HARLEQUIN ICHTHYOSIS:

A CASE OF CLINICAL INTEREST

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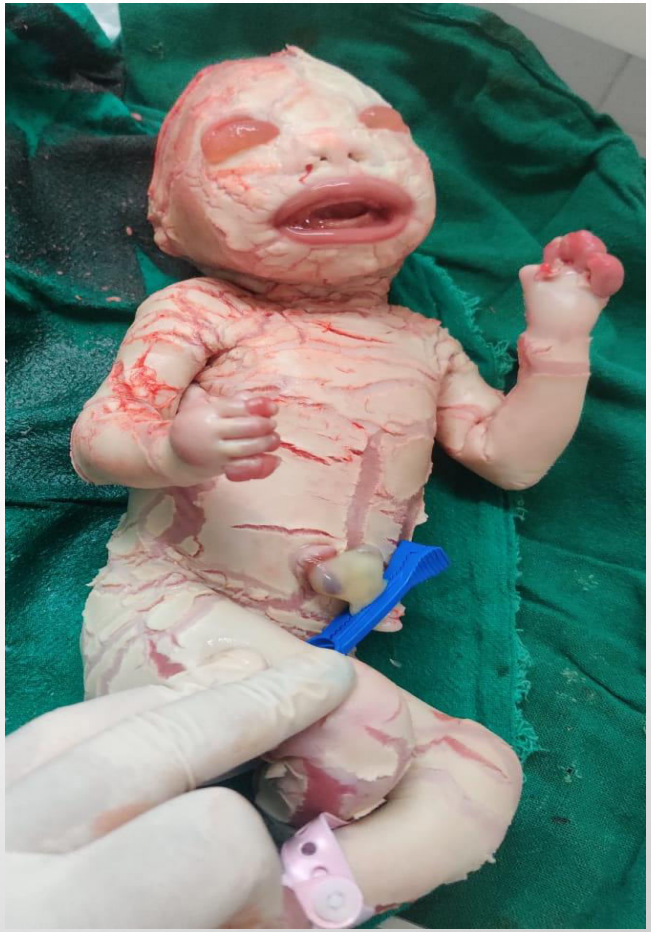
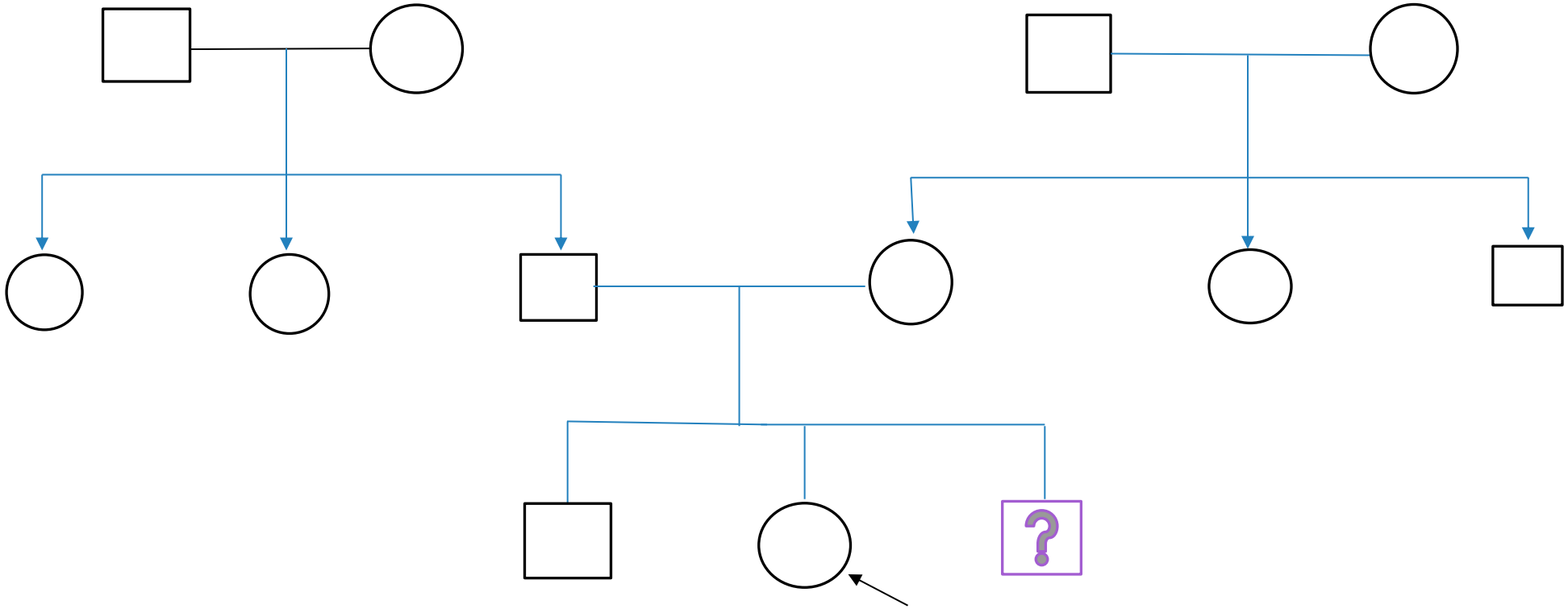
- BABY A
- 33+4 weeks, 1.75KG, Female baby
- Born on 11/10/2021
- **OBSTETRIC HISTORY:** $G_2 P_1 L_1 A_0$
- **ANTENATAL PERIOD:** Irregular ANC visits, Unbooked, Level II USG: Not done
- Emergency LSCS in view of complete placenta previa with severe oligohydramnios
    - Baby cried immediately after birth
    - APGAR score - 9/10 & 10/10 at 1min and 5min

Baby presented with…….



- **Parchment like skin** with cracks and **plaque like scales** all over the body.
- **Microcephaly**.
- **Eclabium** with wide open mouth with protruding tongue
- **Ectropion** with protruding eyes
- **Thick keratotic plaques** with **deep fissures** all over the body.
- **Ears**- very small and underdeveloped, external auditory meatus not visible
- **Absent distal phalanx** of hand and feet (finger and toe nails also absent)
- Genitalia normal

Family History: Non- consanguineous marriage.

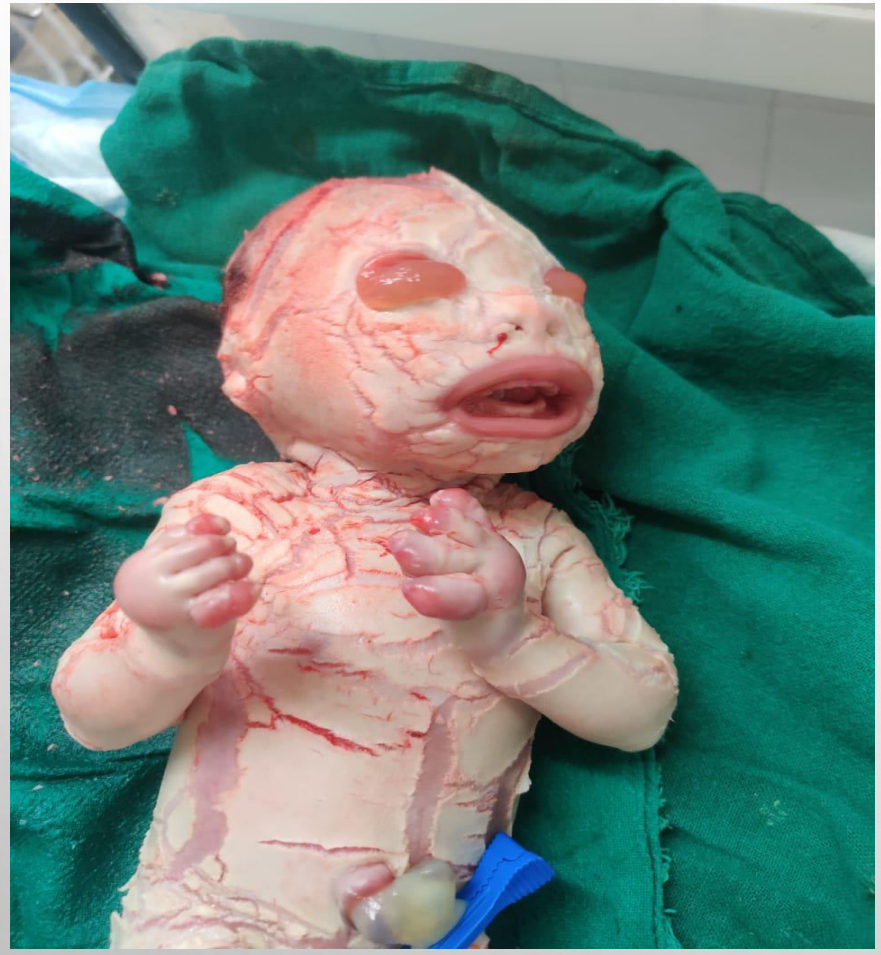


Previous sibling- 2yr old, male child born by full term normal vaginal delivery, alive and healthy

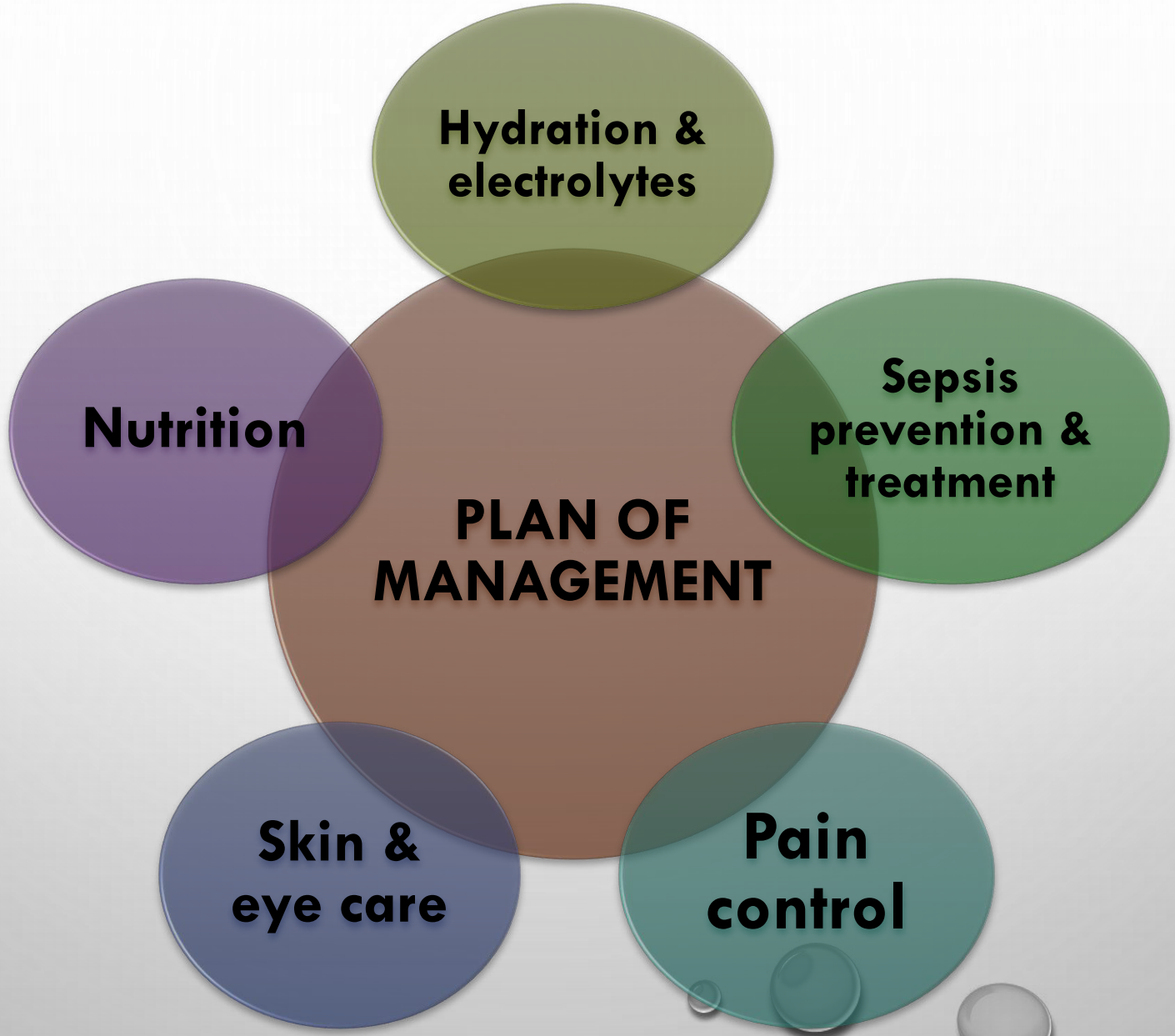
Anthropometry: As per intergrowth -21 charts.

PARAMETER	OBSERVED	EXPECTED	INTERPRETATION
Weight for age	1.75 kg	1.8 kg	b/w 0 and -1 SD
Length for age	40 cm	43 cm	b/w 0 and -1 SD
Head circumference	26 cm	31 cm	< - 3 SD

△ : Singleton/ Female/ Preterm (33+4 wks)/ AGA/ LBW(1.75kg) / Microcephaly/ Harlequin ichthyosis



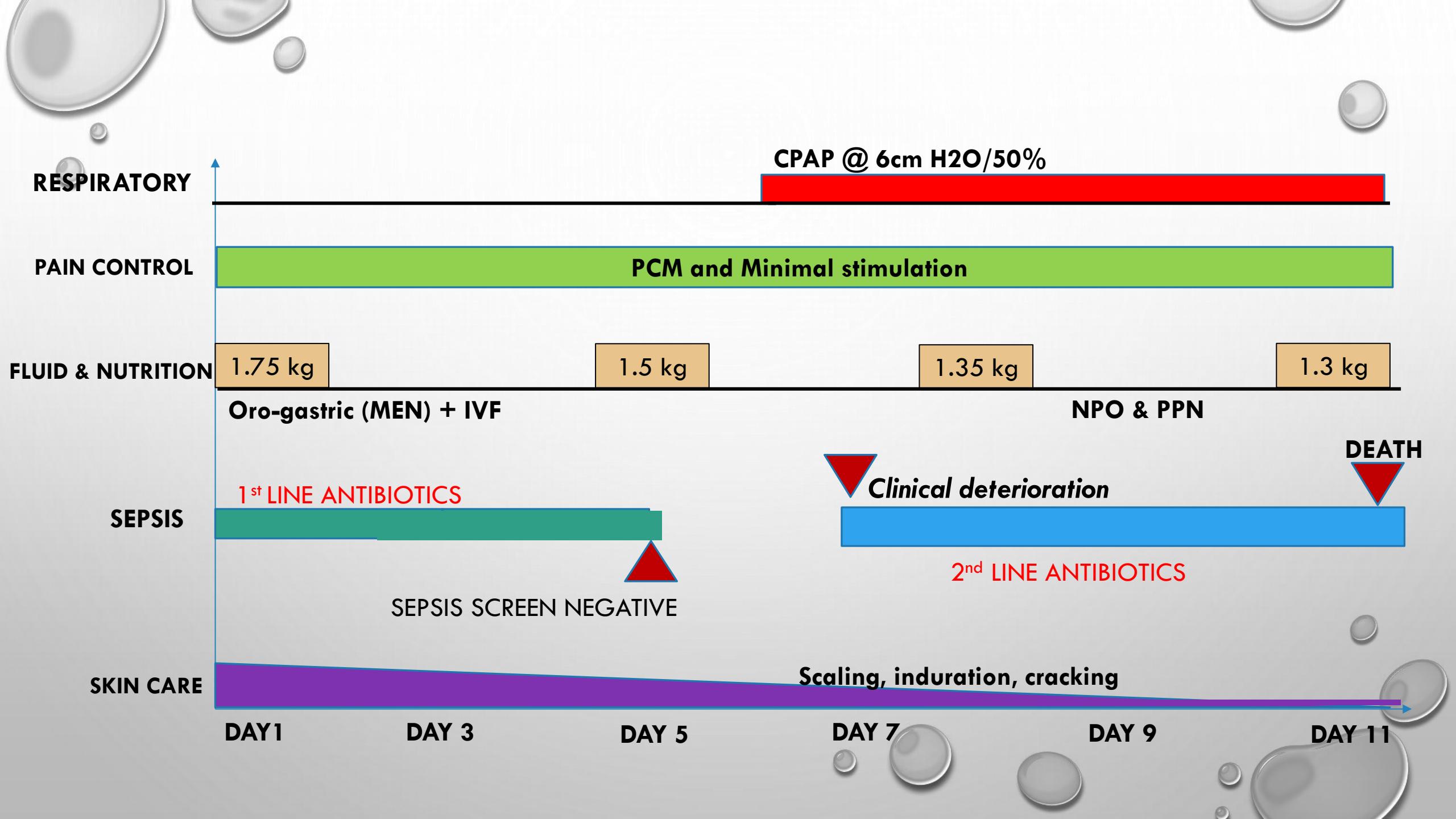
Plan of Management



DERMATOLOGY REFERRAL:

- Diagnosis of Harlequin icthyosis was considered based on the clinical appearance.
- Paraffin gauge dressing
- 2% fusidic acid cream ointment to be applied to cracks and fissures
- Adequate nutritional supplementation
- Antibiotics to be started

OPHTHALMOLOGY REFERRAL: Application of antibiotic eye drops and artificial tears


RESPIRATORY
CPAP @ 6cm H2O/50%
PAIN CONTROL
PCM and Minimal stimulation
FLUID & NUTRITION
1.75 kg
1.5 kg
1.35 kg
1.3 kg
Oro-gastric (MEN) + IVF
NPO & PPN
DEATH
Clinical deterioration
SEPSIS
1st LINE ANTIBIOTICS
2nd LINE ANTIBIOTICS
SEPSIS SCREEN NEGATIVE
SKIN CARE
Scaling, induration, cracking
DAY1
DAY 3
DAY 5
DAY 7
DAY 9
DAY 11

Challenges Faced During Management:

- Establishing IV access
- Maintaining asepsis and difficult handling
- Administration of retinoids
- Parents were not willing to perform genetic analysis

DISCUSSION & REVIEW OF LITERATURE

Harlequin Ichthyosis

ICHTHYOSIS IN NEWBORN

- The ichthyoses encompass a variety of genetic disorders marked by abnormal epidermal differentiation.
- The word ichthyosis comes from the Greek root '*ichthys'* meaning fish,

  referring to the cutaneous scaling that is characteristic of these disorders.
- In patients with ichthyosis, the barrier function of the skin is compromised.

NEONATAL PRESENTATIONS OF ICHTHYOSES:

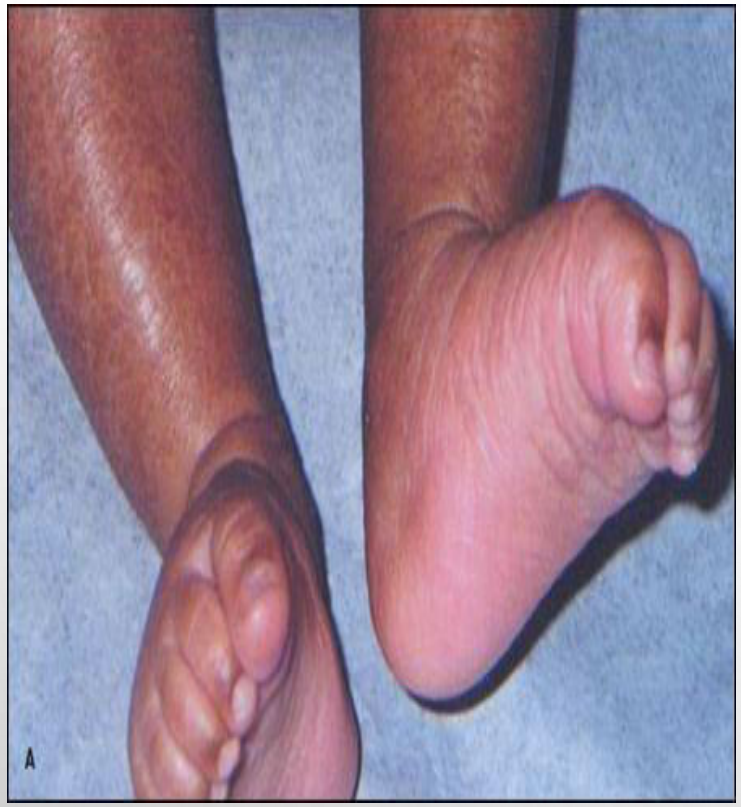
Syndromic (skin and other organs involvement)

- Netherton syndrome
- Sjogren- Larsson syndrome
- Refsum syndrome
- Multiple sulfatase deficiency ichthyosis
- Keratitis- ichthyosis- deafness syndrome
- Conradi- Hunermann- Happle syndrome
- Dorfman- Chanarin syndrome
- IFAP syndrome

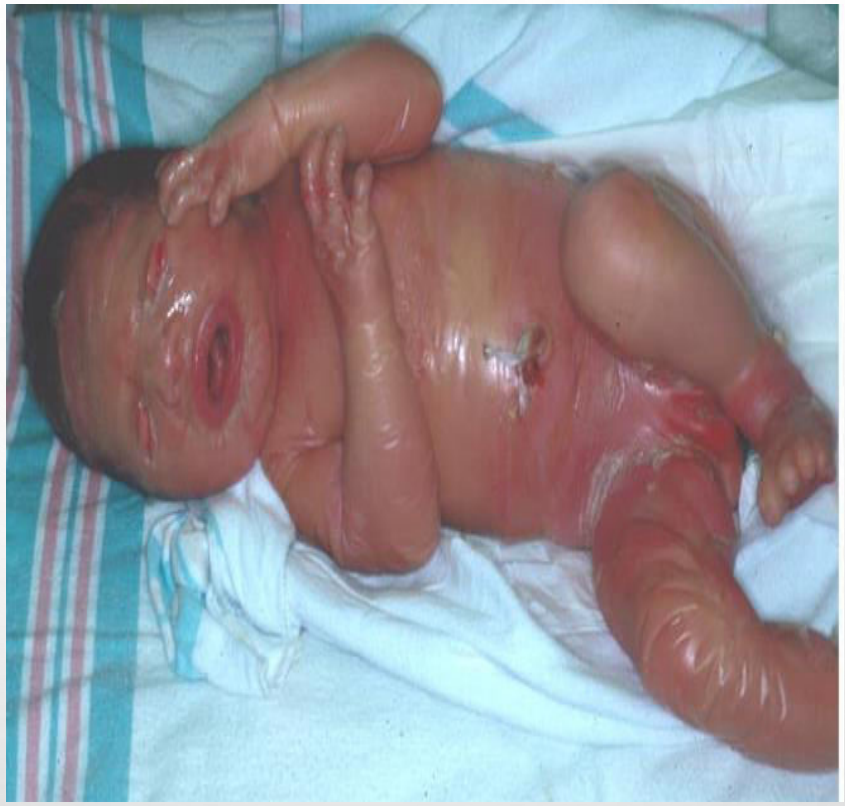
Non syndromic (only skin is involved)

- Common ichthyosis: Ichthyosis vulgaris, recessive X- linked ichthyosis
- Autosomal Recessive Congenital Ichthyosis (ARCI)
  - Harlequin ichthyosis
  - Lamellar ichthyosis
  - Congenital Ichthyosiform Erythroderma
  - Self healing collodion baby
- Keratinopathic ichthyosis
- Other forms
  - Loricrin keratoderma
  - Erythrokeratoderma variabilis
  - Peeling skin disease

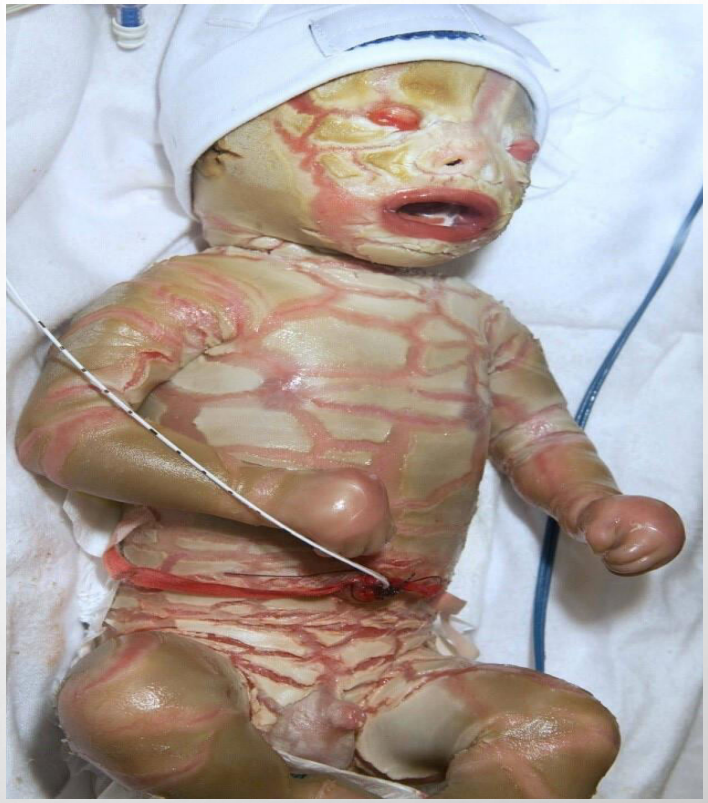
- Classification: Ichthyosis Consensus Conference of 2009.



Ichthyosis vulgaris



Collodion baby



Harlequin ichthyosis

HARLEQUIN ICHTHYOSIS

- *Harlequin ichthyosis (HI)* is a severe erythrodermic ichthyosis that causes a distinctive and distressing appearance at birth.

- The term ‘harlequin’ derives from the newborn’s facial expression and the triangular and diamond shaped pattern of hyperkeratosis like that of a dress of harlequin clown.

- *Race:* no racial predilection is known.
- *Sex*: no increased risk based on sex is known.
- *Incidence:* 1 in 300000

- Gurses D, Kilic I, and Baskan M. 2001. A case of harlequin fetus with psoriasis in his family

GENETICS

- Mutations in the ABCA12 gene on chromosome 2 cause harlequin ichthyosis.
- Autosomal recessive inheritance.
- Consanguineous families - higher incidence of affected off springs.
- ABCA12 protein functions as a lipid transporter from the Golgi apparatus to the lamellar granule at the cell periphery in differentiated keratinocytes.

PATHOGENESIS

- Absent or defective lamellar granules and no intercellular lipid lamellae
- These granules are responsible for secreting lipids that maintain the skin barrier at the interface between the granular cell layer and the cornified layer.
- The lipid abnormality is believed to allow excessive trans epidermal water loss; resulting in severe retention hyperkeratosis.

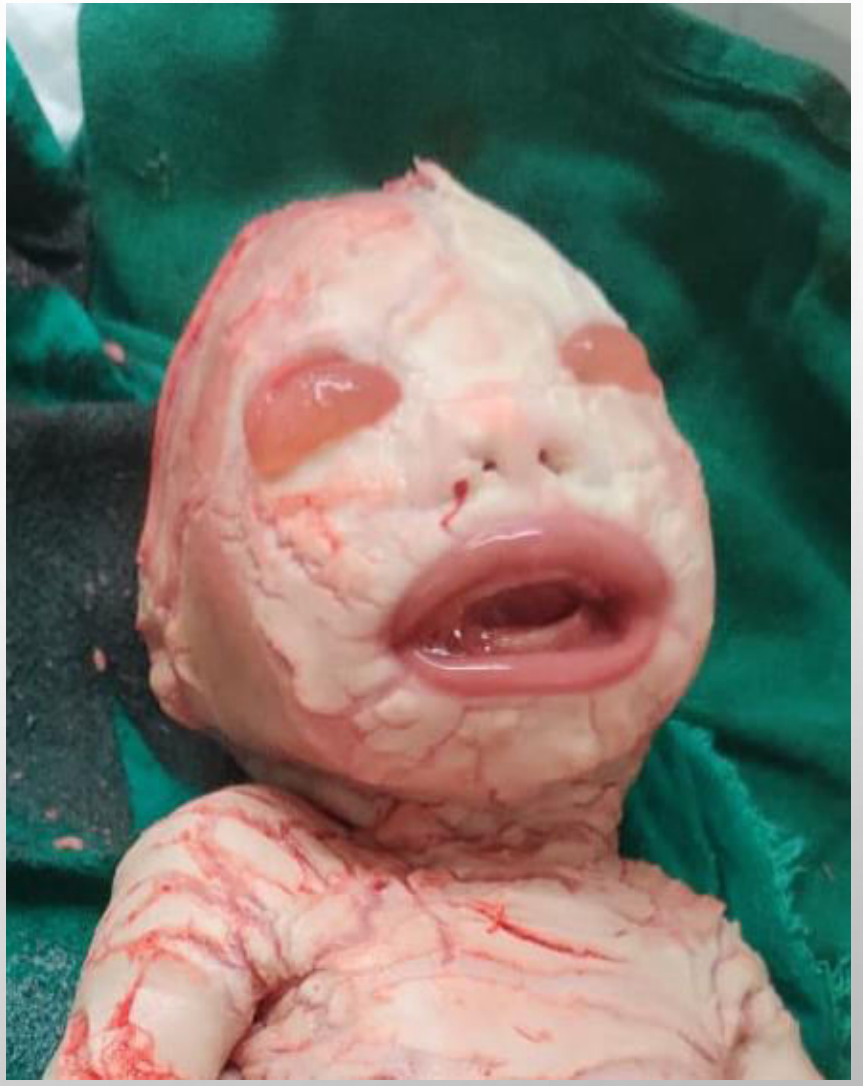
CLINICAL FEATURES

- Affected infant is usually born premature. (Mean age 35 weeks, range: 30-39 weeks)

- ***Skin:***
  - Severely thickened skin with large and shiny plates of hyperkeratotic scale is present at birth.
  - Deep erythematous fissures separate the scales.

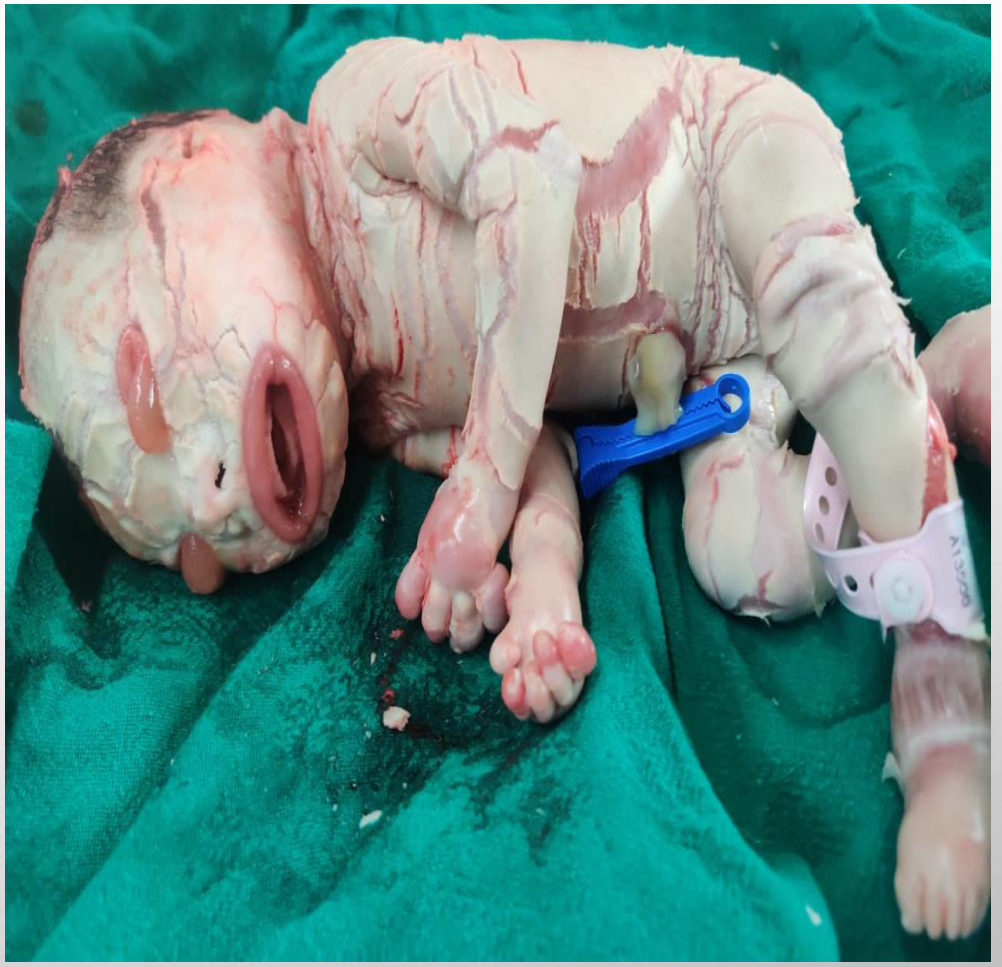
- Rajpopat S, et. al. Harlequin ichthyosis: a review of clinical and molecular findings in 45 cases. Archives of dermatology. 2011 Jun 20;147(6):681-6.

- ***Ears:***
  - Pinna may be small and rudimentary or absent.
- ***Eyes:***
  - Severe ectropion is present. The free edges of the upper and lower eyelids are everted, leaving the conjunctivae at risk for trauma.
- **Lips:**
  - Severe traction on the lips causes eclabium and a fixed, open mouth.
- **Nose:**
  - Nasal hypoplasia and eroded nasal alae may occur.



- The edematous hands and feet encased in hard, mitten-like casts or covered with mucoid membrane.

- Skull appear microcephalic, hair absent.



DIAGNOSIS

- **PURELY CLINICAL**

  - Typical findings at birth

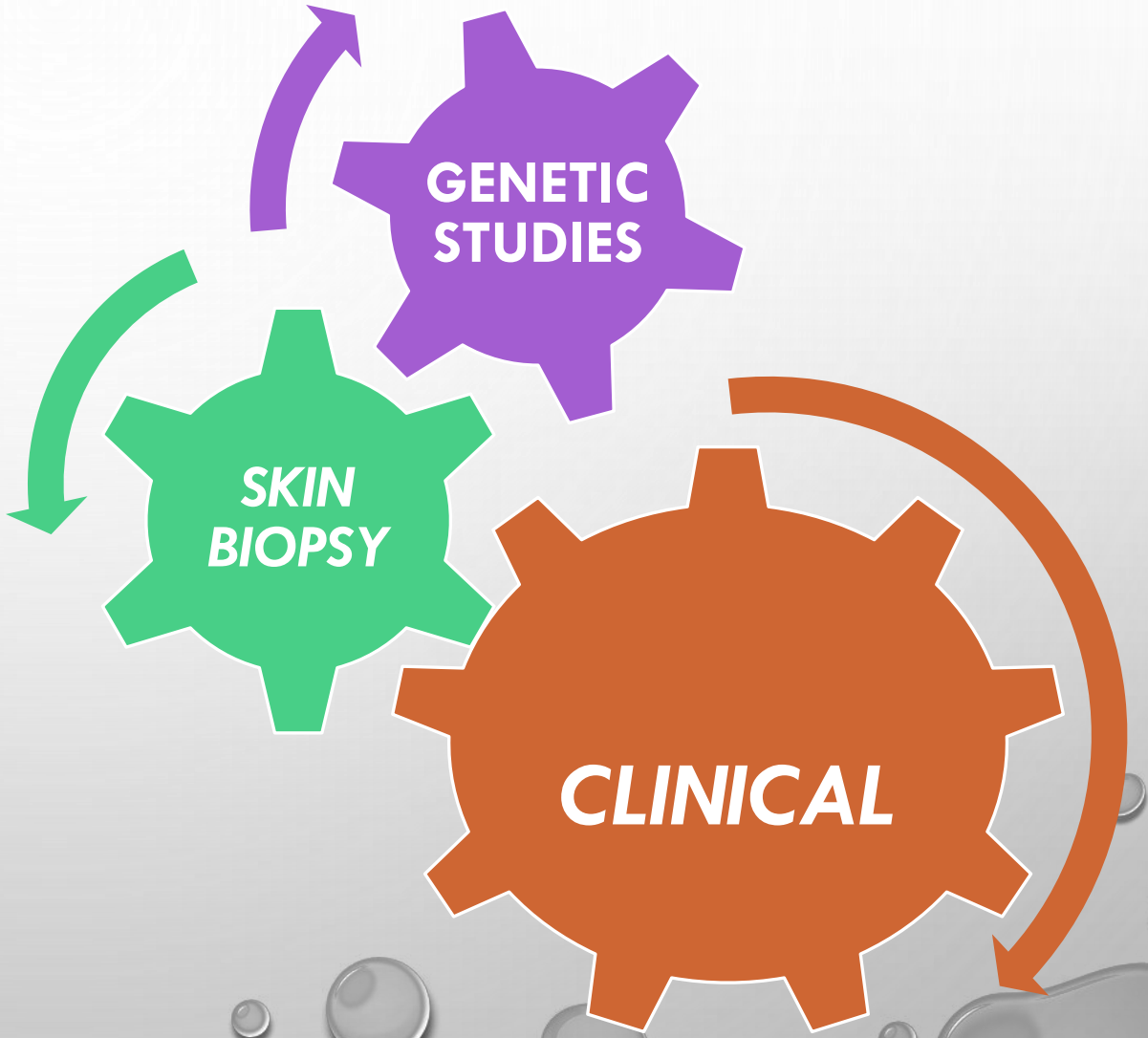
- **SKIN BIOPSY**: Not necessary

- **GENETIC TESTING:** Multigene Panel

  Testing **12 GENES**

- **SINGLE GENE TESTING**: ABCA12

  (HARLEQUIN), TGM1 (ARCI)



PRENATAL DIAGNOSIS

➢***Antenatal USG***: Prenatal diagnosis of HI ***extremely difficult in low risk patients***.

- Most of the characteristic features become apparent later in pregnancy.

➢***USG findings-*** Ectropion, eclabium dysplastic ears, flat nose, IUGR, polyhydramnios and the '***snowflake sign***' .

- ***Fetal DNA analysis:*** Identification of ABCA12 mutations.
- Fetal skin biopsy replaced with direct DNA sequence analysis using fetal DNA from chorionic villi or amniotic fluid samples.

MONITORING

- **Clinical monitoring**
  - Temperature, Respiratory rate, Heart rate and Oxygen saturation.
  - Daily weight
- **Laboratory monitoring**
  - Complete blood count
  - Serum electrolytes
  - Kidney function
  - Liver function
  - Blood cultures

TREATMENT: Multi Disciplinary Approach

- Hydration and electrolytes
- Sepsis prevention and treatment
- Skin care
- Pain management
- Nutrition

- ***Intravenous access*:**

  - Peripheral access is difficult. Umbilical cannulation is preferred

- ***Eye care:***

  - Ophthalmic lubricants to protect the conjunctivae

- ***Skin care:***

Once or twice daily cleansing to hydrate and promote shedding of stratum corneum..

Use frequent applications of wet sodium chloride compresses followed by bland lubricants to soften hard skin and to facilitate desquamation.

Avoid use of medicated ointment

Antibiotics: No consensus on using prophylactic antibiotics in Harlequin Ichthyosis.

- Jaimie et al.; Improved Management of Harlequin Ichthyosis With Advances in Neonatal Intensive Care

- ***Pain control***:

  - Fissuring of the skin is painful and often requires opiate analgesics

- ***Nutrition:***

  - Increased TEWL and skin turnover increases caloric demands in Harlequin ichthyosis neonates.

  - Intravenous fluids are almost always required.

  - Eclabium and jaw constriction interfere with oral feeding. Neonates require supplemental OG/NG tube feeds.

- Digital necrosis is a common complication in Harlequin Ichthyosis requiring surgical interventions (fasciotomy).

- ***Retinoids:***
  - Decrease the cohesiveness of abnormal hyperproliferative keratinocytes. They modulate keratinocyte differentiation.
  - In a recent retrospective review, 83% of neonates with Harlequin ichthyosis given systemic retinoids survived, whereas long-term survival was only 24% in those who did not receive oral retinoids.

    - Rajpopat S et al. A review of clinical and molecular findings in 45 cases.

  - The apparent lifesaving effect of oral retinoids remains unexplained.

    - Leonard m. Et al. Improving outcomes for harlequin ichthyosis.

- ***Acitretin*:** 0.5 to 0.75 mg/kg day.

  - Treatment initiation within 7 days of life.

  - Lack of available liquid formulation.

- ***Isotretinoin***: 2 mg/kg/d.

- Systemic retinoid therapy should be tapered or withdrawn once an improvement is seen.

- Common side effects include cheilitis, fragile skin, dry eyes, and abnormalities in the lipid profile and liver enzymes.

CORRECTIVE GENE THERAPY

- Autologous keratinocyte stem cells are harvested, genetically modified, and generated into sheets of disease-free epithelium with an integrating vector.
- This method has been shown to restore lipid secretion in lamellar granules in Harlequin ichthyosis.
- Risk of insertional mutagenesis with corrective gene therapy.

- Hera Ahmed et al;. Recent Advances in the Genetics and Management of Harlequin Ichthyosis

COMPLICATIONS

- Bacterial sepsis
- Water loss with dehydration and electrolyte abnormalities, and poor temperature regulation
- Poor feeding and failure to thrive
- Contractures and painful fissuring of the hands and the feet, distal limb ischemia.
- Ectropion, keratitis, and other ophthalmologic complications
- Obstruction of external ear canal
- Patients surviving beyond the neonatal period will live with a chronic skin disease, and atopy.

PROGNOSIS

- Almost all Harlequin Ichthyosis children die in infancy with few exceptions.
- *Mortality/morbidity*: The mortality rate is high. With neonatal intensive care and the advent of retinoid therapy, some babies have survived. Mortality data showed that there were 25 survivors (56%), ages 10 months to 25 years and 20 deaths (44%), the age of death ranging from 1 to 52 days.
- Most common reasons for death in the neonatal period are infection, water loss with dehydration and electrolyte abnormalities, and poor temperature regulation

- Rajpopat S et al. A review of clinical and molecular findings in 45 cases.

OUTCOMES

- The first recorded case of Harlequin Ichthyosis was reported in 1750 by Reverend Oliver Hart, who noted an infant who had thick armor like skin with deep grooves.
- Prior to 1985, the longest-surviving case of harlequin ichthyosis lived 9 months.
- Those who survived beyond the neonatal period- chronic skin disease, persistent ectropion, heat and cold intolerance, pruritus, hair and nail abnormalities.
- Physical and occupational therapy

- Nusrit “Nelly" Shaheen, born in 1984 (age 37) is the longest-living survivor of harlequin-type ichthyosis

- *Ryan Gonzales*

FAMILY COUNSELLING

- Autosomal Recessive inheritance- 25% chance of having the disease.
- Birth of a neonate with Harlequin Ichthyosis poses a great challenge for the family.
- Sharing photographs of survivors to family members has been a beneficial intervention.
- Educate and prepare families before discharge for the prolonged care that will be necessary at home.

TAKE HOME MESSAGES

- Harlequin Ichthyosis is a disease with impaired skin barrier function.
- Appropriate neonatal care significantly reduces the mortality.
- Prevention and control of infections is crucial for treatment in the neonatal period.
- After discharge, rational skin care is key for protection and maintenance of normal skin function, as well as improved quality of life.
- Family counselling for the next pregnancy.

THANK YOU