Harlequin ichthyosis (HI) is the most severe phenotype of the autosomal recessive congenital ichthyoses. HI is caused by mutations in the lipid transporter adenosine triphosphate binding cassette A12 (ABCA12). Neonates are born with a distinct clinical appearance, encased in a dense, platelike keratotic scale separated by deep erythematous fissures. Facial features are distorted by severe ectropion, e-clabium (eversion of the lips), flattened nose and rudimentary ears. Skin barrier function is markedly impaired, which can lead to hypernatremic dehydration, impaired thermoregulation, increased metabolic demands, and increased risk of respiratory dysfunction and infection. Historically, infants with HI did not survive beyond the neonatal period; however, recent advances in neonatal intensive care and coordinated multidisciplinary management have greatly improved survival. In this review, the authors combine the growing HI literature with their collective experiences to provide a comprehensive review of the management of neonates with HI.

PATHOPHYSIOLOGY

HI is caused by mutations in the lipid transporter adenosine triphosphate binding cassette A12 (ABCA12). ABCA12 is a member of the subfamily of adenosine triphosphate–binding cassette protein transporters. Its function in the epidermis is to facilitate the delivery of lipid glucosylceramides into lamellar granules, which then deliver them into the extracellular space. Electron microscopy of lamellar granules in HI are abnormally shaped, reduced in number, and in some cases absent.
Less damaging mutations in ABCA12 cause milder forms of congenital ichthyosis phenotypes that fall on the lamellar ichthyosis–congenital ichthyosiform erythroderma spectrum.9–11

The compromised skin barrier is likely related to abnormal lamellar granule maturation and secretion resulting in inadequate delivery of lipids, antimicrobial peptides, and enzymes necessary for keratinocyte desquamation into the extracellular space. As a result, transepidermal water loss (TEWL) is increased, leading to increased metabolic demand,12 risk for hypernatremic dehydration, temperature dysregulation, and increased accumulation of stratum corneum.

Epidemiology, Recognition, and Genetic Testing
HI is recognized at birth by the typical clinical appearance (Fig 1A). Reverend Oliver Hart reported the first case in 1750, and disease incidence has been estimated to be ~1 in 300,000 births.1 HI is inherited in an autosomal recessive fashion. Single-nucleotide polymorphism array technology for homozygosity mapping identified the HI locus at chromosome 2q25.4 Multiple mutations have been reported, including premature termination, insertion, deletion, and frameshift mutations, resulting in an absent or truncated ABCA12 protein.1,3,4 Mutations that permit residual ABCA12 function appear to have a survival advantage over those with early termination mutations.

The optimal time for obtaining a biological sample for genetic testing is shortly after birth to confirm the clinical diagnosis, assist with assessing prognosis, and enable genetic counseling. Access to insurance coverage for the costs of genetic testing may also be easier when performed during hospitalization. Identifying parental carrier status allows for DNA-based prenatal or preimplantation genetic diagnosis in future pregnancies. Next generation sequencing is replacing Sanger sequencing for diagnosis of HI as a less expensive and more efficient alternative. Resources for gene testing for HI in the United States are listed in Table 1.

Prenatal Diagnosis
Advances in fetal DNA analysis and ultrasound technology have replaced the more invasive techniques of fetal skin biopsy.1 Fetal DNA analysis can be offered to parents who had a previous child with HI. Fetal genomic DNA is obtained from amniotic fluid via amniocentesis or chorionic villus sampling.13 New research has shown that messenger RNA analysis using hair samples can also more easily and less invasively be used to identify ABCA12 mutations.14

In some cases, prenatal ultrasonography may allow detection of signs suggestive of HI, including eclabium, ectropion, rudimentary ears, contractures, and dense floating particles in amniotic fluid (“snowflake sign”).15 The application of three-dimensional ultrasound theoretically offers a greatly improved analysis of facial morphology and may aid in prenatal diagnosis; however, detection of these unusual features requires tertiary expertise, and they are not detectable until the second trimester, excluding the option of early termination.16

Clinical Characteristics
Affected neonates are often born prematurely.15 The thickened armorlike skin can cause pseudocontractures that restrict movement, and impaired perfusion can result in digital necrosis. Skin of surviving infants gradually adapts from the aqueous intrauterine to the extraterine environment, with skin phenotype evolving to generalized erythema and scaling, often with associated palmoplantar keratoderma.1,5,17 HI can usually be differentiated from the less severe collodion baby phenotype (CBP) on the basis of clinical appearance. HI features generalized armorlike yellow scale, whereas the classic skin changes of CBP are more translucent and waxy. Ectropion and eclabium are often present in patients with CBP, but are generally far less severe.

Table 1 Resources for Genetic Testing for HI in the United States

<table>
<thead>
<tr>
<th>Organization Name</th>
<th>Web Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeneTests</td>
<td><a href="http://www.genetests.org/">www.genetests.org/</a></td>
</tr>
<tr>
<td>Ichthyosis Registry at Yale</td>
<td><a href="http://www.dermatology.yale.edu/research/ichthyosis.aspx">www.dermatology.yale.edu/research/ichthyosis.aspx</a></td>
</tr>
</tbody>
</table>
Rarely, patients present with an "incomplete" harlequin phenotype, with more severe findings at localized body sites, particularly the head, in the setting of an otherwise collodion presentation. Patients with both phenotypes benefit from ichthyosis gene panel testing and intensive neonatal management.

**NEONATAL MANAGEMENT**

Admission to a tertiary care center with a level III NICU is desirable. Intensive care management is largely supportive and involves a multidisciplinary team, including neonatology, dermatology, genetics, ophthalmology, otolaryngology, orthopedic and plastic surgery, nutrition, physical therapy, and nursing.

Because of the significant morbidity associated with HI, the high risk of respiratory failure requiring intubation, and potential risk of neonatal demise, discussion regarding aggressivity of support should be held with parents and documented early in the course (see Ethical Considerations section below). Beyond complications of prematurity, minimizing TEWL, preventing electrolyte imbalance, temperature dysregulation, respiratory distress, malnutrition, and infection are key to survival and best performed in the NICU (Table 2).

Neonates should be maintained in an incubator with added humidity, as individualized for the patient. Serum electrolytes, urine output, daily weights, prealbumin, and kidney and liver function should be monitored closely (Table 3). Prevention of infection is particularly important. Deep fissuring of the thick scale can penetrate the epidermis and become a source of pain. It is important to provide adequate pain control (see section below).

Many neonates will initially require narcotics. Infants with milder phenotypes may have adequate pain control with acetaminophen or nonsteroidal antiinflammatory agents;20,21

**Securing Lines**

Initial placement of a central venous umbilical line is standard for high-risk neonates and useful in patients with HI for hydration, parenteral nutrition, and laboratory sampling. Alternative access is via peripheral scalp vein or a peripherally inserted central catheter line. A protocol to secure lines in infants with fragile skin has been developed (Fig 2).

**Skin Care**

Skin barrier dysfunction in neonates is especially problematic, given the large body surface-to-weight ratio.22 Skin care should include once to twice daily cleansing to hydrate and promote shedding of the stratum corneum.21 Some suggest daily buffered dilute hypochlorite baths.11 This can be accomplished by dampening roll gauze with warmed 0.125% sodium hypochlorite mixed 1:10 with warmed sterile water. The optimal pH is 8 to 8.5. The gauze can be applied as a wet wrap, occluded with a plastic wrap layer for 10 to 20 minutes.23 A bland emollient should be applied immediately after wet wrap removal. Products, such as petrolatum jelly, extra virgin coconut oil, and sunflower seed oil, are considered safe and may even possess antimicrobial properties.24,25

The authors recommend handling infants with sterile, latex-free gloves and using single use packets of emollient to minimize colonization with pathogenic microbes.19 Application of keratolytic-containing emollients should be avoided in the neonatal period due to the risk of percutaneous toxicity. Respiratory distress has been reported after use of topical salicylic acid.26 Reports on the use of topical ceramide-containing emollients have been conflicting. Although ceramides can stimulate ABCA12 expression through the peroxisome proliferator-activated receptor PPAR , topical application has not been shown to improve barrier function.28

Digital necrosis is a common complication in HI, related to a compartmentlike syndrome from epithelial constriction. Surgical intervention can be digit or limb

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**TABLE 2 Management of HI During the Neonatal Period**

<table>
<thead>
<tr>
<th>Admission to a NICU.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placement in a humidified isoolette at 50%–70% humidification.18</td>
</tr>
<tr>
<td>Monitoring of body temperature to prevent TEWL and associated temperature dysregulation.</td>
</tr>
<tr>
<td>Monitoring of daily body weight and fluid status; daily monitoring of electrolytes to prevent hypernatremic dehydration during the first week and thereafter based on patient’s condition. Meeting high caloric demands and nutrition supplementation.</td>
</tr>
<tr>
<td>Skin care with daily bathing (+ antiseptics) followed by application of bland emollient every 4–6 h. Vigilant monitoring for respiratory compromise with a low threshold for intubation. Vigilant monitoring for infection with surveillance cultures from selected skin sites and folds with a low threshold for antibiotics based on cultured microbes.</td>
</tr>
<tr>
<td>Eye care with application of bland lubricant every 6–12 h; reserve topical antibiotics for conjunctivitis or corneal abscesses. Monitoring of limb and digit perfusion. Consider surgical intervention, splinting, and physical therapy as needed.</td>
</tr>
</tbody>
</table>

**TABLE 3 Monitoring Parameters in HI**

<table>
<thead>
<tr>
<th>Complete blood count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolytes: Na, K, Cl, Mg, P, CO2, glucose, calcium</td>
</tr>
<tr>
<td>Kidney function: blood urea nitrogen, creatinine, urine output</td>
</tr>
<tr>
<td>Liver function*</td>
</tr>
<tr>
<td>Lipid levels*</td>
</tr>
<tr>
<td>Total protein, albumin and prealbumin Daily weights</td>
</tr>
<tr>
<td>Skin surface cultures daily × 1 wk and weekly while in intensive care</td>
</tr>
</tbody>
</table>

| Blood cultures* |
| Vitamin D level* |

*Particularly important if retinoid therapy is instituted.

Low threshold to perform especially with temperature or hemodynamic instability, decreased oral intake, or irritability.
saving (Figs 3, 4, and 5). Several fasciotomy techniques have been described, including a linear band incision technique. Daily application of a topical retinoid (eg, 0.1% tazarotene cream) and soft splinting of the hands and feet may be an alternative to or augment surgical intervention.

**Nutrition**

Increased TEWL and skin turnover increases caloric demands in HI neonates. Furthermore, eclabium and jaw constriction may interfere with oral feeding. Often, neonates require supplemental oropharyngeal or nasogastric tube feeds. Fluid balance, serum protein, albumin, and electrolytes must be monitored carefully. Once an adequate suck and swallow has been established, breastfeeding should be encouraged to enhance bonding between mother and child. Inadequate suck to maintain caloric needs has been noted in infants with HI, and long-term supplemental tube feeding may be required. Frequent emesis has also been observed, but the possibility of associated gastroenteral dysmotility has not been studied.

Vitamin D deficiency and rickets have been reported in neonates with ichthyosis. There is conflicting evidence regarding whether this deficiency is associated with the use of oral retinoids. Lower vitamin D levels have also been associated with increased risk of neonatal sepsis. Monitoring vitamin D levels and
supplementation as necessary may be useful for the care of the HI infant.

Pain Control
Deep fissures and skin sloughing can be a source of pain in neonates.20 Assessing the severity of pain in neonates with HI, however, can be challenging. Newborn pain scales include facial expression as a parameter; most also include extremity tone and respiratory rate. Interpreting each of these can be problematic in infants with HI. The characteristic eclabium results in a fixed facial appearance as if in pain. The respiratory rate can be increased due to restricted tidal volumes. The fingers and toes may remain fixed due to encasement. As such, other parameters, such as heart rate, blood pressure, crying, and state of arousal, become relatively more useful. It is imperative that pain is well managed, and that parents are reassured that this issue has been addressed. Adequate pain control might require the use of narcotics, even if such treatment contributes to a requirement for assisted ventilation. The severity of pain dissipates after the surface layer has been shed, and the underlying skin epithelialized.

Ocular Management
The thick stratum corneum on the eyelids results in bilateral ectropion, placing infants at high risk for conjunctivitis, squinting, and exposure keratitis.1 Lubricant ophthalmic ointment should be applied to lid margins a minimum of every 6 to 12 hours. Surgical correction of ectropion has been reported with full-thickness autografts from the thigh and posterior auricular skin as well as from engineered human skin.34–36 There is no evidence that early surgery results in less ectropion at 6 to 12 months of age than would occur as part of the natural history of HI. Because retinoids promote stratum corneum desquamation, both oral37 and topical retinoids38 may be effective in reducing ectropion. Early ophthalmology evaluation is recommended.

Otologic Management
Reports on the otologic manifestations of HI have noted that patients have signs or symptoms of ear discomfort.39 Possible causes include excessive ear canal debris, dysbiosis, or secondary contact dermatitis. Vigorous ear debridement and skin manipulation should be avoided to minimize the risks of infection. Professional microsuctioning to remove skin debris may help prevent early conductive hearing loss.15,21 Ear drops have also been used to soften keratin plugs in the ear canal. Options include 0.25% acetic acid or 2% aluminum acetate. Avoid the potential percutaneous toxicity of salicylic acid and the risk of Malassezia overgrowth associated with olive oil.40 Early otolaryngology24 and audiology intervention is recommended.

Infection
HI neonates are particularly prone to sepsis. Although the impaired skin barrier is a likely portal,20 there may be a cellular basis for decreased innate immune function related to impaired lamellar granule transport and secretion of various antimicrobial peptides, including the antimicrobial peptides cathelicidin (LL-37) and human β defensin 2.41 There is limited evidence for the benefits of antimicrobial prophylaxis in neonates with HI. The authors recommend serial surveillance swabs for bacterial and fungal cultures from selected sites (eg, skin folds, nares, ear canals, perianal area) daily for the first week of life and once weekly for the remainder of the NICU stay. Early recognition of infection in infants with HI is important, but can be challenging. Many of the findings associated with infection in infants (eg, tachypnea, tachycardia, poor intake) are even less specific in infants with HI. Tachypnea may be due to restricted tidal volumes or to pain. Tachycardia may be a sign of pain or of dehydration. Poor oral intake may be indicative of restricted jaw movement and tiring with feedings. As such, a high index of suspicion for infection needs to be maintained, as well as a low threshold for laboratory workup, blood, spinal fluid, and urine cultures, and initiation of systemic antimicrobial therapy in infants with HI.

Respiratory Function
Respiratory failure and sepsis are the leading causes of early demise in HI.15 Several mechanisms other than infection can contribute to respiratory failure in these infants. Restricting bands of thickened epidermis and painful fissures may compromise chest expansion, and excessive keratotic debris may block nasal respiration in these obligate nose breathers. Pulmonary defects of surfactant secretion have been reported in one mouse model of HI,42 but not in another.43 A low threshold for intubation and mechanical ventilation should be considered for these neonates.44

RETINOID THERAPY
The use of systemic retinoids has become standard-of-care in the
management of HI, following a reported 83% survival among 25 treated infants compared with 24% survival of 21 infants who did not receive an oral retinoid. However, these results must be interpreted with some caution, because half of the untreated infants died within 3 days after birth, which is earlier than when retinoid therapy is usually available for administration. Another study documented a 92% survival rate among 12 infants treated with retinoids compared with 50% among those not treated. The efficacy of oral retinoids is not well understood. Some authors suggest that the reported benefit may be an overall improvement in intensive care in addition to oral retinoid therapy. Several oral retinoids have been used in the management of HI as well as other congenital ichthyoses, including etretinate, isotretinoin, and acitretin. The first successful neonatal use of acitretin in HI was reported in 2001 at a dose of 1 mg/kg per day, started on day 10 of life. Acitretin administration has been the retinoid most often used by the authors. Additionally, compounding isotretinoin rapidly isomerizes the 13-cis molecule to all-trans retinoic acid, which may have greater toxicity than the aromatic acitretin.

Treatment initiation within the first 7 days of life is recommended for all infants who can tolerate the medication. However, neonatal acitretin administration has been hindered by a lack of commercially available liquid formulations in the United States. The authors have found that capsular acitretin is not water soluble, so preparing a liquid requires compounding expertise. Acitretin can be compounded by extracting the powder from 10 mg capsules. The powder is weighed, and the appropriate dose is administered in a small aliquot of warm milk. At Maimonides Medical Center (Brooklyn, NY), an aqueous-based vehicle with a slightly acidic pH to help reduce oxidative degradation (Table 4).

The current literature suggests that the acitretin dose be between 0.5 and 1 mg/kg per day. A 2-day half-life suggests that once daily dosing is sufficient. Surveillance laboratory data includes a complete blood count, comprehensive metabolic panel, and lipids at baseline and monthly. Acitretin should be titrated to the lowest dose possible for individual patients based on clinical improvement with regular skin examinations and monitoring of side effects. Retinoids are typically able to be discontinued by 6 months of age. The early introduction of retinoid therapy is likely related to hastened desquamation (Fig 1B). Retinoids may be especially useful for improving digital and thoracic constrictions, thus improving functional movement and breathing in HI neonates. The benefits of oral retinoid therapy outside of the neonatal period are unclear, because there may be spontaneous skin improvement in HI. As genetic testing expands, more information on genotype/phenotype correlations may provide additional information on which neonates will respond best to retinoid therapy.

In cases where oral retinoid therapy cannot be tolerated, the use of topical retinoids has proved beneficial. A 2014 report of an infant with HI demonstrated improvement in skin with application of 0.1% tazarotene cream to the face, scalp, hands, and feet. One report documented application of a topical retinoid as an effective alternative to systemic therapy with improvement in limb contractures and another for ectropion management. Topical retinoid therapy has also been used successfully in older infants as oral retinoid therapy was tapered.

FAMILY COUNSELING

The birth of a neonate with HI poses a great challenge for the family. During the first several days, parents will need to cope with the initial shock of an affected child, grieve the loss of the anticipated child, and come to an understanding of the long-term medical issues that their child will face. As in other situations in which dysmorphology is strongly manifested, the appearance of the neonate may lead parents to harbor feelings of guilt or resentment and avoid seeing the baby after birth. Bond formation between mother and infant has been shown to be delayed in the NICU setting when a neonate’s appearance was not compatible with a mother’s expectation. There are approaches that can foster bonding between the family and infant. Touch should be encouraged. Sharing photographs of survivors to family members has been a beneficial intervention. It is also important for healthcare teams to educate and prepare families.

TABLE 4 Product Master Formula Card

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acitretin 10 mg capsule</td>
<td>10 mg</td>
</tr>
<tr>
<td>Ora-Plus 5 mL</td>
<td>5 mL</td>
</tr>
</tbody>
</table>

Directions for preparing:
1. Prepare this compound under the chemotherapy hood with mask and gloves.
2. Measure out 5 mL of Ora-Plus via graduated cylinder and add to 1-oz glass amber bottle.
3. Empty the contents of 1 Acitretin 10 mg capsule into the same amber bottle and mix thoroughly.

Expiration date: 5 d with refrigeration
BEYOND THE NEONATAL PERIOD

The severely abnormal keratotic epithelium marking HI at birth gradually transitions over 4 to 6 weeks to a severe ichthyosiform erythroderma secondary to the dryness of a postuterine environment.\(^5\)\(^,\)\(^7\)\(^,\)\(^1\)\(^5\) This condition requires treatment with frequent application of bland emollients and active skin care techniques. Children remain prone to infection, although less so than during the neonatal period. Persistent ectropion requires frequent eye lubrication and protection.\(^1\)\(^5\) As discussed previously, topical retinoids applied to the eyelids may be useful. Additionally, patients can have heat and cold intolerance, pruritus, and hair and nail abnormalities.\(^1\)\(^5\)

Physical and occupational therapy is key to optimizing range of motion in infancy and childhood as the hyperkeratotic skin can lead to encasement and constriction of limbs and digits, affecting fine and gross motor skills.\(^1\)\(^,\)\(^1\)\(^5\)\(^,\)\(^2\)\(^1\) Some infants and children may display impaired cognitive and social functioning, making speech and language therapy necessary.\(^1\)\(^,\)\(^1\)\(^1\)\(^,\)\(^1\)\(^5\) It is important to note that some children with HI are able to function well and attend regular schools.\(^1\)\(^5\)

Children with HI require long-term coordinated, multispecialty care. Enhanced long-term survival may permit recognition of other associated comorbidities, such as synovitis.\(^5\)\(^2\) The mental health of patients and their families should be addressed, including issues of socialization, self-confidence, and quality of life.\(^1\)\(^,\)\(^1\)\(^5\)\(^,\)\(^2\)\(^2\)

**ETHICAL CONSIDERATIONS**

The diagnosis of HI can present ethical challenges for parents and healthcare providers. The striking physical appearance of the newborn with HI may lead to perceptions of decreased amenability to treatment and greater physical pain than are actually the case. Such perceptions can influence decisions regarding aggressivity of care. In a survey exploring the parental perspectives regarding end-of-life care in the PICU, 31% of parents described the way their child looked as being a “very important” consideration.\(^5\)\(^3\)

The influence of appearance on ethical decision-making also extends to health care providers.\(^5\)\(^4\) Specialists knowledgeable in HI should thus make particular effort to ameliorate the potentially disproportionate influence of the physical appearance. It is important that the family and the health care team are helped to understand that the initial appearance is transient, that pain can be controlled, and that the underlying skin disorder can be treated.

At the same time, the long-term problems facing children with HI must be given consideration. These have been outlined previously, and include life-long dermatologic problems, potential for chronic pain, increased risk for neurodevelopmental delay, increased frequency of hospitalization, and possible need for surgical interventions.\(^1\) It is questionable, however, whether the severity of these issues rises to the level that foregoing early intensive care management and retinoid therapy should be considered. A patient with HI is not expected to have the severe neurocognitive disabilities that have been used in other situations to justify nonintervention during an early “window,” in which survival depends on intensive care management.\(^5\)\(^5\)

Currently, infants with HI have a similar survival rate and more favorable neurocognitive outcome than, for example, infants born at 26 weeks gestation\(^5\)\(^6\): a situation in which aggressive intervention is generally initiated where available. At the same time, it must be acknowledged that more difficult ethical scenarios may present themselves; for example, HI patients with additional or complicating medical problems, settings without resources for intensive care, or long-term medical treatment. Consideration of comfort care over intensive care management might be appropriate in such selected situations.

**CONCLUSIONS**

HI is a rare form of congenital ichthyosis that can present many challenges throughout a lifetime, but especially during the neonatal period. An understanding of the ABCA12 mutation and skin barrier disruption provides a basis for therapy. Aggressive and supportive care from an interdisciplinary team is required for effective management; additionally, in the absence of data to the contrary, the authors believe it is advisable to institute early retinoid therapy.

**ACKNOWLEDGMENTS**

We thank Leonard M. Milstone, MD, for insightful advice and critical review of the manuscript. We also thank Anne W. Lucky, MD, Jean Whalen, RNIII, BSN, CPN, and Susan Rowe, RNIII, BSN, CPN, for their assistance in sharing the fragile skin dressing technique and image (Fig 2).

**ABBREVIATIONS**

| ABCA12: adenosine triphosphate binding cassette A12 |
| CBP: colloid baby phenotype |
| HI: harlequin ichthyosis |
| TEWL: transepidermal water loss |
REFERENCES


Improved Management of Harlequin Ichthyosis With Advances in Neonatal Intensive Care

Jaimie B Glick, Brittany G Craiglow, Keith A Choate, Hugo Kato, Robert E Fleming, Elaine Siegfried and Sharon A Glick

_Pediatrics_ 2017;139;
DOI: 10.1542/peds.2016-1003 originally published online December 20, 2016;

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