Symposium - Pediatric Dermatoses

Neonatal dermatological emergencies

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ABSTRACT

The neonates are unique in several ways in comparison with older children and adults which render them highly susceptible to severe, sometimes life threatening dermatological disorders. The neonatal dermatological emergencies are a diagnostic and therapeutic challenge. A wide range of dermatoses such as infections, genodermatoses, metabolic disorders and vascular tumors may require emergency care. The clinical presentation also varies from generalized involvement of skin to localized disease with or without systemic symptoms. Irrespective of the etiology and clinical presentation, these disorders are associated with significant morbidity and mortality. With the availability of effective drugs and monitoring facilities, and awareness of need for immediate care, there has been a significant decline in the fatality rate associated with neonatal dermatological emergencies. Knowledge of clinical presentations, rapid diagnostic methods, emergency care and monitoring of progress of the disease helps in comprehensive multidisciplinary care of neonates with these disorders.

Key words: Neonatal dermatological emergencies, neonatal erythroderma, neonatal intensive care

INTRODUCTION

Dermatological emergencies comprise diseases that demand early diagnosis, hospitalization, careful monitoring and multidisciplinary intensive care to minimize the associated morbidity and mortality. An intensive care unit and a well synchronized team of dermatologist, pediatrician and skilled nursing staff are necessary for the management of patients.[1] This review is focused on clinical presentations, immediate care and monitoring of dermatoses or clinical syndromes which almost always present with significant morbidity and mortality in neonates [Table 1].

Table 1: Mortality rates of neonatal dermatological emergencies

Dermatological emergencies	Mortality rate (%)
Neonatal erythroderma	16
Staphylococcal scalded skin syndrome	<05
Necrotizing fascitis	59
Neonatal varicella	20-23
Neonatal herpes simplex infection	04-85
Candidiasis in neonates	8-40
Kasabach-Merritt phenomenon	20-30
Purpura fulminans	50-100
Kawasaki disease	0.1-2
Sclerema neonatorum	50-100

In a hospital-based Indian study, of total emergency dermatological referrals, 15.5% were neonates, 9.7% were infants, 36.9% were preschool and 37.2% were school going children. Genodermatoses like epidermolysis bullosa, collodion baby and Harlequin ichthyosis (37.5%), and staphylococcal scalded skin syndrome (SSSS) (31.7%) were common in neonates whereas severe atopic and seborrheic dermatitis were common in infants. In preschool and school going children, infections (42.1%) and cutaneous drug reactions (56.4%), respectively, formed majority of cases.[2]

The first 4 weeks of life of an infant is considered as the neonatal period. Neonates are unique in several ways (increased body surface to weight ratio, immature kidney and immunity, risk of intrauterine infection and transepidermal water loss) in comparison with older children and adults which render them highly susceptible to severe dehydration and infections either primary or secondary.

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CLASSIFICATION OF NEONATAL DERMATOLOGICAL EMERGENCIES

The neonatal dermatological emergencies can be clinically classified into two groups: primary dermatological emergencies and dermatoses associated with medical or surgical emergencies [Table 2]. In the former group, the involvement of skin is the primary cause for the mortality or is the major manifestation, and in the latter, cutaneous manifestations are the indicators of impending or underlying severe systemic involvement.

Table 2: Classification of neonatal dermatological emergencies

1. Primary dermatological emergencies
   - A. Neonatal erythroderma
     - Ichthyoses
     - Collodion baby
     - Harlequin ichthyosis
     - Lamellar ichthyosis
     - Congenital ichthyosiform erythroderma
     - Netherton syndrome

     Immunodeficiency disorders
     - Omenn syndrome
     - Graft versus host disease
     - Severe combined immunodeficiency

     Papulosquamous disorders
     - Congenital erythrodermic psoriasis
     - Congenital erythrodermic pityriasis rubra pilaris

     Others
     - Diffuse cutaneous mastocytosis
     - Drug-induced erythroderma (Vancomycin and ceftriaxone)
   - B. Neonatal cutaneous infections

     Bacterial infections
     - Staphylococcal scalded skin syndrome
     - Necrotizing fascitis

     Viral infections
     - Neonatal varicella
     - Neonatal herpes infection

     Fungal infections
     - Candidiasis in newborn
   - C. Vesiculobullous disorders
     - Epidermolysis bullosa
   - D. Metabolic disorders
     - Neonatal biotin deficiency
   - E. Vascular tumors
     - Kasabach- Merritt phenomenon
2. Dermatoses associated with medical or surgical emergencies
   - A. Purpura fulminans
   - B. Kawasaki disease
   - C. Sclerema neonatorum

1. PRIMARY DERMATOLOGICAL EMERGENCIES

A. Neonatal erythroderma (red scaly baby)

Neonatal erythroderma is a rare and potentially life threatening condition irrespective of underlying etiology. The exact incidence of the condition is not known. A hospital-based retrospective study of pediatric patients (neonates and infants) attending a tertiary care children hospital in North India reported an incidence of 0.11% (20/19000).[3]

Causes of neonatal erythroderma [Table 2]

In a retrospective study of erythroderma during the first year of life, 32% of cases had congenital onset of the disease. All the cases belonged to ichthyosis group except for one case of Omenn syndrome. Forty percent of ichthyotic disorders presented with collodion membrane.[4] In a hospital-based, retrospective study from India, ichthyosiform erythroderma constituted 25% of cases.[5] In this study, infections were also included unlike the previous study.[4] Rare causes of neonatal erythroderma include congenital erythrodermic psoriasis, diffuse cutaneous mastocytosis, graft versus host disease and congenital erythrodermic pityriasis rubra pilaris.[6]

Clinical features

The clinical presentation is characterized by generalized erythema and scaling irrespective of the underlying disease. However, certain clinical clues may help in establishing the etiology of the condition [Table 3].[3,4,6] Apart from clinical presentations, family history of erythroderma and atopy, sibling mortality and consanguineous marriage also help in the differential diagnosis. Sibling mortality and family history of erythroderma have been reported in 57% and 66% of cases of Omenn syndrome and Netherton syndrome, respectively. Consanguineous marriage has been reported in 25%, 88% and 33% cases of ichthyoses, Netherton syndrome and primary immunodeficiency respectively. Family history of atopy can be elicited in 33% and 43% of cases of Netherton syndrome and Omenn syndrome, respectively.[4]

Despite clinical and laboratory evaluation, some cases remain undiagnosed. These neonates presented with severely pruritic erythroderma, marked induration of skin, severe alopecia, nail abnormalities, failure to thrive, lymphadenopathy and hepatosplenomegaly. Family history of atopy may be present in 60% of cases. Severe systemic infection occurs in almost all the cases.[4] Leiner's disease is another such entity applied

Table 3: Clinical differential diagnosis of neonatal erythroderma

Clinical presentation	Diseases
Severe pruritic erythroderma with induration, severe alopecia, failure to thrive, lymphadenopathy, hepatosplenomegaly	Immunodeficiency disorders (Omenn syndrome, Severe combined immunodeficiency)
Erythroderma with moderate to severe pruritus, sparse hair, trichorrhexis invaginata (demonstrated at birth by examination of eye brows or eye lashes), diarrhea, failure to thrive	Netherton syndrome
Erythroderma with history of collodion membrane, ectropion, eclabion	Non-bullous ichthyosiform erythroderma
Erythroderma with superficial blisters and erosions	Bullous ichthyosiform erythroderma
Erythroderma with areas of unaffected skin, absence of ectropion	Congenital erythrodermic psoriasis
Erythroderma with areas of unaffected skin, follicular hyperkeratosis, palmoplantar keratoderma	Congenital erythrodermic pityriasis rubra pilaris
Morbiliform rash evolving into erythroderma, fever, lymphadenopathy, hepatosplenomegaly, T cell immunodeficiency	Graft versus host disease (transplacental passage of maternal lymphocytes)
Erythroderma, extensive blistering, diarrhea, vomiting, abdominal cramps, wheezing, pruritus, flushing, hypotension, fever and Darier's sign	Congenital diffuse/ erythrodermic mastocytosis
Newborn encased in a 'armour' like thick, yellow plates of scales with deep red fissures, frog-like face with ectropion, eclabion, and flat nose and ears, digits bound in a tight membrane	Harlequin ichthyosis

to a neonatal erythroderma after other causes have been ruled out. A follow- up study of five infants with Leiner's phenotype revealed immunological abnormalities in all the cases; one had hypogammaglobulinemia, one had combined immunodeficiency which was later diagnosed as Omenn syndrome and three were diagnosed as Netherton syndrome with elevated IgE levels.[7]

Consequences of neonatal erythroderma

The diagnosis of the disease is usually delayed. Hence, the management of the condition is usually aimed at prevention or treatment of consequences and/ or complications of erythroderma. The loss of cutaneous barrier results in interrelated alterations in transepidermal water loss, caloric or heat loss and metabolic rate.

Effect on transepidermal water loss: Normally, in addition to mandatory water loss by the kidneys and gastrointestinal system, additional water losses occur due to evaporation from the skin and respiratory tract. The latter two are not measured usually and hence termed as insensible water loss (IWL). Transepidermal water loss (TEWL) contributes 70% of this insensible water loss.[8]

The TEWL reflects both skin immaturity and the larger surface area to weight ratio. In a normal full-term infant, the TEWL is about 6-8 g/m^2/h (12ml/kg/day). Whereas in preterm infants born at 24-25 weeks gestation, TEWL is 60 g/m^2/h (about 140 ml/kg/day) and then it falls exponentially to 45 g/ m^2/h by 3rd day and to 24 g/m^2/h by 28th day. By 32 weeks of gestation, TEWL normalizes along with skin maturity to that of normal full term infant. The severity of TEWL also depends on ambient humidity. A high ambient humidity reduces TEWL especially in premature infants. In term infants, the susceptibility to change in ambient humidity is very low.[9,10] The TEWL depends on various factors such as ambient and body temperature, microenvironment of neonatal care, activity of baby, phototherapy, gestational age of the baby and skin trauma.[11]

In pediatric patients with ichthyosis, the total body TEWL, depending upon the severity and genetic heterogeneity, ranges from 746 ± 468 ml/day (mean basal TEWL of 39.6 ± 20.6 ml/m^2/h compared to upper limit of normal 8.7 ml/m^2/h) in contrast to 209 ml/day seen in age-matched children with competent skin barrier.[12] An estimation of TEWL from normal and abnormal skin of a collodion baby using evaporimeter at day 4 demonstrated a loss of 18 ± 2 g/m^2/h and 112 ± 2 g/m^2/h of water respectively, at room temperature of 27^{0}C and relative humidity of 25%. The same reduced significantly, in parallel with the clinical improvement of the skin at day 30 to 5.5 ± 2 g/m^2/h and 16 ± 2 g/m^2/h respectively, at room temperature of 23^{0}C and relative humidity of 37%.[11] This significant reduction in TEWL underlines the importance of maintenance of skin barrier, ambient humidity and temperature.

Effect on caloric or heat loss and metabolic rate: The TEWL is always accompanied by heat loss at the rate of 0.58 kcal/ ml. The total caloric loss from daily TEWL

in pediatric patients with ichthyosis ranges from 84 to 1015 kcal (21±9.8 kcal/kg/day with a mean of 433± 272 kcal/day) in contrast to 41- 132 kcal/ day seen in age-matched children.[12] Therefore, it is very difficult to regulate temperature in such babies and hyperpyrexia may occur if the ambient temperature is too high.[9,11] This evaporative caloric loss is compounded by cutaneous hyperplasia and inflammation. These, at the same time, result in increased metabolic rate. Also the resting energy expenditure in the infants with ichthyosis is usually 19% or higher than predicted. Hence the severity of the barrier defect correlates with the increased metabolic demand.[13]

Complications of neonatal erythroderma

The neonates with erythroderma are at increased risk of hypernatremic dehydration, severe systemic infections, hypoalbuminemia and hyperpyrexia or hypothermia as a result of consequences of erythroderma (see above). These complications are more pronounced in collodion baby, Harlequin ichthyosis, severe lamellar ichthyosis, Netherton syndrome and Omenn syndrome resulting in significant mortality and morbidity. Increased skin fragility, fissures, cracks, erosions or immunodeficiency in these disorders result in severe septicemic infections.[3,4,6]

Laboratory investigations

The laboratory evaluation of neonatal erythroderma is facilitated by a few investigations. Serum IgE levels are markedly elevated in Netherton and Omenn syndrome. Histopathological study of skin biopsy specimens preferably taken simultaneously from 2 or 3 different sites contributes to the specific diagnosis only in 45% of cases. Significant orthokeratosis with corneocytes arranged in laminated and compact fashion, prominent hypergranulosis, acanthosis, and absent or few inflammatory cells suggest ichthyoses except Netherton syndrome. In bullous ichthyosiform erythroderma, epidermolytic hyperkeratosis is seen. Omenn syndrome and graft versus host disease are characterized by dermal and epidermal lymphocytic infiltration and keratinocyte necrosis with satellite lymphocytes. Serum electrolyte and albumin levels should be monitored because of increased risk of hypernatremic dehydration (Sodium >160mmol/l), and hypoalbuminemia from enteral and transcutaneous loss of proteins. Bacterial culture from skin swabs from different sites or blood is indicated if secondary bacterial infection or septicemia is suspected.[3,4,6]

Management

Regardless of underlying disease, the management of neonatal erythroderma includes fluid and electrolyte balance, correction of caloric and protein intake, and prevention and treatment of infections.[4] Specific therapy is started once the diagnosis of underlying disease is established.

Fluid and electrolyte balance: In neonatal erythroderma, satisfactory fluid and electrolyte balance is achieved by reduction of high TEWL, and parenteral fluid and electrolyte replacement [Table 4]. Initial fluid calculation is a matter of best clinical judgment influenced by changing clinical circumstances.[9] The adequacy of fluid replacement should be monitored carefully using clinical and laboratory parameters [Table 5]. Further fluid and electrolyte replacement is guided by these parameters.[8]

Table 4: Principles of management of fluid and electrolyte balance in neonates

1. Reduction of TEWL
   - Maintenance of high humidity microenvironment above 60%
   - Nursing the baby under a radiant warmer with humidified body hood
   - Maintenance of body and ambient temperature
   - Application of water impermeable barriers such as emollients
2. Parenteral fluid and electrolyte replacement
   - Replacement of fluid deficit:
     - In moderate (10%) to severe (15%) dehydration, the fluid deficits of 100 ml/kg and 150 ml/kg, respectively, are corrected over 24 h in addition to the maintenance fluid
     - Unless there is an acute blood loss, normal saline is the recommended fluid for immediate intravascular volume support
     - In infants with shock, 10-20 ml/kg of normal saline is given immediately followed by half of the deficit over 8 h. The remaining half is administered over 16 h.
   - Maintenance fluid
     - It is the sum of allowance for urinary water (30-60 ml/kg/day) plus estimated insensible water loss appropriate to gestational age and postnatal day
     - On the first day of life, it ranges from 2.5-3.5 ml/kg/h and increases to 5-6 ml/kg/h by the end of 1 week and thereafter 7-8 ml/kg/h
     - The maintenance fluid of choice is 10% dextrose maintained at 4-6 mg/kg/min (5% dextrose is used in low birth weight babies, <1250 g)
   - Sodium and potassium (2-3 meq/kg/day) should be added only after 48 h
   - Fluid restriction is advised only when there is evidence of volume overload because routine restriction compromises nutrition

Table 5: Clinical and laboratory monitoring

1. Clinical monitoring
   - Serial measurement of body weight
   - Signs of dehydration (unreliable in neonates)
     - Infants with 10% dehydration (100ml/kg) may have sunken eyes and fontanel, cold and clammy skin, poor skin turgor and oliguria
     - Infants with 15% dehydration (150ml/kg) or more may have signs of shock (hypotension, tachycardia and weak pulse) in addition to above features
2. Laboratory monitoring
   - Serum sodium
     - Serum sodium values should be maintained at 135-145 meq/l
     - Hyponatremia with weight loss suggests sodium depletion requiring sodium replacement (2-3meq/kg/day)
     - Hyponatremia with weight gain suggests water excess necessitating fluid restriction
     - Hypernatremia with weight loss suggests dehydration requiring fluid correction over 48 h
     - Hypernatremia with weight gain suggests salt and water excess necessitation fluid and sodium restriction
   - Urine output, specific gravity (SG) and osmolarity
     - Urine specific gravity is an useful guide to fluid therapy
     - The acceptable range for urine output is 1-3 ml/kg/h for SG of 1.005 to 1.012 and for osmolarity of 100-400 mosm/l
   - Blood gas
     - Not required for routine fluid management
     - Useful in acid-base management in patients with shock
   - Blood urea nitrogen and serum creatinine
     - Serum creatinine levels fall exponentially in the first week of life as maternally derived creatinine is excreted
     - Serial measurement of serum creatinine is required
     - Absence of normal decline of serum creatinine is an indicator of renal failure in neonates

Protein and Caloric intake: The supplementation of protein and calorie in neonates with erythroderma must meet the demands of hypermetabolic state and requirements of normal growth and development. There is a little consensus on the formula to compute the amount of calorie delivery or resting energy expenditure. Recently, there has been a change in concepts and guidelines of nutritional support in critically ill children [Table 6].[14]

As the neonate improves and hypermetabolic state reverses, the calorie supply may be increased to even hypercaloric nutritional support. Then the energy needs are roughly equal to the daily fluid requirements of infants. An estimated energy intake of 120-130 kcal/kg/day is required to achieve a normal weight gain of

Table 6: Principles of nutritional support in a critically ill neonate

- During an acute phase of the disease, the aim is to avoid catabolism and not growth
- During hypermetabolic stress, the neonates are unable to utilize excess calories
- A permissive hypocaloric nutritional support is advised during hypermetabolic stress to avoid the complications of excess calorie delivery such as hyperglycemia, secondary inefficient insulinemia and osmotic diuresis
- The calorie delivery is patient tailored on a regular and daily basis depending on individual tolerance
- The target is to avoid hyperglycemia (>126-150 mg/dl) guided by periodic blood sugar estimations
- The recommended calorie intake in critically ill child is 25-30 kcal/kg/24 h
- Glucose infusion of 3-5 mg/kg/min inhibits catabolism of endogenous protein
- The recommended protein intake is 1.5-2.5 g/kg/day
- Enteral nutrition as gavage feeds through nasogastric or nasoduodenal tube is the preferred route of nutritional delivery
- Enteral feeds are commenced at low rate, 10-15% of usual daily requirements
- In hemodynamically unstable neonate, enteral feeding is started after stabilization

15 g/kg/day. The energy intake can be increased by 10-30% depending upon the stressful conditions. The resting energy expenditure in infants with ichthyosis is usually 19% or higher than predicted.[13] The calorie lost from total daily TEWL (see above) may provide a guide to replacement therapy. The glucose infusion should provide 50- 70% of energy requirement. Rest of the calorie is provided by lipids. At least 3% of calorie should be derived from essential fatty acids. Protein needs should be considered in conjunction with energy. The daily requirement of protein is 3-3.5 g/kg/day. Normal requirements of vitamins and minerals should be met as there is little published data of these nutrients in sick children.[14]

Treatment of infections: Widespread cutaneous colonization and/or infection especially with *Staphylococcus aureus* are common in neonates with erythroderma. Antibiotics should be selected based on the results of culture and sensitivity. Parenteral antibiotics are preferred in neonates.[4]

Specific therapy: Topical application of bland emollients such as petrolatum or white soft paraffin helps in maintenance of barrier function of stratum corneum.[4,6] The efficacy of systemic retinoids in the treatment of ichthyosis except Netherton syndrome is well established. However, risk/ benefit ratio is

considered before using retinoids because of increased skin fragility and decreased barrier competence induced by them. The use of topical retinoids and calcipotriol in generalized ichthyosis is limited by their irritancy and expense.[15] Omenn syndrome and severe combined immunodeficiency may need bone marrow transplantation.[4]

B. Neonatal cutaneous infections

Newborns are susceptible to various infections during the perinatal period. Premature and low birth weight infants are particularly predisposed to fatal neonatal infectious disorders. These include staphylococcal scalded skin syndrome (SSSS), necrotizing fascitis, neonatal varicella, neonatal herpes simplex infection (HSV) and cutaneous candidiasis [Table 7].

Staphylococcal scalded skin syndrome follows trivial infective foci elsewhere in the body. The diagnosis is mainly based on typical clinical features [Table 7]. The culture from lesion is sterile because the infection is caused by exfoliative toxins (ET)-A and ET-B produced by *Staphylococcus aureus*.[16,17] Blood culture is usually negative in SSSS as the organism is rarely invasive. However, the neonates are at risk of Gram negative septicemia especially *Pseudomonas aerugenosa*. Tzanck smear from the ruptured blister may aid in the rapid diagnosis. SSSS responds well to antistaphylococcal antibiotics and supportive therapy.[18]

Necrotizing fascitis is primarily a disease of the adults. Though rare in neonates, NF is characterized by a fulminant course. The infection starts as a minimal rash, erythema, induration or cellulitis at the site [Table 7]. Non-invasive imaging techniques help in rapid diagnosis.[19] In probable cases of NF, the lack of resistance of fascial plane on finger pressure or blunt probe dissection during surgery establishes the diagnosis.[20] The infection is polymicrobial in almost 75% of cases on wound culture. The monomicrobial infection which occurs in 25% of cases is usually caused by *Staphylococcus aureus.* A positive blood culture has been reported in 50% of cases among which 75% were monomicrobial and 25% were polymicrobial. Other laboratory findings include leukocytosis with a shift to left, and thrombocytopenia in about half of the patients.[19] Immediate surgical intervention with antibiotics[21] is required because a prolonged lapse of time between the hospital admission and surgical debridement is the only potential determinant associated with an unfavorable outcome.[22] Death usually occurs in 59% of cases before or shortly after surgery due to septicemic shock, disseminated intravascular coagulation and/ or multiple organ failure.[19]

Neonatal varicella is usually transmitted from maternal varicella occurring during last 3 weeks of pregnancy. The manifestation of neonatal varicella during first 10-12 days of life suggests transplacental transmission of the disease. Postnatally acquired neonatal varicella presents after 12 days of life.[23] The severity and mortality of neonatal varicella depends on the day of onset of rash in the mother and neonate [Table 7].[24,25] Disseminated infection with pneumonia, hepatitis or meningo-encephalitis occurs in 20-50% of cases with a mortality of 20-23%. Death from severe pneumonitis and respiratory distress often occurs 4-6 days after the onset of lesions.[23]

Neonatal HSV infection is transmitted from the mother during one of the three distinct time intervals, intrauterine (5%), peripartum (85%) and post partum (10%).[26] Infants born to mothers who have first episode of genital herpes near term are at increased risk of developing neonatal herpes than those born to mothers with recurrent infection.[27] The clinical types of neonatal HSV infection includes skin, eye and/ or mouth (SEM) disease accounting for 45% of cases, disseminated disease accounting for 25% of cases and central nervous system (CNS) disease with or without SEM accounting for 30% of cases.[28] The neonatal HSV infection is considered as spectrum of disease because of overlapping signs and symptoms. Skin vesicles at or soon after birth are the most common clinical presentation of neonatal HSV infection [Table 7]. In disseminated disease, vesicles may not develop during entire course of the disease in over 20% of cases. Fever and lethargy are common in disseminated and CNS disease. CNS involvement in the form of encephalitis, which presents as seizures, is also seen in 60-75% of neonates with disseminated disease. The diagnosis is established by polymerase chain reaction (PCR) which has a sensitivity and specificity ranging from 75 to 100% and 71 to 100% respectively.[29-31] The detection of HSV DNA in CSF at the end of treatment is associated with poor outcomes. The acyclovir therapy should be continued in such patients till the CSF PCR becomes negative. The incidence of mortality associated with various types of neonatal herpes has declined significantly from pre-acyclovir era to the

Table 7: Neonatal cutaneous infections

Infections	Age of onset	Etiology and risk factors	Clinical presentation	Rapid diagnosis	Treatment*	Monitoring
Staphylococcal scalded skin syndrome	Usually between 3 and 16 days, and very rarely occurs within 24 h of birth	Exfoliative toxin A and B producing *Staphylococcus aureus*. Associated with a trivial infective focus in the nasopharynx, conjunctivae, the skin, the inner ear, the umbilicus, or the urinary tract.	Extensive blistering, tender erythema, prominent over flexures and perioral area with positive Nikolsky sign. Sparing of mucus membrane. Fever, malaise, irritability and poor feeding precede the skin lesions.	A Tzanck preparation shows large polygonal epithelial cells with large nuclei and no inflammatory cells.	Intravenous cloxacillin or dicloxacillin or cefotaxime with gentamicin or clindamycin, In case of MRSA vancomycin is used. Replacement of fluid and electrolytes, protein and caloric supplementation	Body weight, signs of dehydration and sepsis, serum sodium, serum creatinine, urine output and specific gravity
Necrotizing fascitis	Neonatal period	Fatal bacterial infection of skin, subcutaneous tissue, superficial fascia and deep fascia. Usually develops in neonates with omphalitis, balanitis, mammitis, post-operative complications and fetal scalp monitoring.	Rapidly enlarging erythema, induration or cellulitis with violaceous discoloration, hemorrhagic bullae and necrosis involving abdominal wall, thorax, back, scalp and extremity in the order of frequency of occurrence. Fever and tachycardia are frequently associated with skin lesions.	USG, CT and MRI reveal thickening of fascial plane and accumulation of fluid between subcutaneous fat tissue and muscular layer	Surgical debridement with broad spectrum antibiotics covering Gram negative, Gram positive and anaerobic organisms. Skin grafting may be required because of poor granulation tissue formation or large post-operative skin defects.	Signs of sepsis and multiorgan failure, and DIC
Neonatal varicella	Onset of lesions between 5 and 10-12 days of life.	Varicella zoster virus. Maternal varicella occurring within 5 days before or 2 days after delivery. Premature infants weighing <1000 g are at increased risk of severe neonatal varicella during first 6 weeks of life.	Generalized vesicles on an erythematous base. Pneumonia, hepatitis and meningo-encephalitis in disseminated infection is fatal.	Detection of viral DNA by PCR. ELISA, direct fluorescent antibody test, indirect immuno-fluorescence. Detection of IgA or IgM is confirmative of active infection	Intravenous Acyclovir 20 mg/kg 8th hourly for 5-7 days. No therapy is recommended if the maternal onset of rash is more than 7 days before the delivery.	Clinical or laboratory signs of meningo-encephalitis, pneumonia, hepatitis and DIC
Neonatal HSV infection	At or soon after birth	HSV-1 and HSV-2. Mothers who have first episode of genital herpes near term (peripartum).	Localized (scalp, face), grouped or generalized vesicles with lethargy, fever, respiratory distress and/or seizures. Disseminated intravascular coagulation, hepatitis and pneumonia indicate disseminated disease.	Detection of viral DNA by PCR. Serology has no role in diagnosis of neonatal HSV infection	Intravenous Acyclovir 20 mg/kg 8th hourly for 21days	Clinical or laboratory signs of encephalitis, pneumonia, hepatitis and DIC
Candidiasis in newborn	At birth or within 6 days of life.	*Candida albicans*. Premature infant of gestational age <27 weeks, weight <1000g, IUD or cervical sutures, and invasive procedures or extensive instrumentation in neonates.	CCC in premature infant weighing <1000g presents as, papulopustular eruptions rapidly progressing to form bullae, or burn-like dermatitis with a tendency to desquamate or erode, multiple denuded areas at birth, or rarely diaper dermatitis Invasive fungal dermatitis with extensive crusting and erosions	KOH preparation from skin lesion shows pseudohyphae and budding yeast cells. Funisitis (infection of umbilical cord) or chorioamnitis is suggestive of CCC.	Intravenous Amphotericin B preparations for 21-28 days. Fluconazole, capsofungin, micafungin, voriconazole in case of intolerance to amphotericin B	Respiratory rate, blood pressure, temperature, and signs of septicemia.

CCC: Congenital cutaneous candidiasis, CT: Computed tomography, DIC: Disseminated intravascular coagulation, ELISA: Enzyme linked immunosorbant assay, HSV: Herpes simplex virus, IUD: Intrauterine device, MRSA: Methicillin resistant *Staphylococcus aureus*, MRI: Magnetic resonance imaging, USG: Ultrasonography. *Intravenous cloxacillin (50-100 mg/kg/day in 4 divided doses), dicoxacillin (12.5-25 mg/kg/day in 4 divided doses), Cefotaxime (50-200 mg/kg/day depending on severity in 2-4 divided doses), gentamicin in the dose of 2.5mg/kg/dose every 12 hourly in neonates <7 days and every 8 hourly in neonates >7 days or clindamycin in the dose of 15-20mg/kg/day, vancomycin (10 mg/kg 8th hourly), Liposomal amphotericin B, initial dose of 1 mg/kg/day as continuous intravenous infusion gradually increased at 1 mg/kg/day over a few days to maximum of 5- 7.5mg/kg/day

present era.[32,33] The high dose and longer duration of acyclovir therapy has shown better results in terms of incidence of neurologic sequele, mortality, morbidity and relapse of the disease especially when HSV-2 is the causative agent.[34] Mortality has declined from 85 to 29% in disseminated disease (DIC, severe hepatitis, pneumonia) and from 50 to 4% in CNS disease (acute neurologic and autonomic dysfunction).[26]

Candidiasis in newborns occurs in two forms, congenital cutaneous candidiasis (CCC) and neonatal candidiasis. The former is acquired *in utero* and the latter during the passage through infected birth canal. The classical clinical presentation of CCC is a generalized erythematous macules, papules and/ or pustules measuring 2-4 mm on an erythematous base distributed predominantly over back, extensor extremities and skin folds, and almost always involving the palms and soles. The diaper area is usually spared and the oral mucosa is rarely involved. Over a span of few days the initial lesions evolve into pustules, vesicles and sometimes, bullae. The infection of nails can also occur occasionally in the form of onychia or paronychia. The lesions generally resolve with desquamation within 1-2 weeks.[35,36] Burn like dermatitis can occur in term infants which precedes systemic involvement.[37] The clinical presentation differs in premature infants weighing <1000g [Table 7]. Neonatal candidiasis on the other hand manifests after 7 days of life and is localized to oral cavity and diaper. However, in extremely low birth weight infants, the neonatal candidiasis may present as invasive fungal dermatitis.[38] In full-term infants, CCC follows a benign and self- limited course. CCC and neonatal candidiasis can progress to systemic candidiasis in neonates with certain risk factors [Table 7].[36] Cultures of blood, urine and cerebrospinal fluid (CSF) should be done whenever systemic infection is suspected, and in all premature infants. Respiratory distress in immediate neonatal period should arouse the suspicion of systemic involvement. Systemic involvement and mortality in neonates with CCC, weighing < 1000g, occur in 67% and 40% of cases respectively when compared to those weighing > 1000g (10% and 8% respectively).[39] Antifungal therapy for CCC in a term infant has not shown any benefit. However, some authors recommend topical or oral therapy to decrease the number of viable organisms on the skin.[40] Respiratory distress, leukocytosis with immature forms, persistent hyperglycemia and glycosuria, positive cultures from blood, urine or CSF, burn like dermatitis, and extensive instrumentation and invasive procedures are the indications for systemic therapy in CCC.[36] Intravenous amphotericin B is the first line of drug [Table 7]. Fluconazole 6 mg/ kg/day intravenously can also be used if the neonate develops intolerance to amphotericin B.[41] Newer broad spectrum systemic antifungals like voriconazole (4 mg/kg/day),[42] capsofungin (25 mg/m^2/day, 1 h infusion)[43] and micafungin (2 mg/kg/day)[44] have been used in combination with or following initial amphotericin B therapy in critically ill neonates with systemic candidiasis.

C. Epidermolysis bullosa

Epidermolysis bullosa (EB) is a group of inheritable mechanobullous disorders with a tendency to develop vesicles and bullae at the site of trivial trauma. Depending upon the level of defect and bullae in the basement membrane zone, EB is divided into three types: EB simplex (EBS), junctional EB (JEB) and dystrophic EB (DEB). Among several subtypes of EB, severe form of EBS-Dowling- Meara (EBS-DM), Herlitz-type JEB (JEB-H) and recessive DEB (RDEB) can be lethal in neonatal period.[45]

Clinical features: In severe cases of EBS-DM, extensive blisters may appear spontaneously particularly in hot environment. Bullae appear more hemorrhagic than in other types of EBS. Hands and feet are the predilected sites. Laryngeal involvement can also occur resulting in a weak cry. These neonates are more susceptible to recurrent infections and septicemia caused by *S. aureus* and *P. aeruginosa*.[46] Death in neonatal period is not infrequent. JEB-H is characterized by generalized cutaneous and mucosal erosions. Blisters and erosions are large and extensive seen at or soon after birth. Severe involvement of back and buttocks is common. Involvement of respiratory epithelium may result in stridor which can be fatal. In RDEB, blisters begin at birth and can be extensive. Extracutaneous involvement including gastrointestinal tract, genitourinary tract and ocular mucosa is common. Variable degree of nail changes is common in both JEB-H and RDEB. In neonatal period, sepsis is the worrisome problem and can lead to death in these severe forms of EB.[45]

Diagnosis: Transmission electron microscopy is the gold standard for the diagnosis of EB. But it is time consuming and labor- intensive. Immunofluorescence study is the preferred method of rapid diagnosis

of EB. Skin biopsy helps in differentiating other vesiculobullous disorders.[45]

Treatment: There is no specific therapy for EB. The neonate should be treated in neonatal intensive care unit specialized in EB. Radiant warmer and incubator should be avoided unless the newborn is of low birth weight. The main goals of care are minimizing new blister formation, maintenance of cooler environment temperature, promotion of wound healing, prevention of sepsis and adequate nutritional supplementation. In addition, correction of fluid and electrolyte imbalance, treatment of sepsis and administration of sufficient calories to meet added metabolic demands is very essential in severe cases.[45]

D. Neonatal biotin deficiency

Holocarboxylase synthetase (HCS) deficiency causes neonatal biotin deficiency which usually manifests during first 6 weeks of life. Biotinidase deficiency causes infantile biotin deficiency after first 3 months of life. Biotin is required for the function of four carboxylase enzymes involved in fatty acid synthesis, gluconeogenesis and amino acid catabolism. These enzymes become active when biotin is linked to inactive apocarboxylase by the enzyme holocarboxylase synthetase.[47]

Clinical features: HCS deficiency causes severe bilaterally symmetrical well demarcated periorificial and intertriginous dermatitis and universal alopecia.[48] The neonate usually presents with severe metabolic acidosis and organic aciduria. Seizures, lethargy, projectile vomiting, abnormal muscle tone, athetosis, progressive loss of consciousness and coma are the other manifestations. HCS deficiency in a newborn presenting as collodion membrane with severe metabolic acidosis has been described. The presence of severe metabolic acidosis in a neonate with collodion membrane or ichthyosis may be considered as an indication for evaluation of HCS deficiency.[47] Neonatal biotin deficiency is fatal if not treated or diagnosed early.[47,48]

Diagnosis: The diagnosis is established by estimation of urinary organic acid excretion. 3-hydroxyisovaleric acid is the major metabolite excreted in biotin deficiency. Low carboxylase activities can be confirmed by enzyme assays. Poor incorporation of biotin into the carboxylases, and low transfer of biotin by the holocarboxylase synthetase enzyme are demonstrated by fibroblast analysis.[49]

Treatment: The dosage of biotin is usually high 20- 40 mg/day and sometimes 100 mg/day may be required. The signs and symptoms resolve completely following biotin therapy. Treatment with biotin gradually improves the biochemical abnormalities in blood and in cerebrospinal fluid (CSF), corrects the carboxylase enzyme activities, and provides clinical stability and a normal neurodevelopmental outcome. The biotin supplementation is required for life long.[48,49]

E. Kasabach-Merritt phenomenon

Kasabach-Merritt phenomenon (KMP) is a clinical syndrome of thrombocytopenic coagulopathy in association with vascular tumor. It is usually seen in infants lesser than 3 months of age. It is caused by sequestration of platelets, accumulation of activated coagulation factors and local fibrinolysis in a vascular tumor. The common underlying vascular tumors are tufted angioma and Kaposi's hemangioendothelioma.[50] The latter is almost always associated with KMP.[51]

Clinical features: The onset of Kasabach-Merritt phenomenon is heralded by a sudden and rapid increase in the volume of the tumor, a change to a deep violet color and by the appearance of ecchymosis. These most commonly occur on the trunk, neck and proximal parts of the limbs. The rapidly enlarging tumor may compress the vital structures and the thrombocytopenia may cause acute hemorrhage in various internal organs (DIC).[52] In an infant, any rapidly growing vascular tumor with or without ecchymosis should be evaluated for both cutaneous and visceral KMP. The disease causes mortality in 20-30% of patients.[53]

Diagnosis: Laboratory evidence of consumptive coagulopathy (prolonged prothrombin and activated partial thromboplastin time, reduced fibrinogen, and elevated D-dimer levels) and thrombocytopenia along with clinical course of the tumor confirm the diagnosis of KMP. Destructive vascular lesions on MRI aid in the diagnosis of visceral KMP.[51]

Treatment: A combination therapy is necessary as no single treatment modality is universally effective. Early initiation of oral corticosteroid therapy with prednisolone at 2-5 mg/kg/day is effective in increasing the platelet count and decreasing the size of the tumor. Prednisolone is ineffective if the coagulopathy is very severe. Vincristine in the dose of 1-1.5 mg/m^2/week as slow intravenous infusion for 7 weeks is also effective and can be used as first line of treatment.[54] Surgical

excision with prior platelet transfusion is recommended for well circumscribed, small and superficial tumor. Embolization is an extremely valuable treatment which results in a rapid and permanent reversal of coagulopathy. Platelet transfusion is indicated prior to surgical procedures including embolization to achieve hemostasis. Otherwise, it is indicated only when there is severe bleeding. Supportive therapy with fresh frozen plasma and cryoprecipitate may be useful.[51]

2. DERMATOSES ASSOCIATED WITH MEDICAL OR SURGICAL EMERGENCIES

A. Purpura fulminans

Purpura fulminans (PF) is an acute syndrome characterized by rapidly progressive skin necrosis and disseminated intravascular coagulation (DIC).[55]

Hereditary (congenital) protein C deficiency manifesting at birth is caused by homozygous or compound heterozygous mutations in PROC gene resulting in absolute deficiency of protein C. The condition is inherited as autosomal recessive disorder.[56]

Acute infectious PF in neonates is commonly caused by group B streptococcal septicemia. Gram negative septicemia due to *Escherichia coli* and *Enterobacter*, and staphylococcal septicemia may also cause PF in neonates.[57]

Clinical features: PF due to homozygous Protein C deficiency manifests from 2 h to 2 weeks after birth. The life threatening thrombotic event involves skin, central nervous system, eyes and kidney.[58] The clinical manifestation is characterized by sudden onset of widespread purpura commonly involving extremities, though any parts of the body may be affected. Soon the lesions enlarge and vesiculate forming hemorrhagic bullae. Subsequently the skin undergoes necrosis resulting in black eschar formation. The margins of the lesions are well demarcated, erythematous and indurated. The cutaneous manifestations culminate in DIC with associated internal bleeding.[59] In acute infectious PF, the characteristic lesions occur in a neonate with associated signs of septicemia.[60]

Diagnosis: The estimation of Protein C activity is a reliable test to diagnose hereditary Protein C deficiency. In homozygous form, the Protein C activity is markedly decreased to <0.02 IU/ml (Lower normal limit, 0.67-0.72 IU/ml). The levels above 0.03-0.05 IU/ml are sufficient to ameliorate the symptoms of PF.[61] Increased D-dimer levels, low fibrinogen, increased fibrinogen degradation products (FDP), low platelet count, and prothrombin fragment 1.2 indicate DIC. These parameters along with clinical response are useful in monitoring and optimizing Protein C therapy.[62] Relevant investigations as indicated by clinical features should be done to know the involvement of central nervous system, kidney and eyes. In acute infectious PF, blood culture should be done to identify the causative organism for septicemia.

Treatment: Irrespective of underlying cause, the neonatal PF must be diagnosed and treated rapidly and aggressively [Table 8].[61] Acute infectious PF can be managed with immediate heparinization, and infusion of FFP (15 ml/kg every 12 h) along with the resuscitation measures for septic shock.[57] Prostacycline, a thromboxane A_2 antagonist, in the initial dose of 5 ng/kg/min, then increased and maintained at 15 ng/kg/min for 48 h has been used successfully in the treatment of acute infectious PF. It has beneficial effects on pulmonary hypertension and thromboxane-induced platelet aggregations which occur in septicemia.[63] The mortality is almost 100% in untreated hereditary neonatal PF,[61] whereas acute infectious PF is associated with 50% mortality.[60]

B. Kawasaki disease

Kawasaki disease is a systemic vasculitis predominantly affecting younger children less than 4 years of age with peak age of onset of 6 to 11 months.[64] The disease is rare in infants below 3 months constituting only 1.7% of total cases.[65] However, there are few reports of neonatal KD. The youngest ever patient is a 2-week-old infant who presented with classical KD.[66] A recent survey suggests that the incidence of KD is rising in India.[67]

Clinical features: Neonatal KD is characterized by atypical presentations and a rapid and severe coronary artery involvement. The atypical presentations include low incidence of conjunctivitis, skin rash and extremity changes, and low C-reactive protein.[68] Lack of awareness of neonatal occurrence of KD is responsible for delay in diagnosis. Classical presentation of KD such as high-grade fever not relieved by antipyretics, generalized erythematous maculopapular rash, bilaterally symmetrical non-pitting edema of hands and feet, fissuring of lips, reddish discoloration of tongue and non-purulent

Table 8: Treatment of neonatal purpura fulminans (Congenital Protein C deficiency)

Drug	Dosage	Duration	Lab monitoring
Plasma derived Protein C concentrate	60-80 ml/kg slow IV bolus every 6 h not exceeding 0.2 ml/min in children <10kg	Till complete* resolution of skin lesions and coagulopathy	Protein C activity: Post- infusion- 1.0 IU/ml Before infusion- 0.25 IU/ml DIC parameters
Fresh frozen plasma	20-30 ml/kg IV every 6 h	Same as above	DIC parameters
Activated human† protein C	20 µg/kg/h intravenous infusion	96 h (sepsis) 10 h (Protein C deficiency)	DIC parameters
Warfarin	Slowly initiated overlapping with Protein C concentrate and titrated to 0.3mg/kg	Long term	International normalized ratio-2.5

DIC: Disseminated intravascular coagulation, *After stabilization, the dosage interval is reduced to twice daily and continued till the desired INR is achieved with warfarin, †Approved only in adults with sepsis. However, it has been used effectively in congenital Protein C deficiency in a neonate, and acute infectious PF in 5-month-old infant

bilateral bulbar conjunctivitis has been reported.[64] Mortality due to KD occurs between 2 and 12 weeks after the onset of illness, and is usually secondary to coronary aneurysms and their complications. Improvement in the early diagnosis and institution of appropriate therapy in the acute phase resulted in decline in mortality from 1-2% (pre IVIg era) to 0.08% (IVIg era).[67] Similarly the coronary artery disease declined from 20-25% to 3-5%.[69]

Diagnosis: Clinical diagnosis of KD in a neonate requires a high index of suspicion. The diagnosis is confirmed by echocardiography. Aneurysmal dilatation of coronary arteries and dysfunction of valves are the common findings on echocardiography. A repeat echocardiography is obtained at 2-3 weeks and again at 6-8 weeks following the onset of illness. Acute phase reactants like C- reactive protein should also be monitored to assess the acute inflammatory phase.[67]

Treatment: The mainstay of treatment is intravenous immunoglobulin (IVIg) along with high dose aspirin. The maximum benefit of IVIg in preventing coronary artery dilatation is seen when it is administrated within first 10 days of illness. The usual dosage schedule is IVIg 2g/kg as single dose and aspirin 30-50 mg/kg/day in three divided doses until the fever subsides (around 14th day), then 10-30 mg/kg/day till complete disappearance of acute inflammation (usually 6-8 weeks).[67] Not all patients respond to single dose of IVIg. Such resistant patients require second dose of IVIg (2g/kg).[69] Persistence of fever, persistently elevated acute phase reactants (systemic inflammation) and new onset dilatation of coronary arteries are indicators of second dose of IVIg.[68] Newer drugs like infliximab (5 mg/kg over 2 h) have been investigated for safety and tolerability in pediatric patients (youngest, 2 months; oldest 5 years) with KD. Infliximab was found to be safe but the efficacy still needs to be addressed.[69]

C. Sclerema neonatorum

Sclerema neonatorum is regarded as end stage of severe systemic disease. Sclerema is an uncommon, life-threatening condition, usually of newborns, with a case-fatality rate ranging from 50 to 100%. Hypothermia, severe malnutrition, septic shock, serum ammonia and C- reactive protein levels are considered as predictors of mortality.[70]

Clinical features: The disease manifests during first 1-2 weeks of life in severely debilitated term and preterm infants. It is characterized by sudden onset of diffuse hardening of skin initially involving the lower legs and later spreading to thighs, buttocks, trunk, and cheeks. The palms, soles and genitalia are usually spared. The skin is cold, smooth, hard and bound down.[71] Neonates with diarrhoea and sepsis presenting with hypothermia, lower serum protein and prealbumin are prone to develop sclerema.[72]

Diagnosis: The diagnosis is mainly based on characteristic clinical features. Histology of the skin biopsy shows thickening of the trabeculae supporting the subcutaneous adipose tissue and a sparse inflammatory infiltrate of lymphocytes, histiocytes and multinucleate giant cells. The laboratory abnormality may include electrolyte disturbances, hypoglycemia and azotemia.[71]

Treatment: Supportive therapy such as maintenance of body temperature, correction of fluid and electrolyte disturbances, and nutritional supplementation may sometimes reduce the inevitable mortality. Systemic corticosteroids, exchange transfusion and antibiotics have improved the survival rate in infants with sepsis.[71]

CONCLUSION

With the availability of effective drugs and monitoring facilities, and awareness of need for immediate care, there has been a significant decline in the fatality rate associated with neonatal dermatological emergencies. Knowledge of clinical presentations, rapid diagnostic methods, emergency care and monitoring the progress of the disease help in comprehensive multidisciplinary care of neonates with these disorders.

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