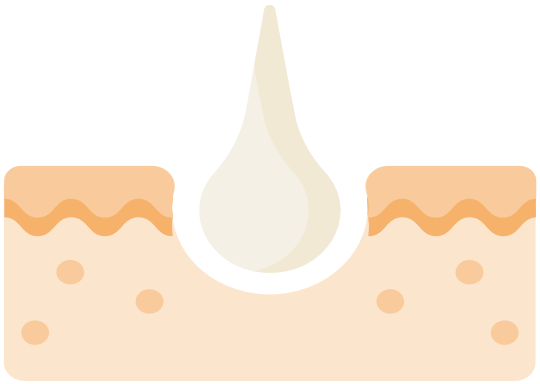

Blistering Disorders

(Blistering Disorders & Pemphigus Vulgaris)

Objectives:

1. To know the definition & classification of Blistering diseases
2. To recognize the primary presentation of different types of main blistering diseases
3. To understand the possible pathogenesis of the main types of blistering diseases
4. To have an overview about managements lines of these diseases

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Color index:

Important

Doctors Notes

Extra

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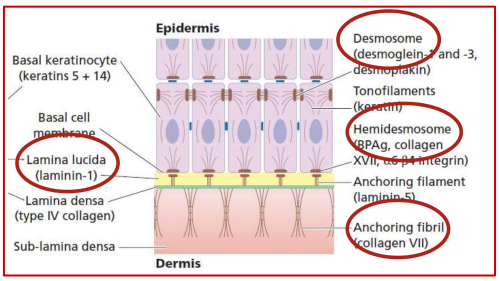
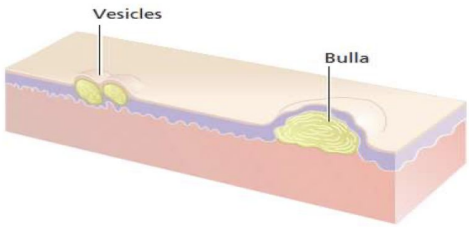
Editing file

Blistering Diseases

Definitions:

- A **vesicle** is an elevation that contains clear fluid (< 5cm in diameter).
- A **bulla** is Localized fluid collection " large vesicle" (> 5 cm in diameter).





It's VERY crucial that you read & understand the following:

★ **Desmosome:** facilitate adhesion between adjacent basal keratinocytes in the epidermis. Composed of: **Desmoglein-1** & **Desmoglein -3** & Desmoplakin.

★ **Hemidesmosome:** facilitate adhesion between basal keratinocytes and basement membrane (connects the epidermis to the dermis). Composed of: **BPAg** & **α6 β4 integrin** & collagen XVII.

★ These structures that form the desmosomes and hemidesmosomes are targeted by autoantibodies resulting in blistering disorders.

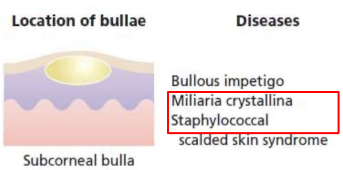
★ **Pemphigus group:** the antibodies will target **Desmoglein-1** and/or **Desmoglein -3** → level of separation is high, separation is between the basal keratinocytes themselves **(intra-epidermal)** resulting in "**flaccid** blisters" = easily ruptured.

★ **Pemphigoid group:** the antibodies will target **BPAg 1 and BPAg 2** → level of separation is under the basal keratinocytes **(subepidermal)** resulting in "**tense** blisters" = hardly ruptured.

CLASSIFICATION OF VESICULOBULLOUS DISEASES:

Subcorneal blister:

- Just beneath the stratum corneum. Very superficial.
- Have the thinner roofs
- Ruptured easily & leave an oozing denuded surface.
- Not caused by autoimmune diseases.

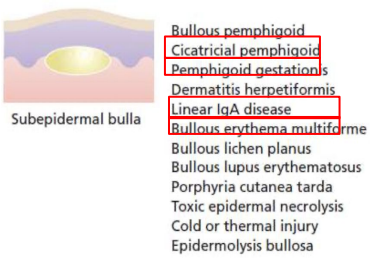


Intra-epidermal blister:

- within the prickle cell layer on the epidermis
- Have thin roofs
- Ruptured easily & leave an oozing denuded surface

Subepidermal blister blister:

- Between the dermis and epidermis
- Their roofs are relatively thick
- Tend to be tense
- May contain blood



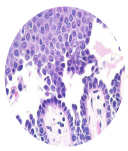
Blistering disorders:

- In Adults: the main group of blistering disorders is associated with autoantibody formation.
- In Children: Genodermatosis, (epidermolysis bullosa), associated mainly with mechanical defects in and around the basement membrane zone.

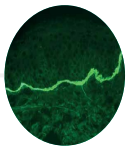
Blistering Diseases

Diagnostic test:

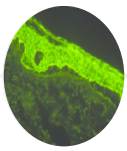
- **Accurate pathological diagnosis requires 2 biopsies; one is taken from a newly intact lesion and one perilesional (1 histopathology + 1 IF).**



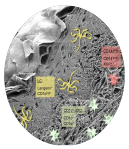
Routine histology
lesional sample in formalin



Direct immunofluorescence
Perilesional skin



Indirect immunofluorescence
patient's serum is added to specific substrates that express antigen of interest



Electron microscope
Used in Genodermatosis because it's not an autoimmune disease.

Blistering disorders:

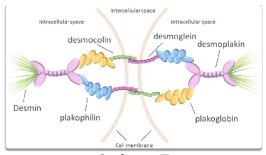
- In Adults: the main group of blistering disorders is associated with autoantibody formation.
- In Children: the main cause of blistering disorders is Genodermatosis (epidermolysis bullosa):
  - Epidermolysis Bullosa is a group of mechanobullous genodermatosis. Rare, present at birth or infancy. Range from localized relatively mild trauma induced blisters to life threatening/debilitating conditions
  - Diagnosis is made based on family history, clinical examination, light and electron microscopy

Autoimmune bullous disease

Loss of intraepidermal adhesion (pemphigus group)	Loss of subepidermal adhesion
I. Pemphigus vulgaris (PV): a. Classic b. Pemphigus vegetans	I. Pemphigoid: a. Bullous pemphigoid b. Cicatricial pemphigoid c. Pemphigoid gestationis
II. Pemphigus foliaceus: a. Classic b. Fogo selvagum c. Pemphigus erythematosus (Senear- Usher Syndrome)	II. Dermatitis herpatiformis
III. Drug induced pemphigus	III.linear IgA dusease: a. Of childhood b. Adult form
IV. Paraneoplastic pemphigus	
V. IgA pemphigus	IV. Epidermolysis bullosa aquisita

Blistering Diseases

1. Pemphigus group:



Structure of the Desmosome

Definition:

a group of disorders with loss of intraepidermal adhesion due to autoantibodies directed against proteins of the desmosomal complex that hold keratinocytes together

Disease	Type of immunoglobulin	Against…
Pemphigus vulgaris (PV)	IgG	Mucosal type → desmoglein 3 Mucocutaneous type → desmoglein 3 & desmoglein 1 (PV almost always starts in the mucus membrane thus the first target is always desmoglein 3 ± desmoglein 1)
Pemphigus foliaceus (PF)	IgG	Desmoglein 1 ONLY (purely cutaneous)
paraneoplastic pemphigus	IgG	plakin molecules in addition to autoantibodies against desmogleins

01 Pemphigus vulgaris:

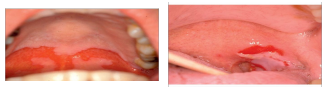
- Severe, potentially fatal disease with intraepidermal blister formation of the skin and oral mucosa caused by IgG autoantibodies against "desmogleins"

Epidemiology: The mean age of onset of disease is 50-60 years (disease of middle age unlike the pemphigoid group which is a disease of old age 80 y.o)

Pathogenesis:

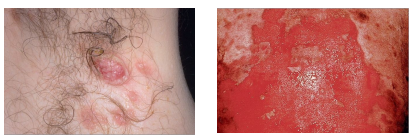
- Genetic predisposition: HLA-DRQ402- DQ0505
- IgG autoantibodies against desmoglein 3 (Dsg 3) and later desmoglein1(Dsg 1). The bound antibodies activate proteases that damage the desmosome, leading to acantholysis = floating cells.
- Serum antibody titer usually correlates with severity of disease and course

Clinical features:



Mucous membrane:

- lesions usually present as painful erosions
- Intact blisters are rare
- Sites: oral mucosa, vermillion lip, throat, esophagus, conjunctivae, nasal mucosa, vagina, penis, anus, labia
- Most common sites: buccal & palatine mucosa
- Vermillion lip -> thick fissured hemorrhagic crust
- throat ->hoarseness, difficulty swallowing
- 70%, anti-Dsg3 (Dsg 3 is the main desmoglein in mucosal surfaces)
- Always check the scalp when confronted with unexplained oral erosions



Skin:

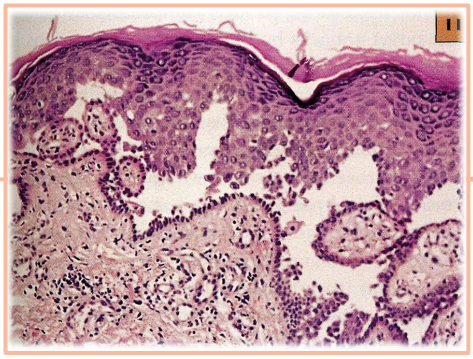
- Primary skin lesions of PV are flaccid, thin-walled, easily ruptured blisters They could arise on either normal-appearing skin or erythematous base
- The blisters are fragile and soon rupture to form painful erosions that ooze and bleed easily, later forming crusts
- Can become generalized
- Lesions that heal often leave hyperpigmented patches with NO scarring
- More generalized disease due to the development of IgG autoantibodies against Dsg1 which is present in the skin along with Dsg3

1. Pemphigus group:

01 Pemphigus vulgaris:

Pathology:

Intraepidermal blister formation due to loss of cell-cell adhesion of keratinocytes (acantholysis) **without** keratinocyte necrosis (unlike Stevens-Johnson syndrome which has keratinocyte necrosis)



Mild dermal perivascular infiltrates

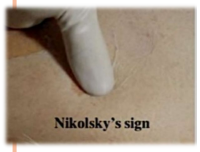
They maintain their attachment to the basement membrane via hemidesmosomes, this giving the appearance of " row of tombstones"

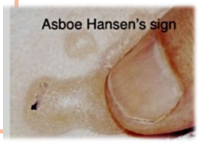
Diagnostic approach:

History (always ask medication Hx)

Physical examination (skin, mucous membranes, nails)

- Nikolsky sign à because of an absence of cohesion within the epidermis, its upper layers easily move laterally with slight pressure or rubbing in active patients with pemphigus
- Asboe-Hansen signà " bulla- spread phenomenon" – gentle pressure on an intact bulla forces the fluid to spread under the skin away from the site of pressure





Investigation

- skin biopsy: from lesional skin, intact vesicles if found
- DIF: from perilesional skin shows deposition of IgG (100%), C3 (80%)
- Indirect IF
- ELISA: to identify anti-Dsg3,1

Differential diagnosis:

When skin is involved:

- Bullous impetigo
- Dyskeratotic acantholytic disorders
- Hailey-Hailey
- Grover disease

When mucus membrane is involved:

- Denture intolerance
- Erosive candidiasis
- Chronic recurrent apothecary
- Erythema multiforme
- Erosive lichen planus
- Herpetic gingivitis

1. Pemphigus group:

01 Pemphigus vulgaris:

Treatment:

- **Systemic corticosteroids** are the mainstay of therapy for pemphigus and immunosuppressive agents are often used for their steroid sparing effect in order to reduce the side effects of the corticosteroids. In the Pemphigoid group the treatment is topical/oral. Not systemic.
- Prednisone at 1.0 mg/Kg/day (usually 60 mg/day) is a typical initial dosage
- The therapeutic effects are clinically estimated by the **number of new blisters per day** and the rate of healing of new lesions, and then the prednisone is gradually tapered

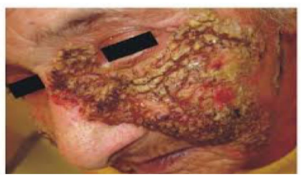
Immunosuppressive agents in combination with oral prednisone:

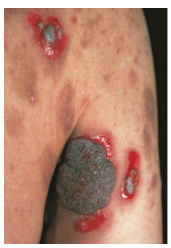
- Azathioprine
- Cyclophosphamide
- Mycophenolate mofetil
- Cyclosporine
- Pulse methylprednisolone
- IVIG
- Rituximab
- Extracorporeal photopheresis

Topical treatments:

- Topical corticosteroids
- Topical antibiotics
- Topical immunomodulators (e.g. topical tacrolimus)

02 Pemphigus vegetans:





Clinical Features:

- It's a vegetative variant of pemphigus vulgaris.
- Characterized by flaccid blisters that become erosion and then form **fungoid vegetations**, especially in **intertriginous areas, the scalp and face**
- **Early lesions start as pustules (rather than vesicles)**, then they soon progress to vegetative plaques

Treatment: same as pemphigus vulgaris

03 Pemphigus foliaceus:

- Is a form of pemphigus in which patients develop scaly, crusted cutaneous erosions often on an erythematous base
- Disease of middle-aged and older patients
- In this form of pemphigus they do not have mucosal involvement even with widespread disease u Lesions have a seborrheic distribution (face, scalp, and upper trunk).
- IgG autoantibodies against **desmoglein 1**
- More often drug induced than pemphigus vulgaris
- Patients with pemphigus foliaceus are not severely ill

1. Pemphigus group:

03 Pemphigus foliaceus:

Diagnostic approach:

History (always ask medication Hx)

Physical examination (skin, mucous membranes, nails)

- Nikolsky sign → present

Investigation

- DIF: from perilesional skin shows superficial deposition of IgG
- ELISA: to identify IgG antibodies against Dsg 1

Treatment

- Same as pemphigus vulgaris but usually more responsive to therapy
- Dapsone maybe helpful

04 Drug induced pemphigus:

Drugs that induce pemphigus can be divided into two groups:

Agents containing the sulfhydryl group:

- Penicillamine
- Captopril
- Piroxicam
- Penicillamine —> PF is seen more than PV, ratio 4:1
- Sulfhydryl group of these drugs interact with the sulfhydryl group of Dsg1 & Dsg 3 (acantholysis without antibody formation)

Agent without sulfhydryl group:

- Beta-blockers
- Cephalosporins
- Penicillins
- Rifampin
- Induce acantholysis via immune mechanism

- Most patients with drug-induced pemphigus go into remission after the offending drug is discontinued

1. Pemphigus group:

05 IgA Pemphigus:

Represents a group of autoimmune intraepidermal blistering diseases

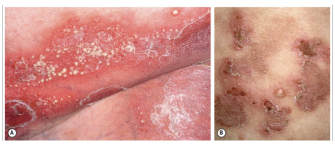
Presenting with:

1. **Vesicopustular** eruption
2. **Neutrophilic infiltration** of the skin
3. Circulating IgA autoantibodies against the cell surface of keratinocytes, but with **NO IgG autoantibodies**

Two distinct types:

1. Subcorneal pustular dermatosis (SPD)
2. Intraepidermal neutrophilic type (IEN)

- Both types present with flaccid vesicles or pustules that coalesce to form an **annular pattern with central crusting**
- **Sunflower-like configuration** of pustules is a characteristic sign of the IEN type
- Most common site: axilla, groin, trunk
- NO mucous membrane involvement
- Pruritus is a significant symptom



Diagnostic approach:

History

Physical examination (skin, mucous membranes, nails)

Investigation

- DIF: **IgA** autoantibodies directed against keratinocyte cell surface (not desmoglein)

Treatment

most cases are responsive to dapsone, if not ,corticosteroids & other immunosuppressive agents

06 Paraneoplastic Pemphigus:

- Associated with underlying neoplasms, both benign and malignant
- Most commonly associated neoplasms:
  - non- Hodgkin lymphoma
  - Chronic lymphocytic leukemia
  - Castleman's disease
  - Malignant and benign thymomas
- Not associated with common tumors such as adenocarcinomas and SCC

1. Pemphigus group:

06 Paraneoplastic Pemphigus:

Clinical features

The most constant clinical feature is the presence of intractable **stomatitis**

Stomatitis is usually the earliest presenting sign and, after treatment, is the one that persists and is extremely resistant to therapy

The Stomatitis consists of erosions and ulcerations that affect all layers of the oropharynx and characteristically extend onto the Vermilion lip

Pseudomembranous conjunctivitis à scarring, blindness Could also affect: esophagus, nasopharynx, vagina, labia, penis

cutaneous findings are "polymorphic":

- Erythematous macules
- Flaccid blisters and erosions (resembling pemphigus)
- Tense blisters (resembling pemphigoid)
- Erythema multiforme like lesions
- Lichenoid eruptions

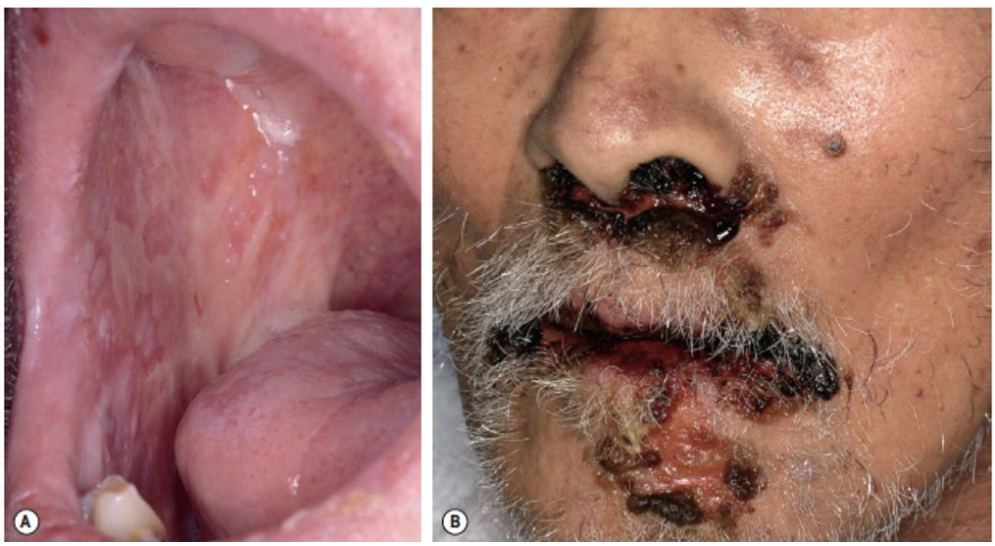
- Histology is rarely helpful

Treatment:

- Treat the underlying tumor Benign tumors: it may take 6-18 months to see complete resolution of lesions after excision of benign neoplasms Malignant tumors:

1. No consensus on a standard effective therapeutic regimen
2. Cutaneous lesions respond more rapidly than the stomatitis, which is refractory to treatment

- Prognosis of paraneoplastic pemphigus is poor due to its resistant nature to treatment



2. Pemphigoid Group:

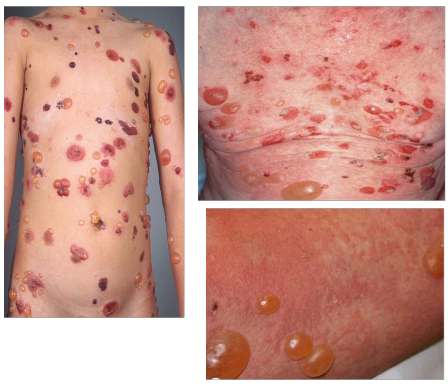
01 Bullous Pemphigoid (BP):

- The most common autoimmune subepidermal blistering disease, caused by autoantibodies to components of hemidesmosomes in the basement membrane zone (BMZ)
- Predominantly affects the elderly (80 years old)

Pathogenesis:

- Tissue-bound and circulating autoantibodies directed initial immune response, since it is transmembrane against two hemidesmosomal proteins:

1. BPAg 1“ BP230”
2. BPAg 2 “BP180” à is most likely to be more involved in the



- Drug-induced bullous pemphigoid:

1. Diuretics (furosemide)
2. D-penicillamine
3. Antibiotics (amoxicillin, ciprofloxacin)
4. Potassium iodide

Clinical features

BP is an **intensely pruritic** eruption with widespread blister formation

Blisters are stable and tense

Non-bullous phase: cutaneous manifestations are non-specific & polymorphic (pruritus, excoriations, eczematous, urticarial lesions)

In early stages and atypical variant: excoriated, eczematous, urticarial lesions
- always keep BP in mind when confronted with an elderly patient with persistent urticarial lesions

Mucosal involvement in < 20 %

Bullous phase: characterized by the development of vesicles and bullae on normal or erythematous skin along with urticarial lesions
- Bullae predominate on the flexural aspects of the limbs and the lower trunk

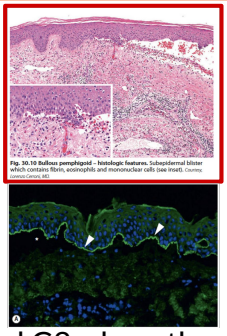
Diagnostic approach:

The diagnosis of BP is based upon the clinical presentation, histologic features, and positive findings on direct and indirect immunofluorescence

History

Physical examination

Investigations



- CBC & Differential —> ↑eosinophils
- ESR ↑
- IgE ↑ eosinophils, ESR & IgE are elevated in 60% of patients with BP
- Skin Biopsy:

• Non-bullous phase → non- specific, eosinophilic inflammatory infiltrate
• Bullous phase → subepidermal blister, accompanied by a dermal inflammatory infiltrate composed of eosinophils

- DIF → from perilesional, uninvolved skin, linear, continuous deposits of IgG and C3 along the epidermal basement membrane

2. Pemphigoid Group:

01 Bullous Pemphigoid (BP):

Treatment:

Mild /localized disease

1. Superpotent topical
2. Doxycycline
3. Oral corticosteroids
4. Dapsone
5. Topical immunomodulators

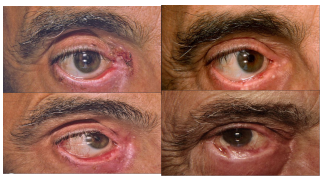
Extensive/persistent cutaneous disease

1. Superpotent topical corticosteroids
2. Oral corticosteroids
3. Azathioprine
4. Methotrexate

02 Cicatricial Pemphigoid:

- Is a chronic, autoimmune, subepithelial blistering disorder characterized by a predominant involvement of the external mucosal surfaces (mainly oral & conjunctival mucosa, but it could affect any mucosal site) and a tendency for **scarring**
- Patients > 65 years

Clinical features

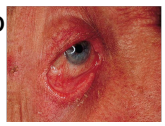


Oral mucosa → lesions less painful than PV

Esophagus & larynx → can develop strictures that may require surgery

Skin: only involved in 25% , face, scalp and upper trunk, atrophic scarring

Conjunctiva:
- affected in 75% of cases.
- Starts unilaterally, within 2 years beco bilateral
- adhesions, ectropion, corneal damage



Genitalia → narrowing of vaginal orifice, adhesions between glans & foreskin

Diagnostic approach:

History

Physical examination

Investigation

- DIF → IgG autoantibodies directed against the basement membrane of mucosa and/or skin
- Indirect IF → salt-split skin

Treatment

- Local therapy such as potent topical corticosteroids is crucial and, in some cases, maybe sufficient
- Oral lesions → topical steroids (mouthwash, topical
- preparations),
- Nasal, pharyngeal, esophageal disease → steroid sprays/ inhalers
- Ocular → topical / systemic cortecosteroids, ophthalmology referral
- Severe disease: Oral corticosteroids, Dapsone, Cyclophosphamide, Azathioprine, Surgical therapy

2. Pemphigoid Group:

03 Pemphigoid Gestationis:

- Synonym: « herpes gestationis » was previously termed herpes gestationis because the morphology of the blisters was similar to that of herpes, however it's not herpetic.
- A form of BP occuring during pregnancy
- Occurs in 1/10000-40000 pregnancies
- No maternal risk, no increase in birth defects. However, pregnancy complications and fetal death occurs in 15-30%
- Erythematous urticarial plaques, alone or with papules, vesicles, blisters in sub-epidermal area, erosions
- Intense pruritus
- Sites: abdomen, proximal extremities
- Rarely appears postpartum, resolve within 3 months
- Occasionally recurs with menses or ingestion of OCP, tends to be worse in next pregnancy
- The antibodies cross the placenta, the newborn can have blisters for a few weeks

Diagnostic approach:

History

Physical examination

Investigation

- Cbc & differential eosinophilia
- DIF & indirect IF

Treatment

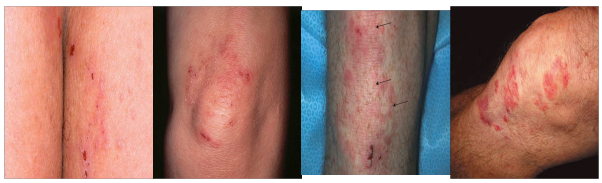
- Topical steroids
- Systemic steroids: avoid in 1st trimester
- Skin care to prevent infection
- Antihistamines for tx of pruritus

04 Dermatitis Herpetiformis:

- Pruritic vesicular disease caused by IgA autoantibodies directed against epidermal transglutaminase.
- DH is characterized by a granular IgA deposition at the basement membrane zone
- DH is a cutaneous manifestation of celiac disease and is associated with gluten sensitivity in virtually all cases
- DH and celiac disease are genetic disorders strongly associated with HLA-DQ2 genotype, in which IgA antiendomysial antibodies are directed against tissue transglutaminases (in the skin → epidermal transglutaminase)

2. Pemphigoid Group:

04 Dermatitis Herpetiformis:



Clinical features

- Sites : extensor surfaces of elbows/knees, sacrum, buttocks, scalp
- Spontaneous remissions may occur, but disease often lifelong
- Grouped 'herpetiform' papules/vesicles/urticarial wheals over an erythematous base, associated with intense pruritus, burning, stinging and **excoriations**

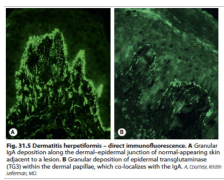
Diagnostic approach:

History

Physical examination

Investigation

- Skin biopsy: subepidermal blister, with neutrophilic microabscesses in the papillary dermis is the hallmark of the disease
- DIF → Granular deposits of IgA in the dermal papillae
- Indirect IF
- ELISA identifies IgA against transglutaminase in 80% of cases
- Jejunal Biopsy flattening of the villi

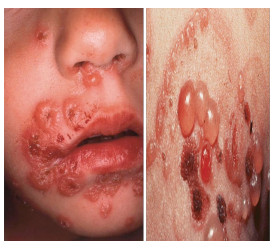


Treatment

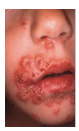
- Gluten free diet
- Dapsone

05 Linear IgA Disease:

- Subepidermal blistering disease caused by deposits of IgA along BMZ
- Linear IgA disease is characterized by on linear IgA deposition at the basement membrane
- Maybe identical to DH but WITHOUT GI involvement , or resemble BP
- Over 50% have mucosal involvement



The childhood form:



- is most frequently termed "Chronic bullous disease of childhood"
- Occurs in children "preschool", and resolves spontaneously
- Characterized by annular erythema and tense blisters **"crown of jewels"**
- They develop predominantly in flexural areas (lower trunk, thigh, groin), axillae, face, mucous membranes
- GI disease is rare
- Usually remits within 2-4 years

2. Pemphigoid Group:

05 Linear IgA Disease:

Diagnostic approach:

History

Physical examination

Investigation

- DIF → linear IgA deposits along the basement membrane
- Indirect IF

Treatment

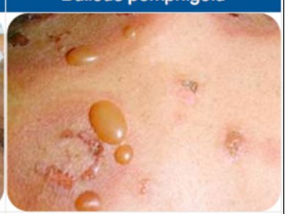
- Dapsone
- Sulfapyridine
- Antibiotics: tetracycline, erythromycin, dicloxacillin
- Antibiotics are a good treatment for the childhood form, and were found to be better than dapsone in this age group

Summary from doctor's slides:

Table 9.1 Distinguishing features of the three main immunobullous diseases.

	Age	Site of blisters	General health	Blisters in mouth
Pemphigus	Middle age	Trunk, flexures and scalp	Poor	Common
Bullous pemphigoid	Old	Often flexural	Good	Rare
Dermatitis herpetiformis	Primarily adults	Elbows, knees, upper back, buttocks	Itchy	Rare

	Nature of blisters	Circulating antibodies	Fixed antibodies	Treatment
Pemphigus	Superficial and flaccid	IgG to intercellular adhesion proteins	IgG in intercellular space	Steroids Immunosuppressives
Bullous pemphigoid	Tense and blood-filled	IgG to basement membrane region	IgG at basement membrane	Steroids Immunosuppressives
Dermatitis herpetiformis	Small, excoriated and grouped	IgG to endomysium and transglutaminase	IgA granular deposits in papillary dermis	Gluten-free diet Dapsone Sulfapyridine

	Pemphigus vulgaris	Bullous pemphigoid
Appearance		
Age	Younger	Older
Mucous membrane involvement	Yes	Rare
Autoantibodies	Against desmoglein 3	Against hemidesmosomes
Blister location	Intraepidermal (superficial)	Subepidermal (deep)
Blister quality	Flaccid, rupture easily	Tense and firm
Nikolsky's sign	Nikolsky **positive**	Nikolsky **negative**
Prognosis	Poor	Favorable