulgaris and X-linked ichthyosis).
Emergency situations may involve all forms of ichthyosis, but are more likely to involve the following forms: Netherton's syndrome (infections, allergies), keratinopathic ichthyoses (bullae, erosion), severe autosomal recessive ichthyosis (caused by *TGM1*, *ABCA12* mutations [ocular and ENT complications]).

Typical long-term treatment prescribed
Topical treatments: emollients, keratolytic agents.
Systemic treatments: oral retinoids.
Treatment for any associated organ damage in syndromic forms.

Pitfalls
Ignoring the dermatological signs of another additional condition.
Underestimating the sometimes severe consequences of skin damage.

Precautions before arriving at the emergency department
Any venepuncture requires a thorough disinfection of the skin to avoid bacteraemia associated with chronic skin colonisation (especially staphylococcus aureus).

Emergency situations and recommendations

Emergency situations

1: acute aggravation of the skin condition (erythema and/or scales and/or functional signs: e.g. pruritus/pain)

- Look for a triggering factor;
- Consider a flare-up of the disease, a cutaneous superinfection (bacterial, fungal, viral, parasitic [scabies]), irritated reaction, eczema flare-up, other dermatological conditions.

2: fluid-filled or erosive lesions

- Look for a triggering factor;
- Consider a bullous flare-up in case of keratinopathic ichthyosis (bullous ichthyosis), eczema, contact allergy, or a bacterial, herpes or fungal infection (candidiasis).

3: fever

- Look soft-tissue infection, generalised sepsis with a cutaneous portal of entry.

4: ophthalmological conditions

Any recent change to the condition of the eyes (conjunctivitis, redness, pain, secretions, etc.) requires an ophthalmological consultation.

5: ENT complications

No topical treatment should be administered without receiving ENT advice.
Main scenarios: partial hearing loss due to an obstruction in the ear canal due a plug formed by the scales, otitis externa, perichondritis caused by infection spreading to the cartilage of the auricle.

6: other:

- **Dehydration in young children (hypernatremia)**
- **Heat discomfort:** cool down and place in a cold environment (wet clothes, spray with water)
- **Acute extra-cutaneous manifestation in syndromic forms**
- **Pain**

- Painful skin:
  * Cracking: eliminate any local/regional infection, disinfect (aqueous or foaming chlorhexidine), apply Vaseline. Treat any peripheral hyperkeratosis, if necessary, after protecting any cracks, using emollients or keratolytic agents (e.g. emollients containing 20-30% urea).

* Skin inflammation (secondary to erythroderma)
* Skin infection
- Muscle and/or joint pain: possible adverse reactions to oral retinoids;
- Bone pain: fracture/compression as an added complication of osteoporosis or vitamin D deficiency.

Traumatic wounds

- Disinfect the skin with an aqueous or foaming chlorhexidine antiseptic**, avoid products containing alcohol or iodinated products** in children (percutaneous toxicity);
- Topical (fusidic acid) or general antibiotic therapy, if justified by the surface area of infected skin and the severity of infection;
- Attach dressings using a tubular strip or net (do not use an adhesive) if scaly skin and there is a risk of detachment, in cases of keratinopathic ichthyosis (skin fragility and risk of bullous lesions).

Emergency recommendations

General recommendations

- Do not use topical or general antibiotic therapy systematically. It is only justified when there is a clinical infection (pain, swelling, pus, pustules or yellow-brown (meliceric) crusts) and not in cases of simple bacterial colonisation;
- Similarly, antiseptics should not be used systematically. If necessary, use aqueous forms (e.g. aqueous chlorhexidine);
- Do not underestimate the potential severity of a skin disease and its impact on other organs/functions;
- Listen to the patient, as they are experts on their condition.

Emergency situation 1: acute worsening of the skin condition

1. Diagnostic emergency measures

- **Clinical elements of the diagnosis:**

  - Positive diagnosis: onset or increase of erythema, often accompanied by an increase in scaling. Skin discomfort, and pain or pruritus;

  - Aetiological diagnosis: look for a triggering factor (intercurrent disease, medication intake, topical applications, unusual activity/contacts, infectious contagion, climatic factors, etc.).

  - Diagnoses to consider:

    - Flare-up of the condition;

    - Cutaneous superinfection:

      - **Bacterial** most commonly: Staphylococcus aureus or other germs: presence of pustular/erosive or crusty lesions **(see Situation 2);**
      - **Fungal**: Candida albicans (pustular lesions in skin folds), dermatophytes (scaly and erythematous lesions that are often difficult to spot on ichthyosis skin);
      - **Viral**: HSV (herpes) or VZV (varicella, herpes zoster): pustular/erosive or crusty lesions, sometimes necrotic **(see Situation 2)**;
      - **Parasitic:** scabies occurring in the presence of ichthyosis loses its usual clinical characteristics (semiology, topography) and often results in an aggravation of the ichthyosis and pruritus in particular. It may involve profuse and highly contagious scabies, as it has a high sarcoptic content, and the diagnosis must always be reported to prevent an epidemic.

    - Irritated reaction: increased erythema, even surface cracking/erosions;

    - **Eczema**: pruritic vesicular/erosive/oozing lesions **(See Situation 2)**;

    - **Other dermatological conditions:** viral rash, toxidermia, etc.

- **Evaluate the severity:**

  - Pain: visual analogue scale (VAS);
  - Pruritus: visual analogue scale (VAS);
  - Erythema: visual analogue scale (VAS) and percentage of body surface area affected;
  - General impact/tolerance: vital signs;
    (Heart rate, BP, breathing rate, temperature).

- Search for signs of sepsis and severity score: qSOFA score in adults (quick SOFA - Sepsis-Related Organ Failure Assessment), paediatric SOFA in children.

- **Emergency investigations:**

- *If general impact*: fluid and electrolyte balance, haematocrit, protein in serum (dehydration); blood cultures (even with no fever).

- *If a skin infection is suspected*: skin samples should be collected from vesicles, pustules, erosions or crusts, for bacteriological, fungal or virological testing. Dermatoscopy examination if scabies is suspected.

- *If fever:* aerobic and anaerobic blood cultures to look for sepsis with a cutaneous portal of entry

- If signs of sepsis, the initial lab tests should include heamatocrit, pH and lactates

2. Immediate therapeutic measures

- **Monitoring:**

  - Blood pressure
  - Heart rate
  - Breathing rate
  - Temperature
  - Diuresis
  - Capillary refill time

- **Symptomatic measures:**

  - Analgesics adapted to the intensity of pain;
  - Antipyretics, if necessary, under usual conditions (no contraindication to the use of NSAIDs);
  - Correct any fluid/electrolyte disorders; ensure volume expansion if hypotension and/or severe dehydration;
  - Warm baths or showers, dampen clothes.

- **Specific treatments:**

  - Secondarily, adjust treatment according to the antibiogram (risk of resistant staphylococcus due to chronic carriage and possible hospital stays);

In case of ***herpes infection***: administer aciclovir or valaciclovir orally or intravenously depending on the age, extent of lesions and presence of general signs (fever). When administered intravenously, hydrate, check and monitor renal function

In case ***of fungal superinfection****: anti-fungal agents per os (terbinafine,* if dermatophytosis; fluconazole, if candidiasis);

- *In case* ***of eczema****:* topical corticosteroids in the absence of clinical superinfection:
  - 1 topical application per day of a potent topical corticosteroid (e.g. betamethasone 0.05% or fluticasone);
  - facial eczema or in children: 1 topical application per day of desonide 0.05%.

Emergency situation 2: fluid-filled or erosive lesions

1. Diagnostic emergency measures

- **Clinical elements of the diagnosis:**

Positive diagnosis: fluid-filled lesions:
- blister: small lesion containing clear fluid;
- bulla: lesion > 1 cm containing clear fluid;
- pustule: lesion with thicker and non-transparent contents;
- erosive (superficial wounds) or oozing (that stain clothing or dressings) lesions.
- final progression into crusts.

- *Aetiological diagnosis*: look for a triggering factor (initial wound, topical applications, unusual activity/contacts, infectious contagion, etc.).

Diagnoses to consider:
- Bullous flare-up of keratinopathic ichthyosis (bullous ichthyosis);
- Eczema (pruritus, oozing):
  - contact allergy;
  - eczema flare-up in a patient with Netherton's syndrome.
- Pustules:
  - Staphylococcal infection;
  - Herpes infection: clustered pustules followed by necrotic lesions; often severe pain;
  - Candidiasis infection: flat and milky-white pustules, often predominantly in skin folds.
- Other causes: toxic dermatitis (acute generalised exanthematous pustulosis, toxic epidermal necrolysis), autoimmune bullous dermatosis, thermal or caustic burns, arthropod-sting reactions.

- **Evaluate the severity:**

- Intensity of pain (VAS 0-10);
- Vital signs
- Risk of dehydration if extensive lesions;
- Extent of lesions: percentage of body surface area affected
- If toxidermia: mucosal erosion, detachment, pain, fever, swelling, adenopathies, skin necrosis.

- **Emergency investigations:**

- Skin samples if infection is suspected: bacteriological, fungal and virological (herpes);

2. Immediate therapeutic measures

- **Monitoring:**

  - Intensity of pain (VAS 0-10);
  - Vital signs

- **Symptomatic measures:**

  - Treat the pain (painkillers - usual procedure), especially before any therapy;
  - Baths/warm showers;
  - Drain any bullae (after collecting samples).

- **Specific treatments:**

- Suspected bacterial infection:

- Smaller sized lesions: disinfect with aqueous chlorhexidine, fusidic acid 2% cream;

- Extensive lesions: probabilistic treatment with systemic antibiotics (oral or IV) for staphylococcus aureus (see Situation 1).

- Suspected fungal infection:

- Topical treatment if limited lesions;
- Systemic treatment if extensive lesions (see Situation 1).

- Suspected herpes infection:

Aciclovir or valaciclovir: See Situation 1.

- Eczema, in the absence of clinical superinfection: topical corticosteroids:

- 1 topical application per day of a potent topical corticosteroid
(e.g. betamethasone 0.05% or fluticasone)
- on the face or in children: 1 topical application per day of desonide 0.05%

- Discontinue all non-essential medicinal products taken orally, if toxidermia is suspected.

Emergency situation 3: fever

1. **Diagnostic emergency measures**

- **Clinical elements of the diagnosis:**

  - An isolated erythrodermic flare-up is sufficient to explain any fever and inflammatory syndrome;
  - However, other causes should be investigated such as soft-tissue infection or generalised sepsis with a cutaneous portal of entry;
  - Superficial bacterial or fungal cutaneous superinfections do not usually cause fever, unlike herpes superinfections.

- **Evaluate the severity:** Severity criteria applicable to general fever.

- **Emergency investigations:**
  - Carefully disinfect the skin (antiseptic compress applied several minutes before the venepuncture);
  - Lab tests: inflammatory syndrome;
  - Collect skin samples for bacteriological, fungal and virological examination of blisters, pustules, erosions or crusts;
  - Aerobic and anaerobic blood cultures;
  - Infectious site located some distance away (urine, lungs, etc.).

2. **Immediate therapeutic measures**

- **Monitoring:**

  - Usual monitoring (heart and breathing rate, BP, temperature, consciousness, diuresis, hydration).

- **Symptomatic measures:**

  - Antipyretics according to tolerance of fever (not contraindicated) and rehydration.

- **Specific treatments:**

- Depending on the diagnosis retained.

Emergency situation 4: ophthalmological conditions

Any recent changes in the condition of the eyes require an emergency ophthalmological consultation.

1. Diagnostic emergency measures

- **Clinical elements of the diagnosis:**

  - ***Conjunctivitis*** (sensation of a foreign body, redness, tearing, without loss of visual acuity):
    - irritated: especially at night, irritating factors (wind, sun, air-conditioning)
    - infectious: purulent secretions, intense redness
    - allergic: pruritus, oedema of the eyelids and conjunctiva

  - ***Keratitis:*** decreased visual acuity, burning sensation, pain, redness, discharge, photophobia.

  Note: total or partial loss of corneal sensitivity is common and the absence of pain may result in a delayed diagnosis

  There is a risk of a perforated cornea and subsequent astigmatism caused by permanent damage to the corneal surface.

- **Evaluate the severity:**

  - Loss of visual acuity;
  - Corneal abnormality during the examination.

- **Emergency investigations:**

  - Examination of the cornea with the naked eye, with/without fluorescein staining: look for opacities and corneal lesions, fluorescein "washing" (Seidel's test - synonymous with perforation of the cornea), signs of conjunctivitis, remove any foreign body under the eyelids, anterior chamber abnormality (hypopyon, etc.);
  - Assessment of monocular visual acuity by getting the patient to "count fingers" at various distances from the eye;
  - Slit-lamp examination by an ophthalmologist.

2. Immediate therapeutic measures

- **Symptomatic measures:**

  - ***Irritative conjunctivitis:*** daily lubricating treatment with tear substitutes: carmellose, carbomer or povidone, hyaluronic acid derivatives, vitamin A ointment (night-time application) and emollients for eyelids with a preference for products with a high viscosity.

  - ***Allergic conjunctivitis:*** usual symptomatic treatment (lubricants/artificial tears) and topical anti-allergic products without preservatives: N-acetyl aspartyl glutamic acid drops, cromoglicic acid, ketotifen or levocabastin.

- **Specific treatments:**

  - ***Infectious conjunctivitis*** (usually bacterial): broad spectrum ophthalmic antibiotic ointment: ciprofloxacin, rifamycin or tobramycin.

  - ***Infectious keratitis*** (bacterial, viral, fungal or parasitic): initially empirical treatment with a broad spectrum antibiotic ophthalmic ointment: ciprofloxacin, rifamycin, or tobramycin, then adjust the treatment according to the isolated germ.

Emergency situation 5: ENT complications

Note: no topical treatment should be administered without receiving ENT advice beforehand.

1. Diagnostic emergency measures

- **Clinical elements of the diagnosis:**

Possible diagnosis based on the main symptoms:

- hearing loss (moderate and fluctuating): obstruction of the auditory canal by tympanic thickening and scales;
- pain and discharge: otitis externa;
- severe pain: look for infection that has spread to the surrounding structures (infection of nearby soft tissue, mastoiditis).

- **Evaluate the severity:**

- Signs of subcutaneous tissue infection: necrosis (severe pain, significant stenosis of the external auditory canal, erythema of the auricle and periauricular region), subcutaneous emphysema with crackling sounds when palpated, redness and heat, and swelling of the face or neck.
- Signs of generalised infection with a cervical or facial portal of entry (fever, tachycardia, hypotension, polypnoea, etc.).

- **Emergency investigations: emergency ENT consultation for otoscopy**

- Suction of squama;
- An ENT specialist should collect a sample of any otorrhoea (for bacteriological and/or fungal testing) after disinfecting the canal;

- Look for any associated tympanic disorder (micro-abscess and/or thickening);

- Audiometric test: look for transmission or mixed hearing loss (labyrinth).

2. Immediate therapeutic measures

- **Adapted monitoring:**

- Otoscopic with regular and gentle suction;
- Audiometric test should not be carried out at the same time as an acute episode.

- **Symptomatic measures:**

- Oral analgesic treatment (general);
- Any aqueous fluid must be removed;
- Avoid repeated local micro-trauma (cotton buds or other);
- Oral antibiotic therapy (amoxicillin in combination with clavulanic acid or ciprofloxacin) if it is suspected that the infection has spread to nearby structures;
- In case of serious infection or mastoiditis, intravenous antibiotic therapy.

- If the eardrum is perforated or cannot be visualised: antibiotic and anti-inflammatory ear drops such as fluoroquinolones/corticosteroids (for at least 10 days) - regular antiseptic washes: diluted iodinated povidone twice a week;
Anti-fungal, if indicated by the sample or if the first topical treatment has failed (administer for at least 3 weeks);
- If the eardrum intact: drops combining antibiotic and anti-inflammatory drugs.

- **Specific treatments:**

- ENT opinion: an otoscopic examination by a specialist is essential to clean out the canal, remove obstructive blockages, collect samples of any discharge from the ear (bacteriological sample), to look any associated tympanic disorder and to perform a hearing test.

- Surgical treatment in cases involving facial cellulitis/extensive involvement of subcutaneous tissues of the face or neck that may require mechanical cleaning, and flattening of necrosis and/or abscesses.

Transport

- **Where should patients be taken?**

- They should be taken to the adult or child emergency department in an hospital with expertise in ichthyosis conditions;

- Ophthalmological or ENT disorders: refer directly for an ophthalmological or ENT consultation.

- **How should patients be transported?**

- No specific requirements for the ichthyosis; however, there is a need for air-conditioned transport in hot weather;

- Usual instructions regarding clinical signs and level of urgency.

- **When should patients be transported?**

- Patients who experience heat discomfort should not be transported during the hottest hours of the day unless the vehicle is air-conditioned.

Precautions for medicinal products (possible interactions, contraindications, precautions for use, etc.)

- Oral retinoids: see product leaflet (main interaction: cyclins)

- Topical treatments can cause side effects through transcutaneous poisoning due to the abnormality of the epidermal barrier.
- **Child <2 years: Contraindication to topical treatment with salicylic acid or lactic acid (should only be used on small sized areas)**
- **Do not use products containing alcohol or iodinated products on extensive areas in children**

Precautions for anaesthesia

- **Limit the placement of venous pathways** and avoid areas of infected or erosive skin (potential portal of entry for infection): some patients are at risk of chronic carriage of methicillin-resistant staphylococcus aureus (MRSA);
Avoid the use of a central venous route (risk of sepsis) unless vital (e.g. resuscitation during major surgery).

- **Adhesives:**
For keratinopathic (bullous) ichthyosis: skin fragility and the risk of bullae (especially in children) require the use of appropriate non-adhesive dressings (self-fixing silicone hydrocellular dressings for the treatment of highly exudative wounds);

- Electrodes:
Avoid using self-adhesive electrodes and patches: risk of detachment in keratinopathic (bullous) ichthyoses and other forms with scales, as they may not stick (lipid film secondary to cream applications) and prevent the conduction of the current.
It is advisable to use the older-style clamps if they are still available in operating theatres. Otherwise, the skin in contact with the patch must be cleaned with a solvent for adhesive dressings.

- **No contraindications to local or general anaesthesia.**
However, careful and gentle intubation (use of gel) is required to limit local trauma.

- **In ectropion** cases, ensure eyelid occlusion during anaesthesia, via eye masks and the application of vitamin A ointment. This ointment should then continue to be administered 2 to 3 times daily.

- Some ichthyosis patients are also more prone to changes in body temperature: **monitor temperature during surgery and prevent hypo- or hyperthermia.**

Supplementary measures when hospitalised

- Encourage the presence of families during emergency admissions and hospitalisation due to the sometimes difficult experience of living with the condition.
- Listen to the family and the patient as they have extensive knowledge of their condition and its specific features.
- After prolonged anaesthesia or following surgery, the skin should be moisturised daily with emollients and should not enter into contact with irritants.

Organ and tissue donation

In view of our current state of knowledge, **when organs are not involved in cases of syndromic ichthyosis**, certain organs and tissues may be donated based on a case-by-case evaluation (individual, clinical and para-clinical evaluation of the donor, organs and treatments administered).

In general and in view of the current state of knowledge:

- **Risk of disease transmission:**
  There is no risk of transmission of the disease through organ or tissue donation.

- **Specific risk linked to the disease or treatment:**
  In case of bacterial or fungal skin superinfection or herpes infection, a risk of transmission of infection by transplantation does exist.

- **Organ donation:**
  If no organ is involved in cases of syndromic ichthyosis, all organs may be transplanted subject to a clinical and para-clinical evaluation of the donor, the organs and any treatments administered. The transplant decision is therefore based on the team's estimation of the risk incurred by the recipient in relation to the expected benefit of the transplant (benefits/risks).

- **Tissue donation:**
  Skin donations are contraindicated.
  Cornea may be transplanted subject to an individual evaluation (a specialist doctor must confirm the absence of any ophthalmological lesions). Corneal donation may be contraindicated in the presence of keratitis corneal scarring. Such scarring can be detected at the time of removal or in a tissue bank.
  Vessels, heart valves, bones can be transplanted subject to an individual evaluation.

Documentary resources:

15- 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. Management of congenital ichthyoses: European guidelines of care, part two. Br J Dermatol. 2019 Mar;180:484-495.

16- 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. Management of congenital ichthyoses: European guidelines of care, part one. Br J Dermatol. 2019 ;180 :272-281.