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Review Article

Pediatric erythroderma – A clinical and therapeutic review

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ABSTRACT

Erythroderma in the pediatric population is uncommon as compared to adults. The most prevalent causes of pediatric erythroderma comprise ichthyoses and metabolic diseases. A good clinical acumen might aid in recognizing the subtle but diagnostic clinical signs in these cases to pinpoint the underlying cause. We propose a flowchart-based clinical approach for diagnosing the underlying causes of pediatric erythroderma. Along with the clinical presentation, specific laboratory investigations and treatment modalities have been highlighted.

Keywords: Erythema, Erythroderma, Neonates, Pediatric, Scale

INTRODUCTION

Erythroderma, also known as exfoliative dermatitis is an inflammatory skin disorder defined by redness and scaling involving more than 90% of the body surface area (BSA).[1] Compared to the adults, it is less frequent in the pediatric age group (1–14 years). Immune deficiency syndrome, ichthyoses, metabolic disorders, and infection are common diseases presenting as erythroderma in neonates and pediatric age groups compared to adult erythroderma.[2,3] Diagnosing erythroderma and managing the disease at this age is a constant challenge for practicing dermatologists and pediatricians.[4] The mortality rate is 25% among neonates with erythroderma.[5] There is an increased transepidermal water loss in children due to the relatively higher BSA. This is further pronounced in the neonates.[6,7]

This review mainly focuses on the clinic's etiological approach and therapeutic management in pediatric erythroderma patients.

The incidence of erythroderma in infants and neonates was 0.11% in a study by Sarkar and Garg in Delhi - 35/100,000 among the total dermatologic outpatient population.[2]

ETIOLOGICAL CLASSIFICATION

Erythroderma is a phenotype, not a diagnosis in itself. There are many underlying etiologies of erythroderma in children. Low incidence, phenotypical heterogeneity, and varying etiologies in the pediatric age group make diagnosing erythroderma challenging.

Various etiologies of erythroderma in the pediatric population are enumerated in Table 1.[1-4]

The clinical clues, additional diagnostic steps, and therapeutic options of various conditions associated with pediatric erythroderma are mentioned in Table 2.[4,5,8-17]

The clinical approach to pediatric erythroderma is shown in Figures 1 and 2. The below-mentioned history should be obtained to reach an etiological diagnosis of erythroderma [Figure 1].

- Family history - Positive family history seen in bullous ichthyosiform erythroderma (BIE), psoriasis, Pityriasis rubra pilaris (PRP), Omenn's syndrome (OS), Netherton's syndrome (NS), atopic dermatitis (AD), seborrheic dermatitis, and selective immunoglobulin A deficiency. A positive family history increases the risk of the same disease in neonates.
- History of consanguinity: NS, primary immunodeficiency disorder (PID), inborn errors of metabolic disorders, and Chanarin-Dorfman syndrome.
- Antenatal history: Harlequin ichthyosis (HI) in the fetus was associated with spontaneous abortion and a history of an unexplained death of siblings to be enquired about in families with PID, NS, and Omen's syndrome.
- Congenital onset ichthyosis, immunodeficiency disorders, and Infections.
- Recurrent infection and diarrhea immunodeficiency disorders.
- Neurological complaints (Ichthyosiform syndromes-Sjogren-Larrson syndrome and trichothiodystrophies, biotinidase deficiency).

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Table 1: Etiologies of pediatric erythroderma.

Causes	Diseases
Ichthyosis (nonsyndromic, syndromic)	• Non-bullous ichthyosiform erythroderma ARCI which includes Harlequin ichthyosis, Lamellar ichthyosis, Bullous ichthyosiform erythroderma, CRIE Syndromic ichthyosis are the following- • Netherton's syndrome • Conradi-Hunermann syndrome • Sjogren-Larssen syndrome • PSS1 • SAM syndrome • KID syndrome • Chanarin-Dorfman syndrome • Trichothiodystrophy • CAPE: CARD14 associated papulosquamous eruption • CHILD syndrome
Immunologic disorders	• Omenn's syndrome • Graft versus host disease • Hypogammaglobulinemia • Di–George's syndrome • SCID • WAS • IPEX, syndrome • Selective IgA deficiency • Gaucher Syndrome type2 • AD/AR -Hyper IgE syndrome • CVID
Metabolic/ nutrition disorders	• Kwashiorkor • Renal failure • Acrodermatitis enteropathica • Cystic fibrosis dermatitis • Leiner's disease • Amino acid disorders • Disorders of biotin metabolism • Essential fatty acid • Urea cycle disorders (citrullinemia) • Menkes disease
Infections and infestation	• Staphylococcal scalded skin syndrome • Scarlet fever • Neonatal cutaneous candidosis • Congenital HSV infection • Toxic shock syndrome • Syphilis (Congenital lues) • Norwegian scabies
Toxicities/drug reactions	• Boric acid toxicity • Stevens-Johnson syndrome • Toxic epidermal necrolysis • Drug-induced erythroderma/exfoliative dermatitis (Ceftriaxone, vancomycin, Antiepileptics sulfonamides, antitubercular drugs, homeopathic, indigenous)
Less common dermatological and non-dermatological causes	• AD • Psoriasis Vulgaris • Diffuse cutaneous mastocytosis • Pityriasis rubra pilaris • Seborrhoeic dermatitis. • Kawasaki's Disease • Dermatomyositis • Sarcoidosis • Pemphigus foliaceus. • Cutaneous T-cell lymphoma • Kindler EB • After cow milk consumption • Hemophagocytic lymphohistiocytosis. • Ectodermal dysplasias • Miliaria • Erythema toxicum neonatorum

IPEX: Immune dysregulation, polyendocrinopathy, and enteropathy, X-linked, WAS: Wiskott-aldrich syndrome, PSS1: Peeling skin syndrome type 1, KID: Keratitis ichthyosis deafness, HSV: Herpes simplex virus, CRIE: Congenital reticular ichthyosiform erythroderma, CVID: Common variable immunodeficiency, AD: Autosomal dominant, IgE: Immunoglobulin E, IgA: Immunoglobulin A, ARCI: Autosomal recessive congenital ichthyosis, PSS1: Peeling skin syndrome 1, CHILD: Congenital hemidysplasia with ichthyosiform erythroderma and limb defects, EB: Epidermolysis bullosa, AR: Autosomal recessive

- Blood transfusion - Graft versus host reaction (GVHR).
- Preceding purulent infection - Staphylococcal scalded skin syndrome (SSSS).
- Concomitant infection in mother- Toxic shock syndrome (TSS), congenital cutaneous candidiasis (CCC).
- Decreased growth: NS, immunodeficiency diseases, metabolic disorders.
- Diarrhea - GVHR, NS, OS, Acrodermatitis enteropathica.
- Periorificial dermatitismetabolic and nutritional disorders.
- Vesicles or Bullae -SSSS, Mastocytosis, BIE.
- Collodion baby – Non-BIE and other ichthyosis.
- Fever- SSSS, GVHR, TSS.
- Atopy- NS, AD.
- Presence of linear epidermal nevus in family members – BIE.
- Male preponderance was found in NS, diffuse cutaneous mastocytosis (DCM), and female preponderance in OS.
- Drug history- Ceftriaxone, vancomycin, and phenytoin can induce NE. Penicillin, aminoglycosides, and cephalosporin can cause erythema.

EXAMINATION

The methodical approach to clinical examination of an erythroderma patient is depicted in Figure 2.

Table 2: Differential diagnoses of pediatric erythroderma.

Disease	Clinical clue	Diagnostic clue	Therapeutic updates (conventional with new)
Ichthyoses			
Non-BIE OR congenital	Collodion membrane shedding of the membrane in the first few weeks, followed by erythroderma with fine white scaling.	Gene panel analysis ALOX12B, ALOXE3, ABCA12, CASP14, CYP4F22, NIPAL4, SDR9C7, CERS3, PNPLA1, SLC27A4	Biologics: Secukinumab, dupilumab and guselkumab are effective.
Lamellar ichthyosis	Dark brown quadrilateral scales, palmoplantar keratoderma, history of collodion baby at birth.	TGM1	• Topical tazarotene applied to treat ectropion. • Encapsulated recombinant human TG1 liposomes applied topically. • Gene therapy: A retroviral vector designed to deliver the TGM1 gene into the keratinocytes of patients with lamellar ichthyosis.
HI	• Very thick (armour-like) scales • Rigid collodion membrane, • Ectropion, eclabium. • Movement restriction.	ABCA12	• Pan-JAK inhibitor tofacitinib has a role in the treatment of HI. • Gene therapy: Corrective gene transfer of the ABCA12 gene with a pCMV-tag4B vector.
BIE	• Congenital erythroderma, • Skin blistering, Keratotic plaques over bony prominences on removal eroded base present. • Peculiar smell present • Palmoplantar keratoderma.	• Skin biopsy • Targeted sequencing KRT1, KRT10 gene	• Gene therapy: Transcription activator-like effector nuclease [TALEN] TALENs for gene editing of the KRT10 gene in BIE.
CRIE	• Reticular ichthyosis. • Yellow-brown scales. • Multiple confetti-like spots.	KRT1 and the KRT10 gene	• Healthy skin reflects the clonal expansion of normal or reverted cells: Cell reversion using revertant stem cells can be a potential future therapy.
Netherton syndrome	Triad • Severe inflammatory congenital erythroderma, with peripheral scaling (ichthyosis linearis circumflexa), • Hair shaft abnormalities (trichorrhexis invaginata/ bamboo hair), • Atopic manifestations with debilitating pruritus	• Trichoscopy • Immunohistochemistry • Targeted sequencing SPINK5 gene.	• Calcineurin inhibitors Narrow-band UVB phototherapy, dupilumab. • Biologics like secukinumab, Ixekinumab Ustekinumab are effective. • Epithelial sheets of Keratinocytes expressing SPINK5 with lentiviral vector. • Topical application of GSK951 can inhibit KLK5 activity in the skin. SFTI inhibit KLK5, KLK14 and KLK7. • Recombinant human alpha 1-antitrypsin gel with substance SXR1096. • Gene therapy: replication-defective HSV-1 vector encoding human SPINK5 (KB104) for topical administration.
CHS	• Congenital erythroderma: ichthyosiform erythroderma distributed in a linear blotchy pattern. • Follicular atrophoderma, • Cicatricial alopecia in older children. • Flattened spilt nail, skeletal abnormalities • Cataract, micropthlmia, microcornea. • Laryngeal, tracheal stenosis.	• X-ray: Chondrodysplasia punctate -calcium deposition on the vertebra, ribs, trachea, • Stippled epiphysis, • EBP Gene.	Dupilumab

(*Contd...*)

Table 2: (*Continued*).

Disease	Clinical clue	Diagnostic clue	Therapeutic updates (conventional with new)
Sjögren-Larsson syndrome	• Yellowish scale • Psychomotor retardation • Spastic di-/tetraplegia	• Comprehensive neuropediatric evaluation • Targeted sequencing ALDH3A2 gene	• Zileuton helps in patients with pruritus. • Topical application of ADX -102 1% (Reproxalap) NS2 cream, an aldehyde, binds small molecules for SLS. • Gene therapy: Transferred FALDH in keratinocytes using rAAV-2
Chanarin-Dorfman syndrome	• Non BIE • Short stature, hepatomegaly, cataract, myopathy, hearing loss, intellectual disability.	• Peripheral blood smear (Jordan's anomaly: Lipid vacuoles in granulocyte) • Targeted sequencing CGI85 (ABDH5) gene	• Acitretin • Low-fat diet (low long-chain fatty acid and minimal saturated fat) • Ursodiol, • Vitamin E
CAPE : CARD14 associated papulosquamous eruption	• Inflammatory dermatosis. • Palmoplantar keratoderma • Erythroderma. • Typical facial plaques on the cheek, chin and upper lip.	• CARD14	• Ustekinumab
CHILD syndrome	• Congenital hemidysplasia • Ichthyosiform erythroderma • Limb defects	(NSDHL) gene	• Lipid replacement for CHILD syndrome: 2% lovastatin/2% cholesterol lotion, • 2.5%. 5% simvastatin monotherapy
TTD	• Erythroderma at birth, icthyosis. • Brittle hair due sulfur deficiency, • Mental and growth retardation • Abnormal facies (receding chin, small nose, large ear, microcephaly)	ERCC2, ERCC3, TTDA, TTDN1.	• Photoprotection. • Dupilumab
KID syndrome	• Corneal vascularisation. • Erythrokeratoderma skin lesions • Sensorineural deafness.	GJB2, connexin-26 gene. AP1B1	• Clinically monitor for infections and erosions in intertriginous folds • Dilute bleach baths during periods of repeated cutaneous infections. • Gene therapy; siRNA
PSS1	• Erythroderma and superficial peeling of the skin	CDSN.	Protein replacement therapy with delivery of liposome-encapsulated recombinant human corneo-desmosin
SAM syndrome: A congenital form of ichthyosis stands for severe dermatitis, multiple allergies, and metabolic wasting syndrome.	• Erythroderma • Hyperkeratosis • Pruritus • Recurrent sepsis • Severe growth retardation	Mutations of DSG1 or DSP gene	• Secukinumab, ustekinumab found to be effective.
Transient neonatal dermatoses			
ETN	• Erythematous macules central papule or pustule. • Lesions wax and last for 2 weeks.	Peripheral eosinophilia. Pustule scraping reveals eosinophils.	• No therapy is needed, it resolves spontaneously.
Miliaria Rubra	• Occurs between the 11th and 15th day of life • Affects sites of friction or occlusion • 1–3 mm erythematous, non-follicular papules or papulovesicles • Only variant of miliaria can progress to erythroderma.	Clinical diagnosis.	• Stay in a cooler area, apply icepacks.

(*Contd...*)

Table 2: (*Continued*).

Disease	Clinical clue	Diagnostic clue	Therapeutic updates (conventional with new)
Benign erythematous skin disorders.			
Atopic dermatitis	• Involves the scalp, cheeks and extensor surfaces of the extremities. • Diaper region is spared • May be associated with a rare food hypersensitivity known as eosinophilic gastroenteritis, mostly to cow's milk protein	Clinical diagnosis	• New: Dupilumab, tralokinumab, have role in atopic dermatitis.
Seborrheic dermatitis	• Greasy scales on the scalp (cradle cap) with frequent involvement of the skinfolds of the neck, axillae, and groin	Clinical diagnosis	• Shampoo containing zinc pyrithione/ selenium disulfide • Topical antifungals and topical steroid • Oral antifungals • New – 1% Tapinarof ointment, 0.1% ruxolitinib cream, oral apremilast
Psoriasis	• Sharply delineated plaques. • Palms, soles and scalp usually involved. • Involves the diaper area (Koebner phenomenon).	• Clinical diagnosis. • HLA B17 positive	• Usually requires systemic retinoid. • Biologics: adalimumab, etanercept, ustekinumab, ixekizumab, Secukinumab has role in psoriasis
Erythrodermic pityriasis rubra pilaris	• Erythroderma with areas of unaffected skin ("nappes claires"), follicular hyperkeratosis, palmoplantar keratoderma	• Clinical diagnosis • Skin biopsy in clinically atypical cases. • Mutations of CARD14gene.	• Oral Retinoids • Newer Anti TNF, Risankizumab, Ustekinumab shown to be promising.
Infection			
Staphylococcal scalded skin syndrome	• Acute onset of fever, systemic toxicity, • Positive Nikolsky sign. • Periorificial accentuation. • The erythema progresses rapidly to widespread peeling and erosions.	Acantholytic intraepi dermal blistering with cleft in the granular layer just below stratum corneum	Intravenous cloxacillin or dicloxacillin or cefotaxime with gentamicin or clindamycin, In case of MRSA vancomycin is used.
Congenital and neonatal candidiasis	• Widely spread macules, papules and pustules. • Lesions are present over the palms and soles. • Oral cavity and napkin area spared. • Funisitis (infection of the umbilical cord) or chorioamnionitis is suggestive of CCC	KOH preparation from skin lesion shows pseudohyphae and budding yeast cells. Positive culture of candida species	Intravenous amphotericin B preparations for 21–28 days. Fluconazole, capsofungin, micafungin, voriconazole in case of intolerance to amphotericin B
Congenital herpes simplex infection	• Erythema and scaling or crusted erosions on an erythematous base	Multinucleated giant cells on Tzanck smears of vesicular lesions viral DNA detection by PCR	Intravenous Acyclovir 20 mg/kg 8th hourly for 21 days.
Scarlet fever	• Fever, • The rash starts 1–2 days after fever and pharyngitis. • Sandpaper-like erythematous rash blanches on pressure. • Pastia's lines: Accentuated purpuric rash in flexures. • Palm and sole spared. • Strawberry tongue.	RADT: Detect Group A Streptococci. Throat culture.	• Injectible antibiotics. (penicillin/ amoxicillin)

(*Contd...*)

Table 2: (*Continued*).

Disease	Clinical clue	Diagnostic clue	Therapeutic updates (conventional with new)
Kawasaki disease	• High-grade fever, generalized red maculopapular rash, • Bilaterally symmetrical nonpitting edema of hands and feet • Fissuring of lips, reddish discoloration of tongue, and non-purulent bilateral bulbar conjunctivitis.	• C- reactive protein raised. • Echocardiography: Aneurysmal dilatation of coronary arteries and dysfunction of valves	• IVIg along with high-dose aspirin IVIg 2 g/kg as a single dose and aspirin 30 50 mg/kg/day • Infliximab (5 mg/kg over 2 h)
Immunodeficiency syndrome			
Omenn's syndrome	• Erythroderma, • Failure to thrive, • Lymphadenopathy • Recurrent infections • Hepatosplenomegaly	• Lymphocyte phenotyping • Gene panel analysis • Evaluation in PID referral center	• Bone marrow–derived and umbilical cord blood–derived hematopoietic stem cell transplantations. • Lentivirus-based gene therapy in a murine model shows positive response.
Graft versus host reaction (transplacental passage of maternal lymphocytes)	• Nonspecific morbilliform rash which gradually progresses to erythroderma with epidermal sloughing • Alopecia	• Lymphocyte phenotyping • Chimerism analysis • Evaluation in PID referral center	• Cyclosporine • Bone marrow transplantation
Wiskott-Aldrich syndrome	• Eczematous dermatitis • Purpura • Thrombocytopenia	• Blood count • Targeted sequencing of WAS gene • Evaluation in PID referral center	• Bone marrow transplantation
IPEX syndrome	• Failure to thrive • Diabetes, enteropathy	• Endocrinologic and GIT workup • Targeted sequencing of FOXP3 gene • Evaluation in PID referral centre	• Immunosuppressive therapy, especially rapamycin, hematopoietic stem cell transplantation
Drug-induced erythroderma: Toxic epidermal necrolysis.	• Prior intake of drugs: (Sulphonamides, anticonvulsants, NSAIDs, penicillins.) • Purpuric spots developing into blister and subsequent peeling off • Nikolsky's sign: positive.	Clinical diagnosis histology: subepidermal blister and full-thickness epidermal necrosis.	• Incriminating drugs are withdrawn, and timely symptomatic treatment with cyclosporine or systemic steroids. • IVIg also has a role.
Metabolic and nutriti onal disorders			
HCS deficiency	• Lethargy, seizures • Metabolic acidosis	• Newborn screening, blood gas analysis • Urine organic and amino acid analysis • HCS activity in leukocytes, genetic testing	Oral biotin therapy with 20–40 mg/day and sometimes 100 mg/day may be required.
Methylmalonic acidemia	• Neurologic symptoms, respiratory distress • Metabolic acidosis	Newborn screening, blood gas analysis Urine organic/amino acid analysis, genetic testing	Cobalamin and carnitine (levocarnitine 100 mg/kg/day) supplements. Low protein diet.
Acrodermatitis enteropathica	• Diarrhea • Peri-orificial rash before it generalizes • Alopecia	Low serum zinc levels, alkaline phosphatase levels	Lifelong zinc supplementation. (3 mg/kg/day elemental zinc).

(*Contd...*)

Table 2: (*Continued*).

Disease	Clinical clue	Diagnostic clue	Therapeutic updates (conventional with new)
Others			
Diffuse cutaneous mastocytosis.	• Skin is thickened, lichenified, erythematous and leathery appearance • Darier's sign. • Bullous manifestations occur in first 2 or 3 years of life. • Systemic symptoms: flushing attacks, • Respiratory difficulty and diarrhea	A dense, band of mast cellinfiltrate in the upper dermis is pathognomic of mastocytosis. Special stains like Giemsa and toluidine blue confirms presence of mast cells.	H1- and H2-receptor antagonists, disodium cromoglycate and ketotifen (mast cell stabilizer) are helpful. Epi-Pen (self-injectable adrenaline): Children with a history of anaphylaxis should carry.
Leiner's disease	• Erythema, infiltration and desquamation in the seborrheic localization with rapid progression to erythroderma • Diarrhea	Complement C5 deficiency	Symptomatic management Antibacterial and antifungal treatment for infection. Prednisolone start dose 1–2 mg/kg/day and maintainance dose 0.5 mg/kg/day tapered gradually.

BIE: Bullous ichthyosiform erythroderma, IPEX: Immune dysregulation, polyendocrinopathy, and enteropathy, X-linked, PID: Primary immunodeficiency disorder, HLA: Human leukocyte antigen, HCS: Holocarboxylase synthetase, NSAIDs: Nonsteroidal anti-inflammatory drugs, IVIg; Intravenous immunoglobulin, RADT: Rapid antigen detection test, TNF: Tumor necrosis factor alpha, ETN: Erythema toxicum neonatorum, CCC: Congenital cutaneous candidiasis, DSG1: Desmoglein-1, DSP: Desmoplakin, CDSN: Corneodesmosin gene, PSS1: Peeling skin syndrome type 1, KID: Keratitis ichthyosis deafness, TTD: Trichothiodystrophy, rAAV-2: recombinant adeno-associated virus-2 vectors, CHS: Conradi–Hunermann syndrome, HSV: Herpes simplex virus, SFTI: Sunflower trypsin inhibitor, CRIE: Congenital reticular ichthyosiform erythroderma, PCR: Polymerase chain reaction, HI: Harlequin ichthyosis, TG1: Transglutaminase 1, JAK: Janus kinase inhibitor, EBP: Emopamil binding protein, NS2: A novel Aldehyde Trap, FALDH: Fatty aldehyde dehydrogenae, UVB: Ultraviolet radiation, CAPE: CARD 14 associated papulosquamous eruptions, CHILD: Congenital hemidysplasia with ichthyosiform erythroderma and limb defects, SAM:Severe dermatities,multiple allergies and metabolic wasting, KOH: Potassium hydroxide, MRSA: methicillin resistant staphylococcus aureus, GIT:gastrointestinal tract, TGM1: Transglutaminase 1

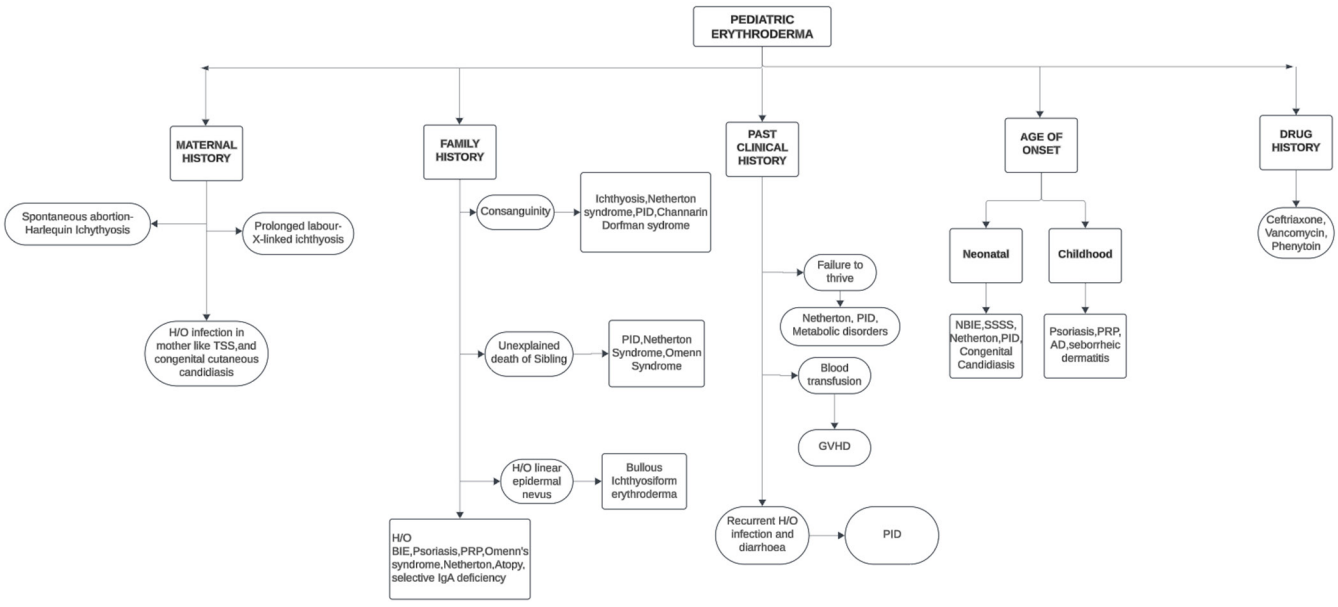

Figure 1: Clinical history-wise approach to a case of pediatric erythroderma.
PID: Primary immunodeficient disease, GVHD: Graft versus host disease, PRP: Pityriasis rubra pilaris, AD: Atopic dermatitis, SD: Seborrheic dermatitis

Table 3: Laboratory investigations in pediatric erythroderma.

Laboratory test	Variation expected from normal range.	Specific alteration
Complete blood count, leucocyte diff. and platelets	↓↑ Low Hb% (Anemia) Leukocytosis Raised Eosinophil count Thrombocytopenia	Common Cystic fibrosis, malnutrition SSSS, TSS. Omenn syndrome NS AD. WAS
Sodium/potassium	↓↑ Hypernatremia	Common NS
Serum albumin	↓	Common
Serum creatinine and serum urea	↑	Common
Erythrocyte sedimentation rate	↑	Common
C-reactive protein	↑	Common
Capillary blood gas	Ketoacidosis	Common Holocarboxylase synthetase deficiency.
NK cells	↓	NS
IgE, IgG, and IgA	↓↑	NS, Omenn, AD, WAS, IPEX, IgA deficiency
T and B lymphocytes	↓	PID
Complement level		Leiner's disease
Serum zinc and alkaline phosphatase	↓	Acrodermatitis enteropathica
Biotinidase and holocarboxylase essays	↓	Biotinidase and holocarboxylase deficiency
Serum tryptase	↑	Diffuse cutaneous mastocytosis
Serum creatine kinase	↑	Chanarin-dorfman syndrome;
Ceruloplasmin and serum copper	↑	Menkes disease
Glucose	↓	Common
Amino acids (urine)	↑	NS
Serum ammonia Essential fatty acids assay	↑	Metabolic diseases
Serum calcium	↓	DiGeorge
Sweat chloride levels		Cystic fibrosis
Sr HLA B17		Congenital psoriasis

NK: Natural killer, SSSS: Staphylococcal scalded skin syndrome, TSS: Toxic shock syndrome, NS: Netherton syndrome, IgE: Immunoglobulin E, IgG: Immunoglobulin G, IgA: Immunoglobulin A, Hb: Hemoglobin, AD: Atopic dermatitis, WAS: Wiskott-aldrich syndrome, IPEX: Immune dysregulation, polyendocrinopathy, and enteropathy, X-linked, PID: Primary immunodeficiency disorder, HLA: Human leukocyte antigen

General

- Shock- TSS, toxic epidermal necrolysis (TEN)
- Lymphadenopathy – OS, GVHR, AD
- Hepatosplenomegaly-OS, GVHR.

Systemic

- Ophthalmologicalcataract - Conradi-Hunermann syndrome (CHS), neutral lipid storage disease, fundus-glistening dots
- Auditory- Keratitis ichthyosis deafness (KID) syndrome, neutral lipid storage disease
- Respiratory - cystic fibrosis
- CNS- Trichothiodystrophy (TTD) (spasticity, mental retardation).

Mucocutaneous

- Collodion membrane: Inherited ichthyoses are the most common related disorders associated with the collodion membrane. It is commonly associated with inherited Ichthyosis. Ichthyosis with confetti, lamellar ichthyosis (LI), Gaucher disease, holocarboxylase deficiency, ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome.[18-20]
- Type of scales (ichthyosiform or fine scales), Neonatal scaling, and exfoliative erythroderma suggest ichthyoses and NS. Rough, dry, scaly skin is commonly seen in ichthyosis; brown and dark scaling (frequently with collodion membrane) is typical for LI, while brown and fine white scaling with erythroderma is suggestive for congenital ichthyosiform erythroderma (CIE). Annular scaling suggests NS, but the typical ichthyosis linearis

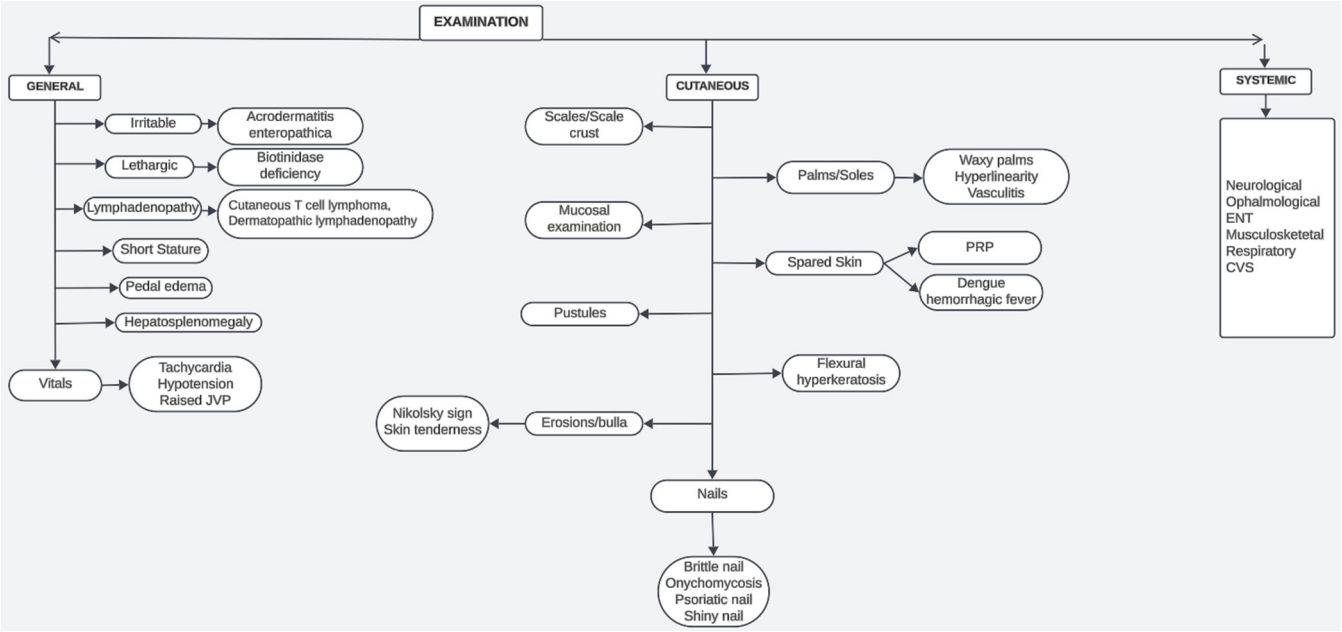

Figure 2: Dermatological and systemic examination-wise approach.
JVP: Jugular venous pressure, PRP: Pityriasis rubra pilaris, ENT: Ear, nose, and throat, CVS: Cardiovascular system

circumscripta may not always be present. Psoriasis: Silvery white scaling. Recalcitrant diaper dermatitis with generalization clues to erythrodermic psoriasis. Greasy scales on the scalp (cradle cap) and skin folds (axilla, neck, retro auricular, and diaper areas) suggest seborrheic dermatitis. Metabolic diseases such as holocarboxylase, biotinidase, or acrodermatitis enteropathica may present with psoriasiform scaling. Collarete scales are typical for CCC. Perioral scale crusts are seen in SSSS.

- Spared areas – PRP.
- Typical lesions include (keratotic follicular papules of PRP and well-defined erythematous scaly plaques of psoriasis). Blistering can be seen in epidermolytic ichthyosis, SSSS, and DCM, pemphigus foliaceus.
- Pustule: In CCC, papules and pustules may evolve into Neonatal erythroderma and spare the oral cavity and diaper area. Palms and soles may be involved in widely scattered spots on the placenta and umbilical cord, providing diagnostic clues.
- Skin indurationimmunodeficiency, AD, neuroichthyosis, generalized cutaneous mastocytosis (peau d'orange).
- Darier's signMastocytosis.
- Positive Nikolsky's sign- SSSS, Boric acid toxicity.
- Skin tenderness - SSSS, TEN, TSS.
- Distribution (flexor or extensor).
- Sparing of napkin area and axillae – AD.
- Nail changesparonychia and dystrophy in CCC.
- Alopecia- frequently occurs in OS, GVHR, NS, Biotin metabolism disorders, citrullinemia, TTD (brittle hair), AEC Syndrome, and acrodermatitis enteropathica.
- Hair dysplasia - NS (bamboo hair-trichorrhexis invaginata, nodosa).
- Mucosal examination.
- Palmoplantar thickening – PRP.
- Swirled pattern of erythroderma – CHS.
- Ectrodactyly, cleft lipectodermal dysplasia.
- Pruritus manifests in PID, NS, scabies, or desmosomal disorders, such as severe dermatitis, multiple allergies and metabolic wasting (SAM) syndrome, psoriasis, AD, and seborrhoeic dermatitis.

INVESTIGATIONS

Skin biopsy

It is essential, and as in adults, it is advisable to take 2–3 specimens simultaneously from different sites. A skin biopsy can aid in establishing the diagnosis in ~40% of cases of erythroderma. A biopsy proves beneficial in around 50% of cases of ichthyosis spongiotic reactions found in eczematous conditions. A spongiotic reaction pattern with keratinocyte necrosis, satellite cell lymphocytes, and lymphocytic infiltration with or without eosinophils indicates a diagnosis of PID. Lipid vacuoles in biopsy are suggestive of neutral lipid storage disease. Decreased IHC staining with Lympho-epithelial Kazal-type related inhibitor is useful in distinguishing NS from other desmosomal disorders such as severe dermatitis, atopic diatheses, and metabolic wasting (SAM) syndrome.
Histopathology aids in determining the level of detachment, but immunofluorescence on skin biopsies is more specific. This helps in narrowing the diagnosis.

In cases of vesiculobullous diseases of the newborn, the "jelly roll" frozen technique is an alternative to punch biopsy. The process entails encasing the sloughed skin in a cotton-tipped applicator, followed by conducting a frozen section analysis.

- Skin, eyes, nose, and umbilical swabs for gram stain and culture sensitivity – SSSS, TSS, CCC High vaginal swabs from mother - *Staphylococcus aureus* or CCC.
- Culture of urine, blood, and Cerebrospinal fluid – Candidiasis.
- Potassium hydroxide (KOH) mount – Candidiasis.
- Tzanck smear - Pemphigus foliaceous (acantholytic cell), herpes simplex virus infection (multinucleated giant cell)
- Wet Mount - Sarcoptes mite (Norwegian scabies).

Laboratory investigations

Laboratory tests in general in erythroderma and specific tests required for the disease are given in Table 3.

Hair analysis

Various investigative tools, such as dermoscopy, reflectance confocal microscopy, optical microscopy, and electron microscopy, should be used to assess the hair.

- NS: Trichorrhexis invaginata (bamboo hair),
- Trichothyodystrophy: Alternate dark and light bands-tiger skin pattern.

Molecular genetic analysis establishes the diagnosis in PIDs, metabolic disorders, and all types of ichthyoses (syndromic and non-syndromic).

Imaging investigation

Chest X-ray finding

X-linked agammaglobulinemia is characterized by sparse tonsillar and adenoidal lymphoid tissue.

Common variable immunodeficiency: Bronchiectasis, bronchial wall thickness, and atelectasis. Severe combined immunodeficiency disease [SCID] and DiGeorge syndrome [DGS]: The lack of a thymic shadow, a constricted upper mediastinal outline, and the presence of retrosternal lucency. X-ray long bones – CHN.

Audiometry

KID syndrome.

TREATMENT

General measures

Erythroderma, regardless of its underlying cause, remains a potentially life-threatening condition in pediatric patients. Temperature, pulse, respiratory rate, blood pressure, and input-output need to be strictly monitored. Electrolytes and metabolic acidosis are to be looked for and managed carefully. There is a risk of hypernatremic dehydration and hypo or hyperpyrexia in erythrodermic neonates and infants. A warm, humid environment should be maintained for these infants to lessen their metabolic needs.[16] Therefore, adequate oral or parenteral fluid intake and monitoring of serum electrolytes are mandatory. Life-threatening complications such as septicemia, hypoalbuminemia, and cardiac failure should be addressed timely.[2]

Protein and caloric intake: Optimal protein and calorie supplementation should be done to meet the metabolic requirements in erythroderma. An estimated energy intake of 120–130 kcal/kg/day is required to gain a normal weight. The daily protein requirement is 3–3.5 g/kg/day.[21]

The application of emollients, including white paraffin and wet wrapping, is essential for maintaining skin hydration and preventing fissures.

If needed, 0.01% potassium permanganate soaks and systemic antibiotics should be given in blisters and erosions found in conditions such as BIE, SSSS, and cutaneous mastocytosis. Due to the increased transcutaneous absorption observed in pediatric erythroderma, it is imperative to avoid topical preparations containing salicylic or lactic acid to prevent potential toxicity.[1]

Topical corticosteroids should be prescribed cautiously and only after the definitive disease diagnosis warrants their need.

Specific measures

Oral or intravenous antibiotics, antifungals, and antiscabicidal drugs should be prescribed to treat underlying diseases such as bacterial infections, CCC, and scabies infestation.

Drug-induced erythroderma requires the immediate discontinuation of the culprit drug and may need a short course of oral corticosteroids or systemic immunosuppressants.

Cyclosporine, methotrexate, acitretin, and phototherapy have been the mainstay of managing Pediatric psoriasis. Retinoids, both topical and systemic, have a definitive role in the management of pediatric ichthyosis. Topical tretinoin and tazarotene have been effective in reducing scaling, ectropion, and palmoplantar thickening in various hereditary ichthyosis such as X-linked recessive ichthyosis, LI, ichthyosis vulgaris, and ichthyosis bullosa of Siemens. Systemic isotretinoin and acitretin use have shown significant responses in autosomal recessive congenital ichthyosis, HI, and congenital ichthyosiform erythroderma. The recommended dose of isotretinoin and acitretin for pediatric patients with these conditions is 0.5–1 mg/kg/day.[22] AD patients are treated with a short course of systemic steroids.

Immunosuppressants are needed to manage dermatomyositis, pemphigus foliaceus, and sarcoidosis. Bone marrow transplantation is required for immunodeficiency cases.

RECENT ADVANCES

- Modified Stoss therapy consists of oral administration of 60000 IU of cholecalciferol daily for 10 days, which seems effective in congenital ichthyosis. It helps in the reduction of scales and stiffness along with ectropion

correction in children with congenital ichthyosis. Vitamin D has a role in regulating the genes involved in terminal differentiation and desquamation of epidermal keratinocytes.[22] Significant reduction in scaling is seen as early as day 5, and skin stiffness and texture normalize by the end of a month. Vitamin D plays a crucial role in the regulation of genes that are associated with the terminal differentiation and shedding of epidermal keratinocytes.[23]

- A retinoic acid metabolismblocking agent, liarozole, an alternative to systemic retinoid therapy, can be given orally in patients with LI.[24]
    - Topical water in oil emulsion of 10% Nacetylcysteine in combination with 5% urea can be applied in erythroderma due to LI and epidermolytic ichthyosis.[25]
    - TMB-001 is an innovative topical isotretinoin ointment that employs a unique polyethylene glycol delivery system to address congenital ichthyosis, offering benefits such as hydration, lubrication, and a reduction in scaling.[26]
- There are recommendations for using biologics to treat severe psoriasis, including erythrodermic psoriasis.[11]
- Adalimumab, a Tumor necrosis factor (TNF)-α blocker, is approved for use in pediatric psoriasis (ages 4 years and above).
- Etanercept, a TNF receptor fusion protein, is approved for pediatric psoriasis in patients aged 4–17 years, and it is given in doses of 0.8 mg/kg (max 50 mg/dose) every week.
- Ixekizumab, a monoclonal antibody targeting interleukin (IL)-17, is approved in 2021 for psoriasis in age group 6–17 years with dose: <25 kg: 40 mg at week 0, 20 mg every 4 weeks, 25–50 kg: 80 mg at week 0, 40 mg every 4 weeks, ≥50 kg: 160 mg at week 0, 80 mg every 4 weeks.
- Secukinumab, another monoclonal antibody targeting IL-17A, has proven sustained efficacy in pediatric patients with moderate-to-severe psoriasis approved in the year 2022. For age group 6–17 years with dose <50 kg: 75 mg ≥50 kg: 150 mg at weeks 0, 1, 2, 3, and 4, and every 4 weeks after that.
- Ustekinumab, a monoclonal antibody, targets the p40 subunit common to IL-12 and IL-23, effective in pediatric patients (6–12 years of age) with moderate-to-severe psoriasis with dose (<60 kg: 0.75 mg/kg; ≥60–≤100 kg: 45 mg; >100 kg: 90 mg).
- Dupilumab, a monoclonal antibody that targets the IL-4R alpha subunit, has been approved for AD treatment for pediatric patients over 6 months of age in the year 2023 with dose:
    - 5–<15 kg: Day 1: 200 mg, then 200 mg every 4 weeks
    - 15–<30 kg: Day 1: 300 mg (6 months–5 years) or 600 mg (6–17 years), then 300 mg every 4 weeks.
- Tralokinumab, a monoclonal antibody to IL-13, is also now approved for AD in adolescents aged 12–17 years with a loading dose of 600 mg on Day 1, followed by 300 mg every other week.

CONCLUSION

Erythroderma in children requires a specialized clinical and diagnostic approach. The causes of pediatric erythroderma are different from those in adults. Treatment typically involves multiple approaches, including disease-specific topical and systemic therapy, addressing calorie, protein, and fluid deficits, and ensuring proper thermoregulation. Pharmacological management of pediatric erythroderma needs diligent monitoring in view of their high BSA, the need to complete their vaccination, and in view of their physical growth.

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