Pediatric Bullous Disease

Lehigh Valley Health Network/PCOM
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Overview

- Briefly review the various categories of pediatric bullous dermatoses
- Discuss some of the most common, board relevant and life threatening pediatric bullous diseases
  - Clinical features
  - Pathogenesis
  - Histopathology and immunofluorescence findings
- Updates on new studies and treatment options
Pediatric Bullous Disease

- **Infectious**
  - Staphylococcal scalded skin syndrome
    - Bullous impetigo
  - Bullous tinea, eczema herpeticum
  - Blistering distal dactylitis
  - Bullous scabies
  - Varicella virus, herpes simplex virus

- **Infectious or medication induced**
  - Stevens Johnson Syndrome & Toxic epidermal necrolysis

- **Hereditary**
  - Epidermolysis Bullosa (EB)
    - Subtypes (simplex, junctional, dystrophic)
  - Kindler syndrome
  - Bullous CIE- Epidermolytic Hyperkeratosis
  - Incontinentia Pigmenti

- **Autoimmune**
  - Linear IgA bullous dermatosis of childhood
  - Dermatitis herpetiformis
  - Bullous systemic lupus erythematosus
  - Epidermolysis bullosa acquisita
  - Bullous pemphigoid (BP)
  - Pemphigus (folicaceous, vulgaris, drug induced PNP, IgA)
  - Herpes gestionis

- **Miscellaneous**
  - Contact dermatitis
  - Phytodermatitis
  - Phytophotodermatitis
  - Bullous Erythema Multiforme
  - Bullous Fixed drug
  - Bullous Mastocytosis
  - Porphyrias
Pediatric Bullous Disease

- Blisters- Fluid filled lesions on skin or mucous membranes
  - Vesicles <1cm (Hurwitz)
  - Bullae ≥1cm

- Nikolsky sign
  - Spread of blister with lateral pressure

- Asboe-Hansen sign
  - Spread of blister with perpendicular pressure

Infectious Bullous Disease

- Staphylococcal Scalded Skin Syndrome (SSSS)
  - Bullous impetigo
- Bullous tinea, eczema herpeticum
- Blistering distal dactylitis
- Bullous scabies
- Varicella virus, herpes simplex virus
Staphylococcal Scalded Skin Syndrome (SSSS)

Clinical Presentation

• Neonates and young children
  – Irritability, fever, malaise, poor feeding
  – Due to infection of conjunctivae, nares, perioral region or perineum
  – Generalized erythema then fragile sterile blisters of flexures
    • Positive Nikolsky sign
  – Perioral radial fissuring is common
    • No mucous membrane involvement
http://pediatrics.ucsf.edu/blog/unknowns-part-2#.VcZGCbqdLzI

Pathogenesis

- Toxin mediated disease produced by *S. aureus* type 71 of phage group II
  - Exfoliative toxins ETA and ETB
  - Targets desmoglein 1 in superficial epidermis (stratum granulosum)
    - Bullous impetigo localized form
  - Poor renal clearance and low titers of antibodies

Diagnosis

- Bacterial culture from pustule or site of colonization (nares, nasopharynx, perineum)
  - Blisters are typically sterile
SSSS Treatment

- Eradicate toxin producing bacteria
  - Anti-staphylococcal antibiotics
    - SSSS requires systemic therapy
      - Penicillinase resistant penicillin, 1st or 2nd generation cephalosporins, clindamycin, vancomycin
    - Bullous impetigo may be treated topically or systemically

- Studies suggested fresh frozen plasma or IVIG to neutralize exfoliative toxin
Stevens Johnson Syndrome (SJS) & Toxic Epidermal Necrolysis (TEN)

Clinical presentation

• Life threatening
  – Older children and adults

• Prodromal period 1-14 days
  – High fever, malaise, poor feeding, arthralgias, cough
  – Mucosal symptoms may precede skin findings by 1-2 days

• Painful erythematous or purpuric macules, develop dusky color and bullae become confluent

• Full thickness epidermal detachment
  • Positive Nikolsky and Asboe-Hansen signs

• Visceral involvement and lab abnormalities
SJS/TEN

SJS/TEN

Spectrum of disease based upon surface area of epidermal detachment

SJS

SJS/TEN overlap

TEN

<10%

10-30%

>30%

Surface area of epidermal detachment
Detached epidermis

SJS — Stevens-Johnson syndrome
TEN — Toxic epidermal necrolysis

• Lower chance of mortality
• 70% experience morbidity with long term sequelae

SCORTEN is a scoring system that better predicts morbidity in pediatric patients:
- Days on mechanical ventilation
- Infectious complications

<table>
<thead>
<tr>
<th>SCORTEN</th>
<th>Points</th>
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<tbody>
<tr>
<td>Age &gt;40 years</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate &gt;120 bpm</td>
<td>1</td>
</tr>
<tr>
<td>Cancer or hematologic malignancy</td>
<td>1</td>
</tr>
<tr>
<td>BSA involved on day 1 above 10%</td>
<td>1</td>
</tr>
<tr>
<td>Serum urea level (&gt;10 mmol/l)</td>
<td>1</td>
</tr>
<tr>
<td>Serum bicarbonate level (&lt;20 mmol/l)</td>
<td>1</td>
</tr>
<tr>
<td>Serum glucose level (&gt;14 mmol/l)</td>
<td>1</td>
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<table>
<thead>
<tr>
<th>SCORTEN</th>
<th>Mortality rate (%)</th>
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<tbody>
<tr>
<td>0–1</td>
<td>3.2</td>
</tr>
<tr>
<td>2</td>
<td>12.1</td>
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<tr>
<td>3</td>
<td>35.8</td>
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<tr>
<td>4</td>
<td>58.3</td>
</tr>
<tr>
<td>&gt;5</td>
<td>90</td>
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</table>

SJS/TEN histopathology

SJS/TEN

• Pathogenesis
  – SJS- *Mycoplasma pneumoniae* infection and medications
  – TEN- medications (antibiotics & anticonvulsants in children)
  – Fas-Fas ligand mediated keratinocyte apoptosis

• Treatment
  – Discontinue medications, treat underlying infection, supportive care, wound care and prevention of infection
    • IVIG
    • Systemic corticosteroids
    • Anti-TNF alpha
    • Cyclophosphamide
    • Cyclosporine

• Retrospective study by Ahluwalia et al demonstrated corticosteroids as monotherapy or with IVIG result in shorter length of stay and fewer febrile days in mycoplasma-associated SJS
Hereditary Bullous Diseases

- Epidermolysis Bullosa
  - Simplex
  - Junctional
  - Dystrophic
- Kindler syndrome
- Congenital Ichthyosiform Erythroderma
  - Bullous and non-bullous
- Incontinentia Pigmenti
Epidermolysis Bullosa (EB)

Group of >30 inherited blistering disorders

- Blisters and scarring from minor trauma due to skin fragility from inherited structural defects
- **EB Simplex**
  Split: Epidermal Basal Layer
- **Junctional EB**
  Split: Basement Membrane (Lamina Lucida)
- **Dystrophic EB**
  Split: Dermal (Sublamina Densa)
- **Kindler syndrome**

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Epidermolysis Bullosa

A: EBS-localized (Weber–Cockayne)

B: Dominant DEB (Cockayne–Touraine)

C: Recessive DEB-severe generalized

D: Recessive DEB-severe generalized

E: EBS Dowling-Meara

F: EBS Dowling-Meara

# EB Simplex

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Inheritance</th>
<th>Defective Protein</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBS-Dowling-Meara (herpetiformis)</td>
<td>AD</td>
<td>K5/K14</td>
<td>Onset at birth, mucosal membrane involvement, nail dystrophy, scarring, early death</td>
</tr>
<tr>
<td>EBS-localized (Weber-Cockayne)</td>
<td>AD</td>
<td>K5/K14</td>
<td>Onset childhood, palmoplantar bullae/erosions, heals without scarring</td>
</tr>
<tr>
<td>EBS-other generalized (Koebner)</td>
<td>AD</td>
<td>K5/K14</td>
<td>Generalized bullae at birth, PPL, nail dystrophy, heals without scarring</td>
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<tr>
<td>EBS Muscular Dystrophy</td>
<td>AR</td>
<td>Plectin</td>
<td>Widespread bullae at birth, muscular dystrophy, scarring, early death</td>
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<tr>
<td>EBS Mottled Pigmentation</td>
<td></td>
<td></td>
<td>Resembles localized and generalized EBS, reticulated hyperpigmentation over trunk</td>
</tr>
<tr>
<td>Subtype</td>
<td>Inheritance</td>
<td>Defective Protein</td>
<td>Clinical</td>
</tr>
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<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Herlitz</td>
<td>AR</td>
<td>Laminin 332 (5)</td>
<td>Nonhealing exuberant granulation tissue, enamel defects, mucosal involvement, early death</td>
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<tr>
<td>Non-Herlitz</td>
<td>AR</td>
<td>Laminin 332 (5) or BPAG2 (Type XVII collagen)</td>
<td>Heals with atrophic scars, widespread bullae at birth, scarring alopecia</td>
</tr>
<tr>
<td>JEB with Pyloric Atresia</td>
<td>AR</td>
<td>Alpha 6 beta 4 integrin</td>
<td>Severe congenital blistering, pyloric atresia, hydrenephrosis, mucosal erosions, aplasia cutis congenita, malformed ears</td>
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# Dystrophic EB

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<th>Defective Protein</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recessive DEB-severe generalized (Hallopeau-Siemens)</td>
<td>AR</td>
<td>Type VII collagen</td>
<td>Severe widespread bulla at birth, heals with atrophic scarring, “mitten deformity”, mucosal scarring, esophageal involvement, high risk of SCCs</td>
</tr>
<tr>
<td>Recessive DEB, other</td>
<td>AR</td>
<td>Type VII collagen</td>
<td>Less severe than the HS variant, skin changes localized to acral bone prominences</td>
</tr>
<tr>
<td>Dominant DEB (Cockayne-Touraine)</td>
<td>AD</td>
<td>Type VII collagen</td>
<td>Bullae mainly over extremities, heals with scarring, nail dystrophy</td>
</tr>
<tr>
<td>Pasini Variant (DDEB-P)</td>
<td>AD</td>
<td>Type VII collagen</td>
<td>Similar to Cockayne subtype + white perifollicular papules</td>
</tr>
</tbody>
</table>

Epidermolysis bullosa acquisita (EBA) – autoimmune T-cell mediated and neutrophilic blistering disease

Type VII collagen with linear IgG +/- C3 in sublamina densa (U-serrated pattern)

- Subtypes: inflammatory, non-inflammatory & cicatricial pemphigoid
# Kindler Syndrome

<table>
<thead>
<tr>
<th>Name</th>
<th>Inheritance</th>
<th>Defective Protein</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kindler Syndrome</td>
<td>AR</td>
<td>Kindlin-1 (mediates anchoring between anchoring fibrils and ECM) due to mutation in KIND1 (FERMT1)</td>
<td>Acral blistering during infancy +/- digital webbing, PPK, photosensitivity, progressive poikiloderma “cigarette paper”atrophy, gingivitis, colitis, stenoses, ectropion</td>
</tr>
</tbody>
</table>


- Paller et al. Harwitz Clinical Pediatric Dermatology a Textbook of Skin Disorders of Childhood and Adolescence, 2011.
EB

Diagnosis
• Genetic analysis
• Transmission electron microscopy
• Immunofluorescence antigen mapping (IFM)

Treatment
• Avoidance of mechanical trauma
• Preventing infections
• Non-adherent dressings
  • Prevent “mitten deformity” (pseudosyndactyly) in DEB
  • Petrolatum-impregnated gauze, soft silicone dressings
• Biopsy non-healing ulcers to exclude SCC
• Multidisciplinary approach

Mitten deformity

New Therapies Dystrophic EB

- Gene therapy
  - Viral vector used to insert functional collagen into skin
- Cell-based therapy
  - Intradermal injections of allogenic fibroblasts used to generate new collagen
- Protein therapy
  - Recombinant collagen produced in vitro is injected into blistering skin
- Bone marrow derived stem cell transplantation
  - Donor cells localize to skin and Type VII collagen deposition at DEJ
Autoimmune Bullous Diseases

- Linear IgA bullous dermatosis
- Dermatitis herpetiformis
- Bullous systemic lupus erythematosus
- Epidermolysis Bullosa Acquisita
- Bullous pemphigoid
- Pemphigus (foliaceous, vulgaris, PNP, drug-induced)
Linear IgA Bullous Dermatosis (LABD)

Chronic bullous disease of childhood

- **Clinical Presentation**
  - Tense, clear or hemorrhagic bullae
    - lower trunk, thighs & groin
  - Annular or rosette-like lesions with sausage-shaped blisters
  - Annular erythema with blisters
    - “Crown of jewels”

LABD Pathogenesis

- Immune-mediated subepidermal blistering disease in both adults and children
  - Idiopathic, autoimmune disorders, malignancy
  - Medications: vancomycin, amoxicillin-clavulanate, TMP-SMX

- Linear IgA deposits in two distinct patterns:
  - Classic
    - IgA antibodies to 97-kDa and/or 120 kD fragment of BP180
    - Split in the lamina lucida
  - Recently described

*Type VII Collagen Is the Major Autoantigen for Sublamina Densa–Type Linear IgA Bullous Dermatosis*

*Journal of Investigative Dermatology (2015) 135, 626–629; doi:10.1038/jid.2014.381; published online 23 October 2014*
LABD Histopathology and DIF

H&E: Subepidermal bullae with edema of adjacent dermal papillae and dermal infiltrate of neutrophils, eosinophils, mononuclear cells

DIF: linear IgA along DEJ
IIF: Epidermal side of salt split skin

LABD Treatment

- Spontaneous remission often occurs within months-years
  - typically by puberty
- Dapsone
  - Clinical improvement 48-72 hours
- Oral corticosteroids
- Antibiotics: dicloxacillin, erythromycin, tetracycline (age >9), trimethoprim/sulfamethoxazole
- Refractory: mycophenolate mofetil, azathioprine, IVIG
Dermatitis Herpetiformis (DH)

- DH is the specific cutaneous manifestation of celiac disease
  - Sensitivity to gluten found in wheat, barley, and rye
    - Gliaden soluble fraction
    - >90% of patients with DH have evidence of gluten sensitive enteropathy
    - 20% have intestinal symptoms of celiac disease
- Genetic association with HLA-DQ2 and DQ8
**Dermatitis Herpetiformis (DH)**

- Symmetric grouped vesicles or herpetiform polymorphic lesions
  - Extensor surfaces
  - Knees, elbows, sacral region, shoulders, buttocks, neck, face & scalp
- Intensely pruritic
  - Associated diseases
    - Hashimoto’s thyroiditis
    - Insulin dependent diabetes
    - Enteropathy associated T-cell lymphoma
- IgA autoantibodies to tissue transglutaminase (endomysial)
  - Form complexes in the papillary dermis with epidermal transglutaminase-3
DH Clinical Features

DH Histopathology and DIF

H&E: subepidermal vesicles and blisters with accumulation of neutrophils at the papillary tips

DIF: Granular or fibrillar IgA at the tips of the dermal papillae, along BMZ


DH Treatment

- Gluten free diet
- Dapsone
  - sulfasalazine, sulfapyridine, sulfamethoxypyridazine
- Superpotent topical corticosteroids
- Systemic corticosteroids or antihistamines for pruritis
- Case reports:
  - topical dapsone, cyclosporin A, azathioprine, colchicine, heparin, tetracyclines, nicotinamide, mycophenolate mofetil, and rituximab
DH Potential New Therapies

• Prevention
  – Late introduction of gluten to infants with first degree relatives with celiac disease

• Enzyme therapy
  – Supplemental bacterial-derived peptidases may promote digestion of gluten proteins
    • ALV003, is currently in clinical trials and has shown promising safety and efficacy data.
  – Pretreatment of foods with peptidases to decrease gluten content
DH Potential New Therapies

• **Immunomodulatory strategies**
  – Selective inhibition of TTG in the small intestine to counter the immunotoxic response to dietary gluten

• **Correction of the intestinal barrier defect**
  – An investigational agent, larazotide acetate, a zonulin inhibitor, decreases intestinal permeability abnormalities and exposure to dietary gluten
Bullous Systemic Lupus Erythematosus (BSLE)

Clinical presentation
- Recurrent blistering disease
- Pruritic vesicles and tense bullae in patients with SLE
- Sun exposed sites
- 30% have mucosal lesions
- Young African American women & adolescents

Pathogenesis:
- Circulating antibodies to type VII collagen (same as EBA)
  - HLA-DR2 positive
Bullous SLE


Bullous SLE Histopathology

H&E: Subepidermal blister with neutrophil predominant inflammation

DIF: “full house” continuous granular pattern at BMZ of IgG, IgM, IgA, C1q and/or C3
- U-serrated pattern

IIF: Dermal side of salt split skin

BSLE Treatment Update

- Review article by Duan et al in the Journal of Immunology Research 2015 on the treatment of BSLE:
  - Dapsone resulted in dramatic response
    - Methotrexate
    - Prednisolone
    - Colchicine
    - Azathioprine
    - Cyclophosphamide
    - Mycophenolate mofetil
    - Rituximab

- Prognosis:
  - Determined largely by visceral manifestations of SLE
  - Good response to dapsone correlates with better prognosis
Summary

• Many diseases present with blisters and bullae in the pediatric population

• Diagnosis is made based on thorough clinical history, physical exam, biopsy, immunofluorescence findings and/or serology

• Studies to further delineate pathogenesis and treatment options to improve patient outcomes
References

References


References


Thank you!

- AOCD
- Stephen Purcell, D.O.
- Tanya Ermolovich, D.O.

- Co-residents
- LVHN
- ADA