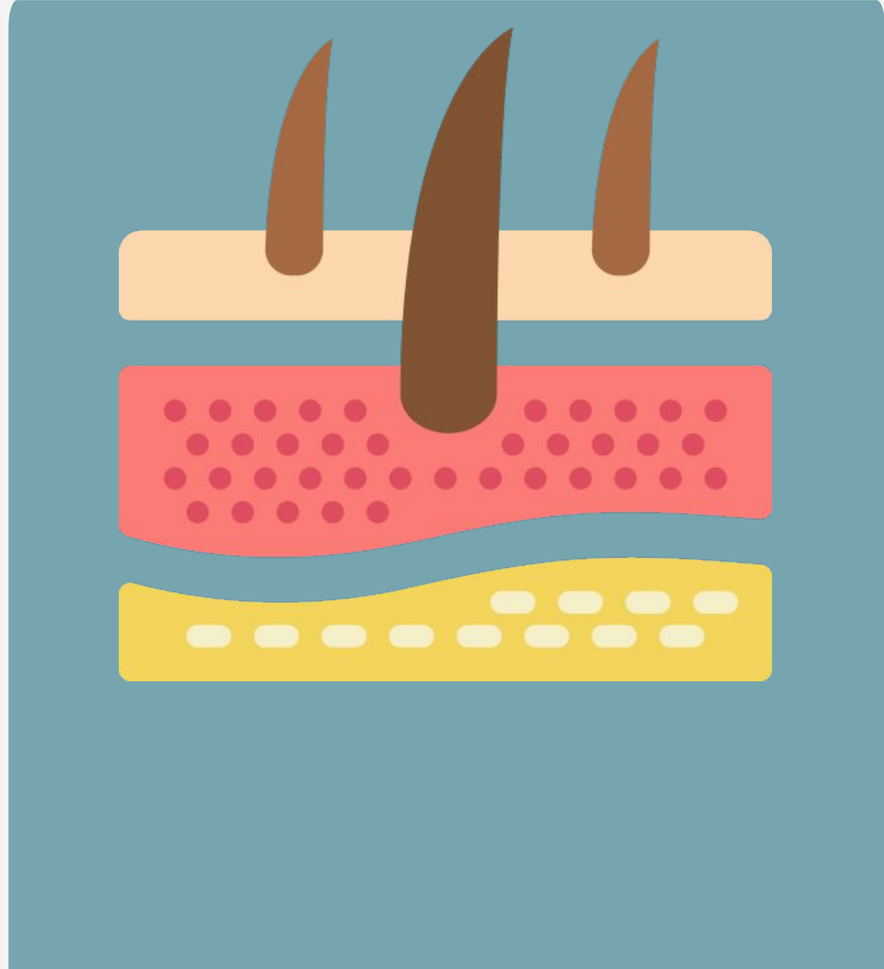


9-Blistering Disorders

Objectives:
Not given

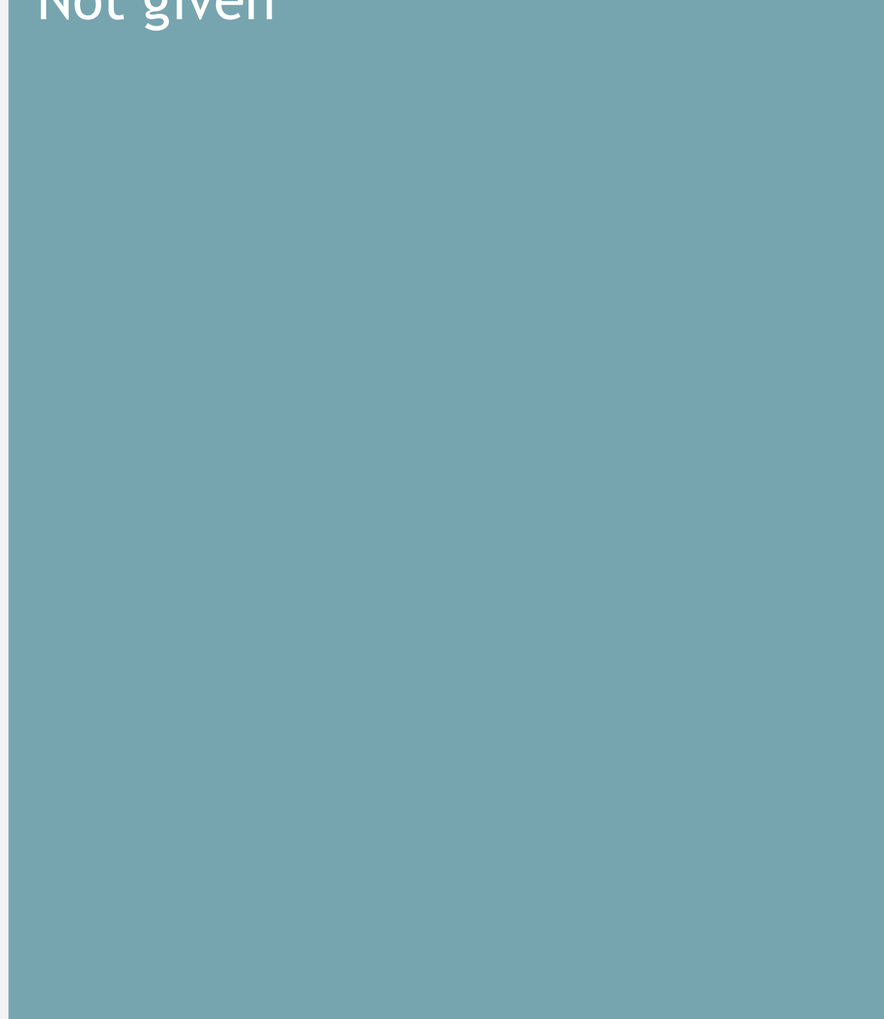
Done by: AlHanouf AlJaloud, Shahad AlTayash
Abduljabbar Alyamani, Abdulaziz Bin Dakhil
Revised by: Anas AlSaif, Rotana Khateeb

References: Doctor slides, Team 436

Color Index:

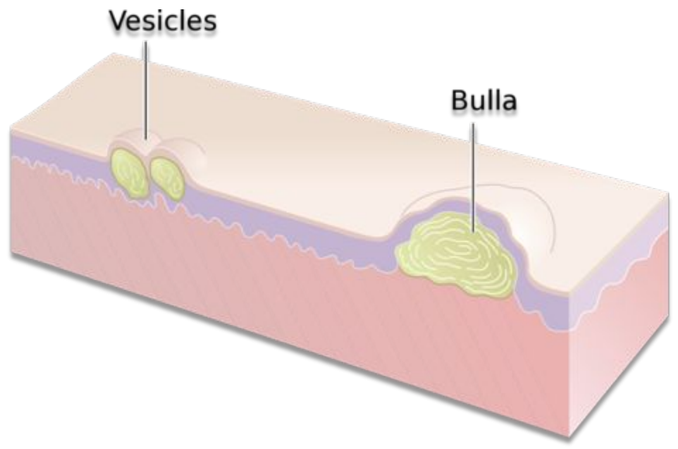
- Important
- Doctor's Notes
- Extra

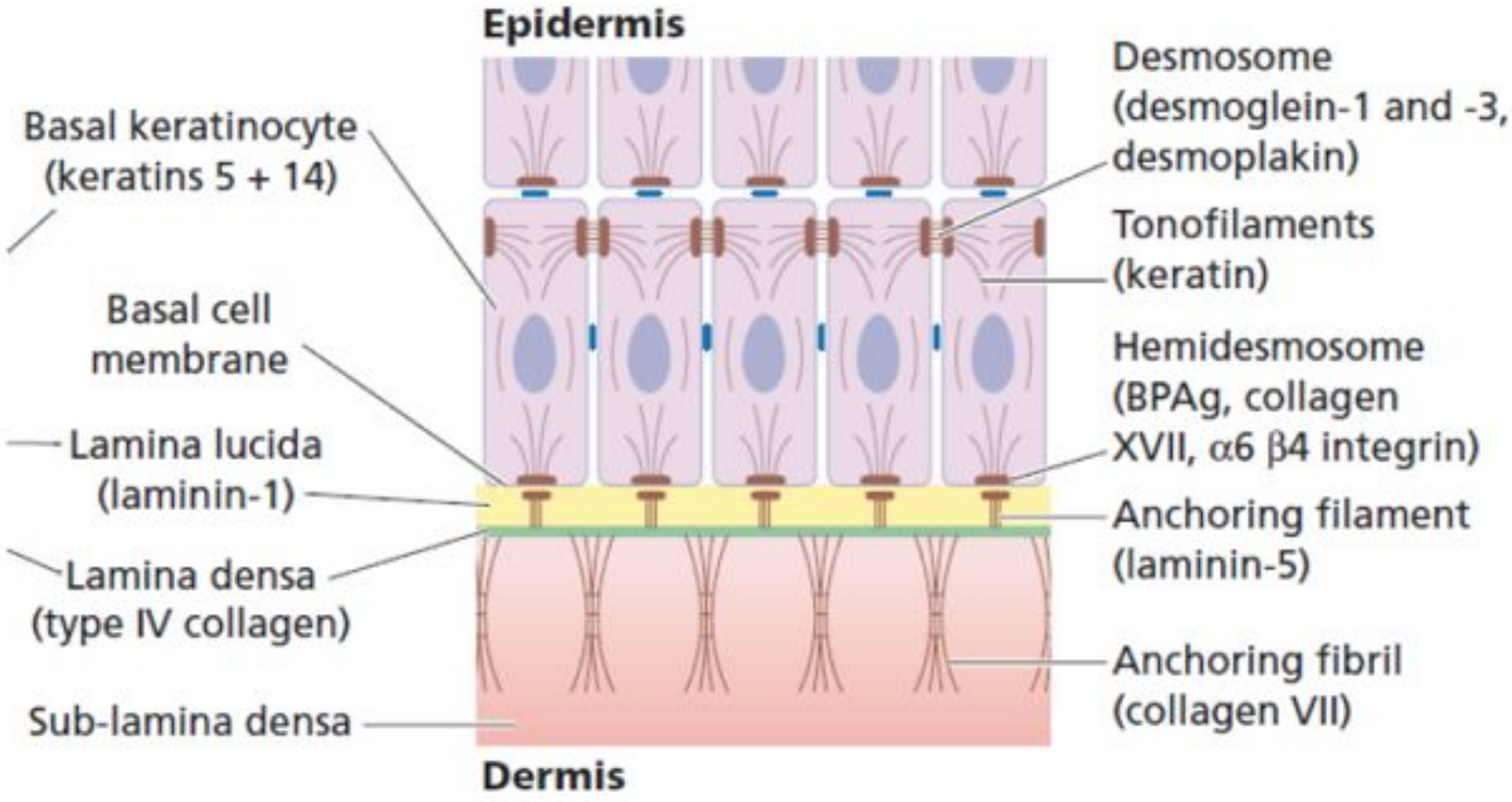
Editing File



Blistering Disorders

- **Vesicle**:
  - An elevation that contains clear fluid (< 5cm in diameter)
- **Bulla**:
  - Localized fluid collection "large vesicle" (> 5 cm in diameter)





Dermo-edidermal junction

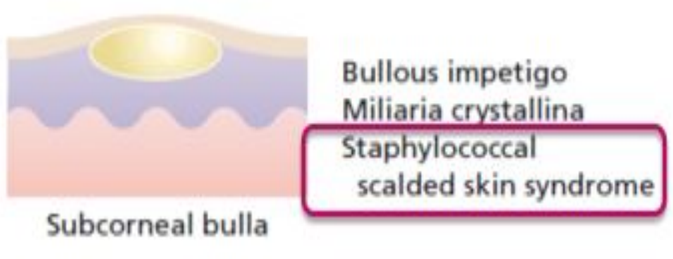
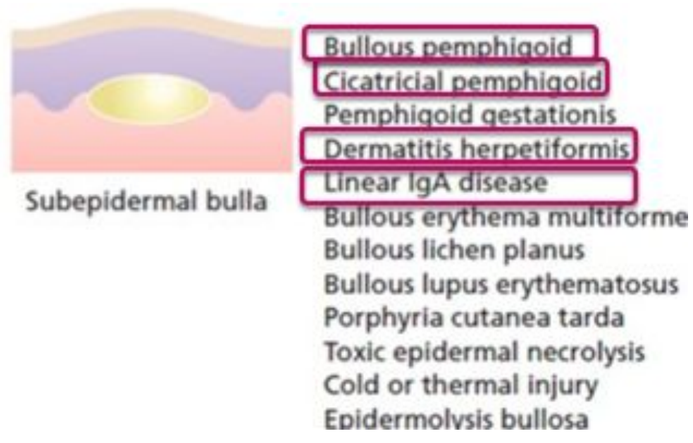
This junction is important for blistering diseases.

- **Desmosome**:
  - Breaking of desmosomes -> detached “separated” keratinocytes -> floating cells (Acantholysis)
  - **Desmoplakin:** between the walls of the cells
  - **Desmoglein:** intracellular between the cells
- **Laminin 5:** between the dermis and epidermis
  - Lamina lucida and densa represent the basement membrane and most of the autoimmune blistering disease happens there.
- **Hemidesmosome:** between anchoring filament & keratinocyte

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

Blistering Disorders

Classification Of Vesiculo-bullous Diseases (based on location):

Subcorneal Blisters	Intraepidermal Blisters	Subepidermal Blisters
• Just **beneath the stratum corneum**. Very superficial. • Have **thinner** roofs. • **Rupture easily.** • Leave an **oozing** denuded Surface. like bullous impetigo, it has subcorneal blisters that ruptures easily. 	• Within the **prickle cell layer** of the epidermis. (spinous layer) • Have **thin** roofs. • **Rupture easily.** Still superficial. • Leave an **oozing** denuded surface. • Like eczema • Flaccid blisters • Pemphigus is always intraepidermal 	• Between the **epidermis** and **dermis.** basement membrane, or dermo epidermal junction. • Their roofs are relatively **Thick** • Tend to be **tense** • May contain **blood** 

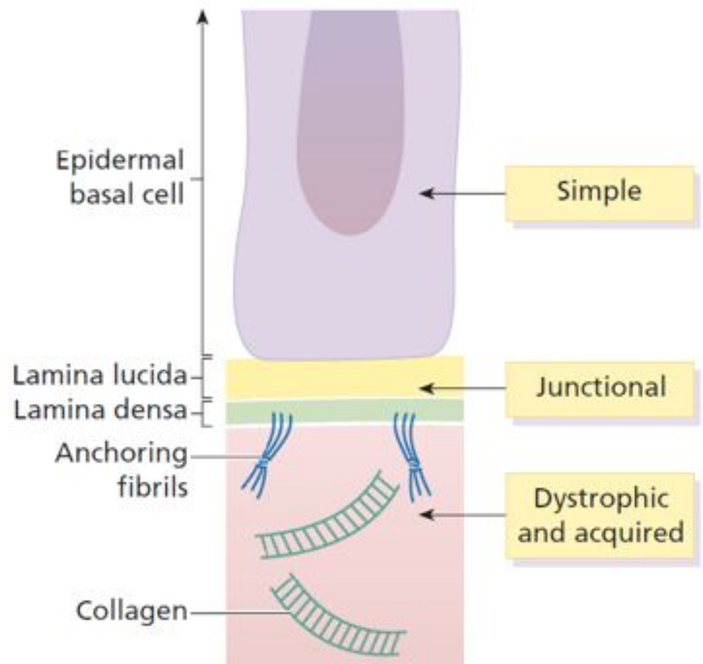
Diagnosis: In general

- Accurate pathological diagnosis **requires a biopsy** of a small newly formed lesions **and** perilesional skin of immunopathological studies.
- In the case of blisters in **children**, **electron microscopy may be required.**
- **Diagnostic tests:**
  - **Routine Histology:** lesional sample in formalin
  - **Direct immunofluorescence:** Perilesional skin Use Normal saline
  - **Indirect immunofluorescence:** patient's serum is added to specific substrates that express antigen of interest
  - **Electron microscopy**

Epidermolysis Bullosa:

Blistering Disorders In Children

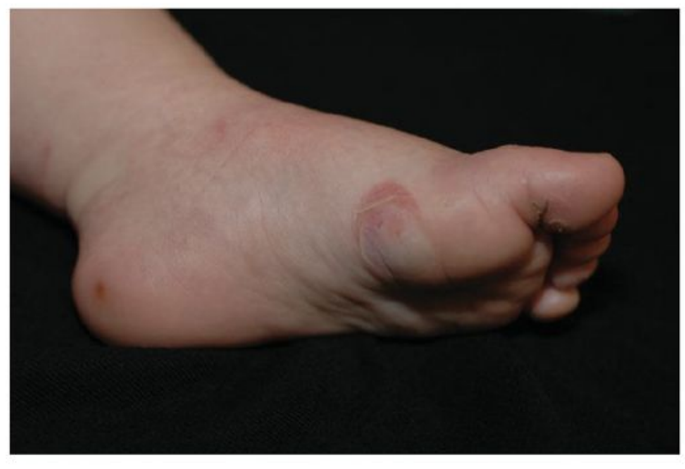
- Group of mechanobullous genodermatosis
- Rare
- Usually present at birth or infancy
- Range from localized relatively mild trauma induced blisters to life threatening/debilitating conditions
- Diagnosis is made based on:
  - Family history, clinical examination, light and electron microscopy



- **The main subsets are:**
  - **Epidermolysis bullosa simplex**:
    - mainly autosomal dominant
  - **Junctional epidermolysis bullosa:**
    - Autosomal recessive
  - **Dystrophic epidermolysis bullosa:**
    - Both autosomal dominant and autosomal recessive

1. Epidermolysis Bullosa Simplex:

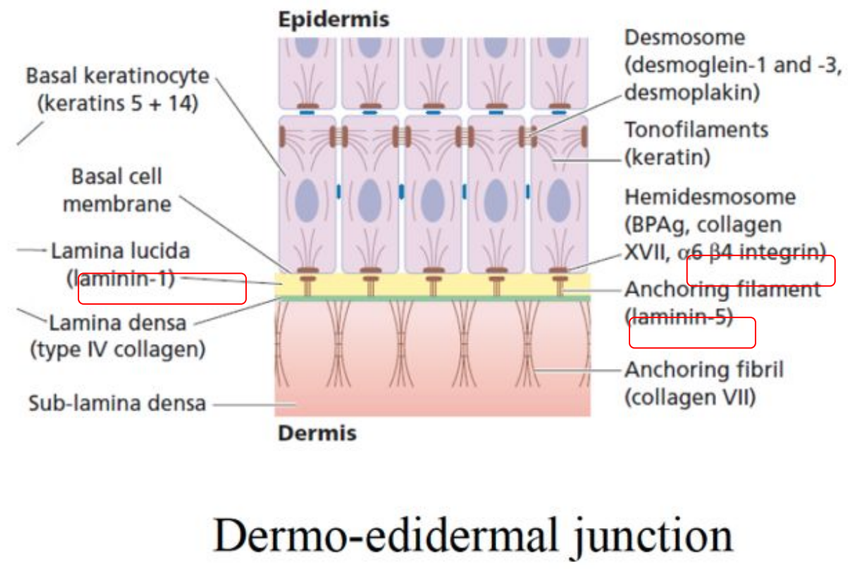
- Majority are **autosomal dominant**
- The pathological damage lies within the epidermis
- The main defect lies in defective genes coding for keratin 5 and 14 in **the basal layer**
- Blisters may be present at birth, or when the child starts to walk or crawl, and they tend to develop mild blistering on the knees , hands, feet and other sites of friction
- The blisters quickly rupture and **heal with no scarring**



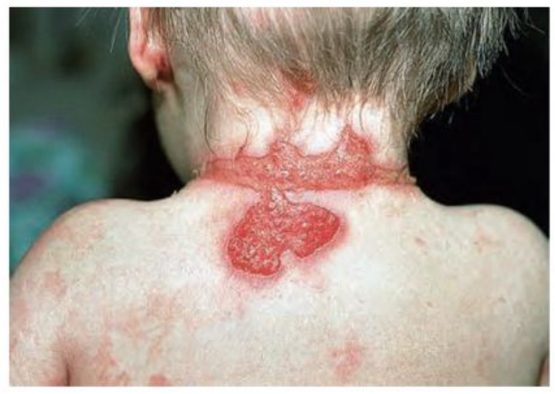
Epidermolysis bullosa simplex Localized flaccid bullae on the foot of an infant.

2. Junctional epidermolysis bullosa:

- Autosomal recessive
- The genes which are abnormal is :
  - Laminin 5, in 2 types of Junctional EB
  - α6 β4 in the third type
- Split is at the level of the lamina lucida
- **Clinical features:**
  - May be present at birth either as blisters (often around nails) or as raw denuded areas
  - Mucous membranes may be severely involved
  - Teeth are commonly abnormal



Dermo-edidermal junction



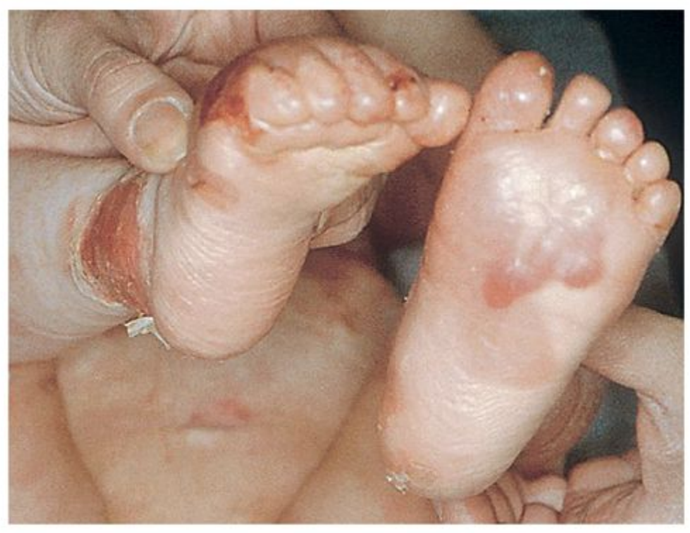
Junctional epidermolysis bullosa –
chronic nonhealing granulation tissue around the neck

Epidermolysis Bullosa:

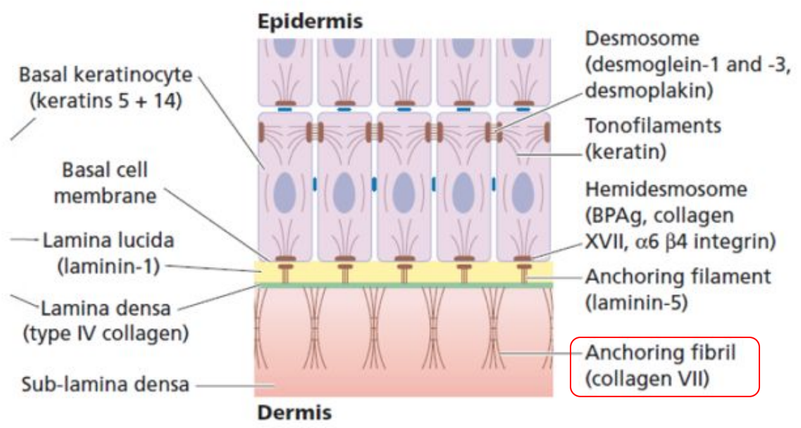
Blistering Disorders In Children

3. Dystrophic epidermolysis bullosa:

- Autosomal dominant or autosomal recessive
- All types are associated with defects in **type 7 collagen** gene which causes defective anchoring fibrils
- Squamous cell carcinoma may develop on scar sites
- In the **dominant** variant:
  - Blisters develop later in infancy or early childhood on friction sites and heal with scarring
  - **Hair** and **teeth** develop normally
- In the **recessive** variant:
  - Large bullae are present at birth and they heal with scarring
  - **Mucous membranes**, **hair**, **nails** and **teeth** may be abnormal



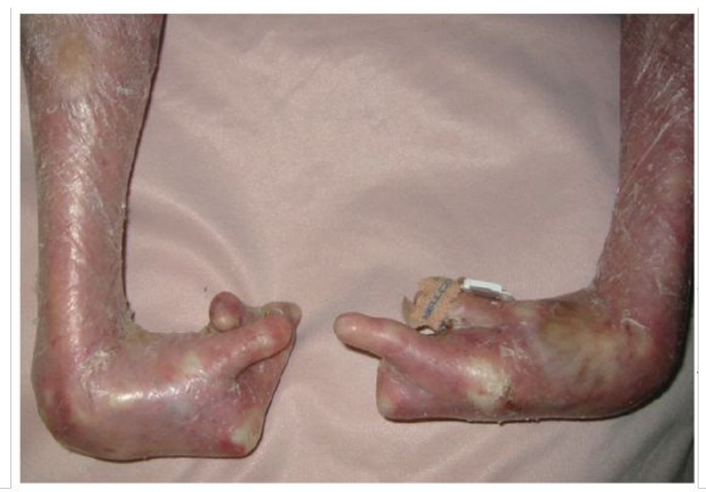
Recessive dystrophic epidermolysis bullosa in a newborn



Dermo-edidermal junction

Investigations:

- Skin Biopsy will show subepidermal splits.
- Direct immunofluorescence reveals IgA along the basement membrane of epidermis in a linear pattern.

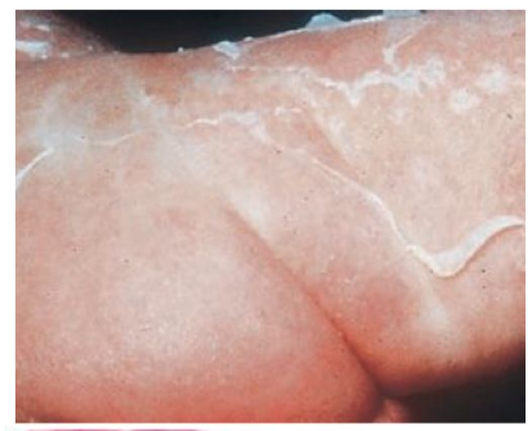


Recessive dystrophic epidermolysis bullosa in a child

- **Treatment of epidermolysis Bullosa:**
  - Team management
  - Biopsies
  - Prevention of frictional bullae
  - Occupational therapy
  - Dental care
  - Skilled nursing care
  - Oral dapsone 50-200mg daily (Ad/E) .
    - Dapsone is the drug of choice, act as anti-neutrophilic (anti-inflammatory)
  - **Sulphonamides** and immunosuppressants.
  - Erythromycin
  - Flucloxacillin: 7 cases reported from KKUH.

Staphylococcal scalded skin syndrome (SSSS) Talked about it in prev. lecture

- Caused by an epidermolytic toxin of certain types of Staph aureus, which splits the epidermis at the level of the **granular layer** by cleaving **desmoglein 1.** pemphigus diseases also attack desmoglein.
- Commoner in **children**
- Rapidly expanding **shallow blisters** which rupture quickly leaving painful raw areas, heal without scarring.
- Swabs need to be taken and sent for bacterial cultures
- Treatment is with **systemic anti staphylococcal antibiotics**
- Dressings.



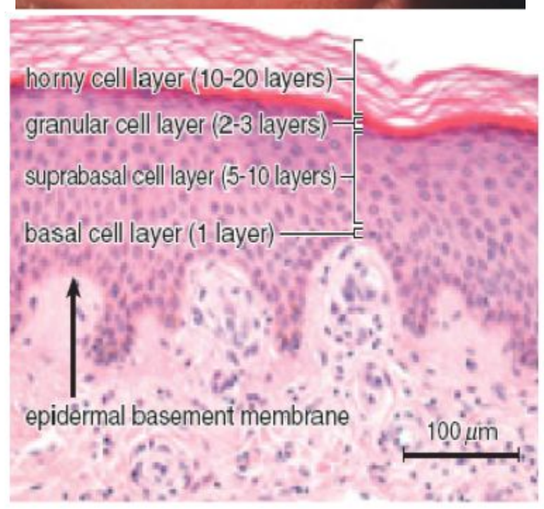


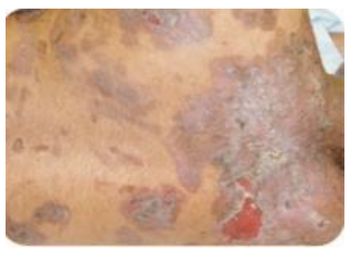
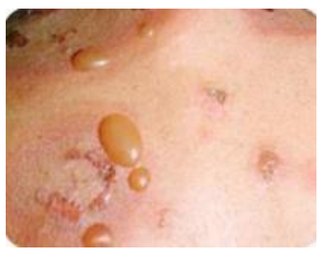
Fig. 1.4 The four layers of the epidermis

Autoimmune Bullous Diseases Classification and Overview

Lecture actually starts here.

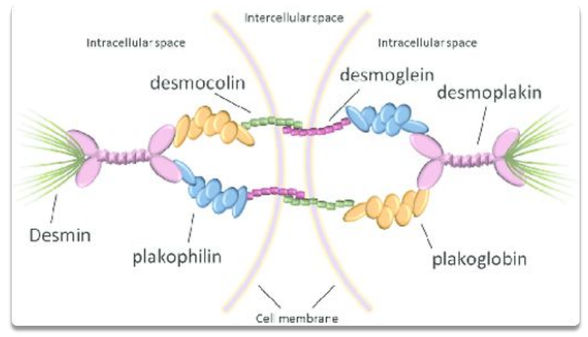
Autoimmune Bullous Diseases	
Pemphigus group: Loss of intraepidermal adhesion	**1. Pemphigus vulgaris (PV):** a. Classic b. Pemphigus vegetans sometimes present to dentists because of painful oral ulcers
	2. Pemphigus foliaceus: a. Classic b. Fogo selvagem rare c. Pemphigus erythematosus (Senear- Usher Syndrome)
	3. Drug Induced pemphigus
	4. Paraneoplastic pemphigus
	5. IgA pemphigus
Pemphigoid group: Loss of subepidermal adhesion	**1. Pemphigoid** a. Bullous pemphigoid b. Cicatricial pemphigoid c. Pemphigoid gestationis
	2. Dermatitis herpetiformis
	3. Linear IgA disease a. Of Childhood chronic bullous disease of childhood b. Adult form
	4. Epidermolysis bullosa acquisita

Extra

	Pemphigus vulgaris	Bullous pemphigoid
Appearance		
Age	Younger 40-60	Older 60-70
Mucus 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

Extra	Pemphigus	Bullous Pemphigoid	Dermatitis Herpetiformis
Age	middle age	old	primarily adults
General health	poor	good	itchy
Circulting Abs	IgG to intercellular adhesion proteins	IgG to basement membrane region	IgG to endomysium and transglutaminase
Fixed antibodies	IgG in intercellular space	IgG at basement membrane	**IgA granular** deposits in p**apillary dermis**
Nature of blisters	superficial, and flaccid	tense, and blood filled	Small, excoriated and grouped
Site of blisters	trunk, flexures, and scalp	often flexural	elbows, knees, upper back, buttocks
Blisters in mouth	common	rare	rare
Treatment	Steroids Immunosuppressives	Steroids Immunosuppressives	Dapsone Sulfapyridine Gluten free diet

Skin biopsy is needed most of the time to confirm the diagnosis and knows the depth



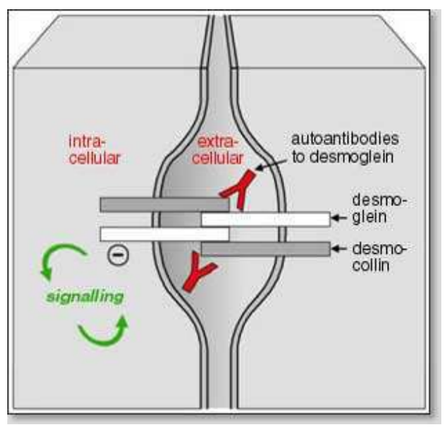
The Pemphigus Group:

- A group of disorders with loss of intraepidermal adhesion due to autoantibodies directed against proteins of the **desmosomal** complex that hold **keratinocytes together.**
- There are four sub-clinical variants of pemphigus:
  - **Vulgaris is the most common** pemphigus variant, and the form usually responsible for **oral lesion**. Other variant include: Fallacious, vegetens, erythematous.
- The Desmosome is a complex structure, with many of its components being targets for autoantibodies.
- Patients with **PV** and **PF** have IgG autoantibodies against **desmoglein 3** and **desmoglein 1**, respectively. **Desmoglein 3** represent the Mucosa, **Desmoglein 1** represent the Skin.
- While patients with **paraneoplastic pemphigus** have IgG autoantibodies against **plakin** molecules in addition to autoantibodies against desmogleins.

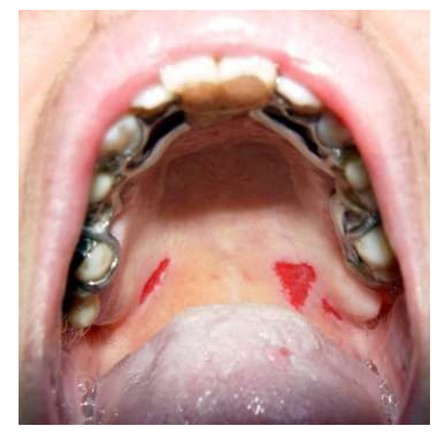
  - **Pemphigus vulgaris (PV):**
    - Mucosal type:
      - IgG autoantibodies against **desmoglein 3** (mucosa only)
    - Mucocutaneous type:
      - IgG autoantibodies against **desmoglein 3 and 1** (skin & mucosa)
  - **Pemphigus foliaceus (PF):**
    - IgG autoantibodies against **desmoglein 1** (skin only, also IgA)
  - **Paraneoplastic pemphigus:**
    - IgG autoantibodies against **Plakin molecules** in addition to desmogleins.
    - extensive skin and mucosal involvement.

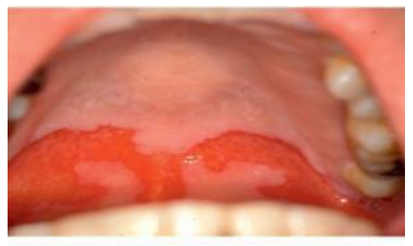
1. Pemphigus Vulgaris:

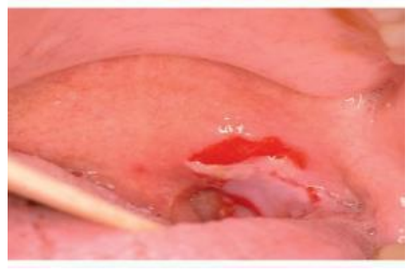
- Severe, potentially fatal disease with <u>intraepidermal blister</u> formation of the skin and oral mucosa caused by <u>IgG autoantibodies</u> against desmogleins



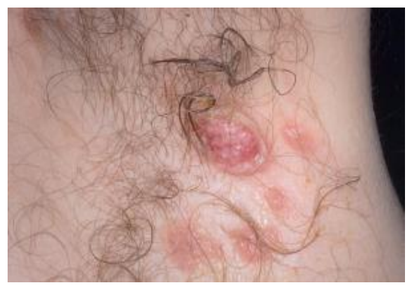
- **Epidemiology**:
  - The mean age of onset of disease is 5<u>0-60 years.</u> Middle aged. more in jewish.
- **Pathogenesis:**
  - Genetic predisposition: HLA-DRQ402- DQ0505
  - IgG autoantibodies against desmoglein 3 (Dsg 3) and later desmoglein 1 (Dsg 1). It usually starts orally (Dsg 3)
  - The bound antibodies activate **proteases** that damage the desmosome, leading to acantholysis. Type 2 reaction, so its difficult to diagnose from the serum, better to do it on the tissue because the immune reaction happens there.
  - Serum antibody titer usually correlates with severity of disease and course
  - Secondary infection and disturbance of fluid electrolyte balance are common complication
- **Clinical features:**
  - **Mucous membranes:**
    - lesions usually present as painful erosions and ulcers
    - Intact blisters are rare because its intraepidermal that rupture easily, ask if there was a blister before the erosion.
    - **Sites**: <u>oral mucosa, vermillion lip, throat</u>, esophagus, conjunctivae, nasal mucosa, vagina, penis, anus, labia.
    - **Most common sites:** buccal & palatine mucosa first area to examine
    - **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.
    - Pemphigus usually starts in the oral mucosa, so pts would go to dentist and they start them on antifungal treatment thinking that this is an infection, but they won't benefit.
    - Patient may take a year and half to reach the diagnosis and may lose weight.

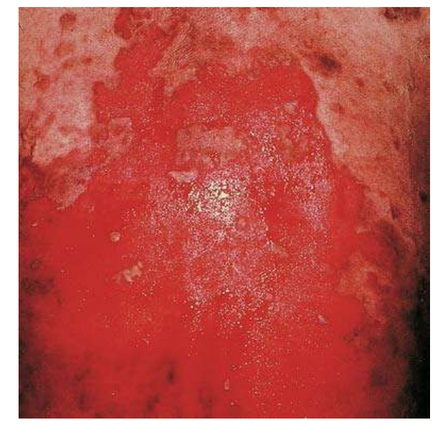




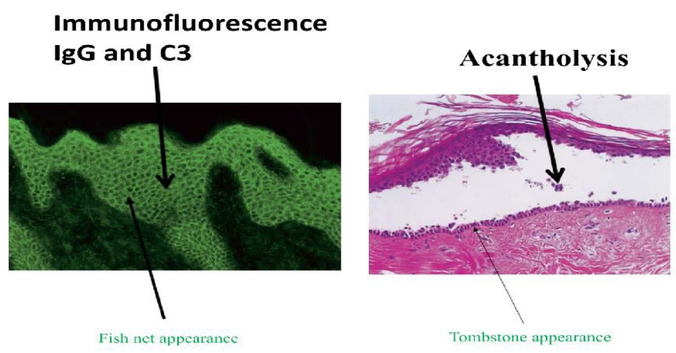


- **Skin:**
  - Primary skin lesions of PV are fragile, **flaccid, thin-walled, easily ruptured blisters.**
  - The blisters are fragile. They rupture to form <u>painful erosions</u> that ooze and bleed easily, later forming crusts. Crust and erosions are secondary lesions.
  - They could arise on either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

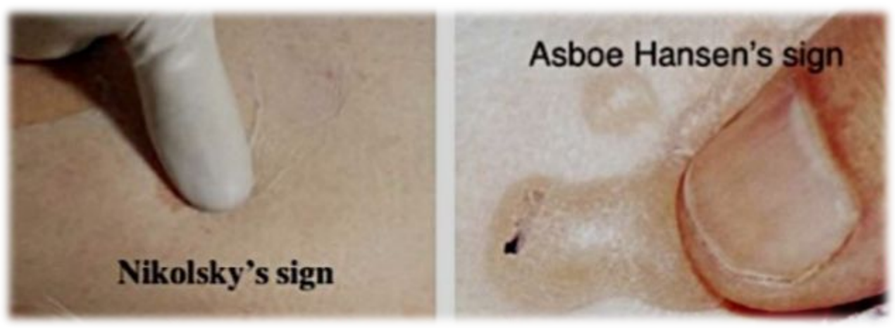




- **Pathology:**
  - Intraepidermal blister formation due to loss of cell-cell adhesion of keratinocytes (**acantholysis**) **without keratinocyte necrosis**. This is how we differentiate between it and steven/TEN.
  - They maintain their **attachment to the basement membrane** via **hemidesmosomes**, this giving the appearance of **"row of tombstones"**
  - Mild dermal perivascular infiltrates



- **Diagnostic Approach:**
  - **History**: always ask medication Hx
  - **Physical examination**: skin, mucous membranes, nails
    - **Nikolsky sign:** 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. Its positive in severe cases usually, but not due to detachment of the dermo epidermal junction.
    - **Asboe-Hansen sign: "bulla- spread phenomenon"** gentle pressure on an intact bulla forces the fluid to spread under the skin away from the site of pressure



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

- **Treatment:**
  - **Systemic corticosteroids** are the mainstay of therapy for pemphigus
    - **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** or immunomodulators are often used for their steroid sparing effect in order to <u>reduce the side effects of the corticosteroids</u>
  - Antibiotic to treat superinfection

- **Immunosuppressive agents in combination with <u>oral</u> prednisone:**

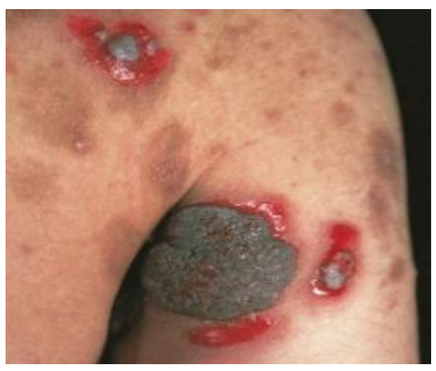
Azathioprine first line	Cyclophosphamide 2nd line	Mycophenolate mofetil	Cyclosporine
Pulse methylprednisolone	IVIG requires many sessions and costly	Rituximab for severe cases	Extracorporeal photopheresis

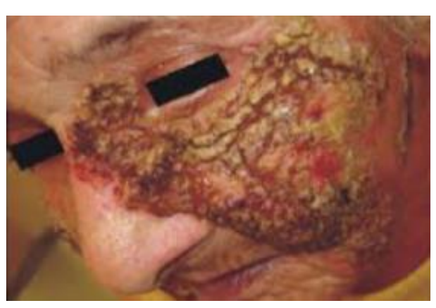
- **<u>Topical</u> treatments:**
  - Corticosteroid
  - Antibiotics
  - Immunomodulators (e.g. topical tacrolimus)

Differential diagnosis:

When skin is involved	When mucous membranes is involved
● Bullous impetigo ● Dyskeratotic acantholytic disorders: ○ Hailey-Hailey ○ Grover disease	● Denture intolerance ● Erosive candidiasis ● Chronic recurrent aphthae ● Erythema multiforme ● Erosive lichen planus ● Herpetic ginigivitis

Pemphigus Vegetans:

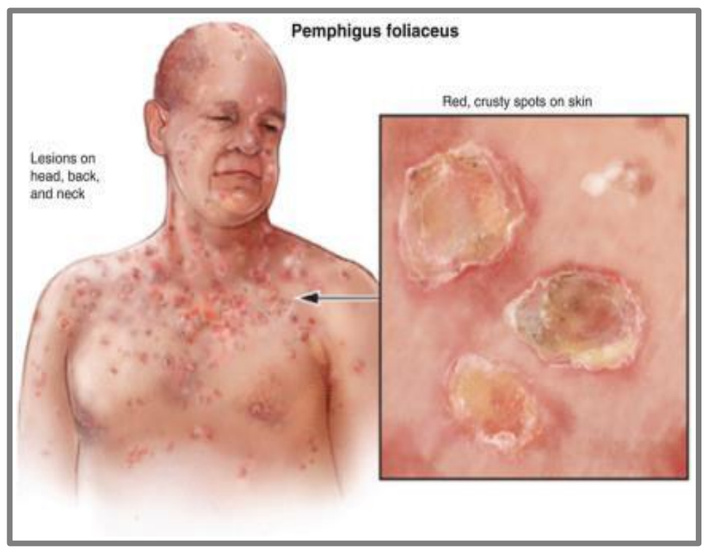




- Is a **rare** vegetative variant of pemphigus vulgaris
- **Clinical Features:** The difference is in the location and primary lesion.
  - Characterized by **flaccid blisters** that become erosions and then form fungoid vegetations, especially in **intertriginous areas, the scalp and face**.
  - Early lesions **start as pustules** (rather than vesicles), then they soon progress to **vegetative plaques,** with thick crust. All types other than vulgaris have crusts
- **Treatment:** same as pemphigus vulgaris

2. Pemphigus Foliaceus:

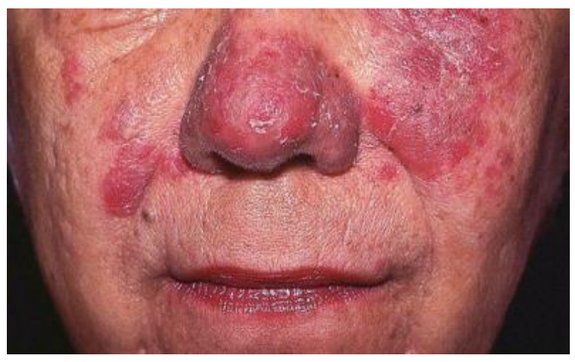
- Is a form of pemphigus in which patients develop **scaly, crusted cutaneous erosions**
- often on an erythematous base.
- Disease of middle-aged and older patients
- In this form of pemphigus they **do not have mucosal involvement** even with widespread disease because the IgG autoantibodies are against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



- **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** may be helpful which is directed against neutrophils.

Pemphigus Erythematosus: (Senar-Usher Syndrome)

- **Localized** variant of **Pemphigus foliaceus.**
- **Scaly, crusted lesions** of **pemphigus foliaceus** over the **malar region** and in other **seborrheic areas.** Ddx of rosacea, or SLE
- Patients have immunologic features of both Lupus erythematosus and pemphigus (i.e. IgG and C3 deposition on cell surface of keratinocytes as well as the basement membrane zone, in addition to circulating ANA), but It does not meet criteria of Diagnosis of lupus.
- **Very rare**, only reported in few patients.



3. Drug Induced Pemphigus:

- Most patients go into remission after the offending drug is discontinued.
- **Drugs that induce pemphigus can be divided into two groups:**

Agents with the sulfhydryl group	Agents without the sulfhydryl group
• **Penicillamine**: ○ PF is seen more than PV, ratio 4:1 • **Captopril** • Piroxicam Sulfhydryl group of these drugs interacts with the sulfhydryl groups of Dsg1 & Dsg 3 (acantholysis without antibody formation)	• Beta- blockers • Cephalosporins • Penicillins • Rifampin • Antiepileptic: phenytoin and carbamazepine. Induce acantholysis via immune mechanisms

5. IgA Pemphigus:

All other pemphigus and caused by IgG, and its pemphigus because of its intra epidermal location.

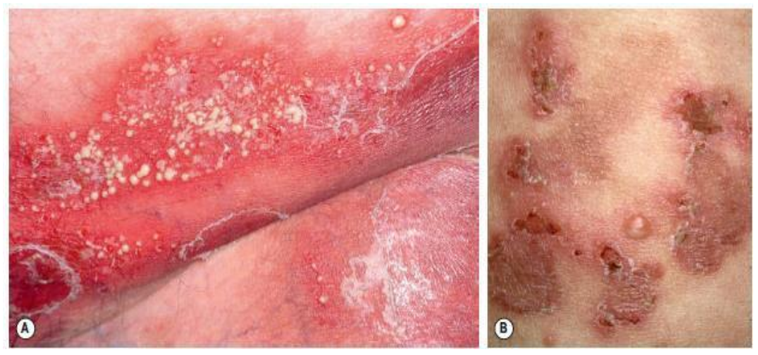
Represents a group of autoimmune intraepidermal blistering diseases presenting with:

- Vesiculo**pustular** eruption
- **Neutrophilic** infiltration of the skin so we can use dapsone!
- Circulating **IgA autoantibodies** against the cell surface of keratinocytes, but **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:

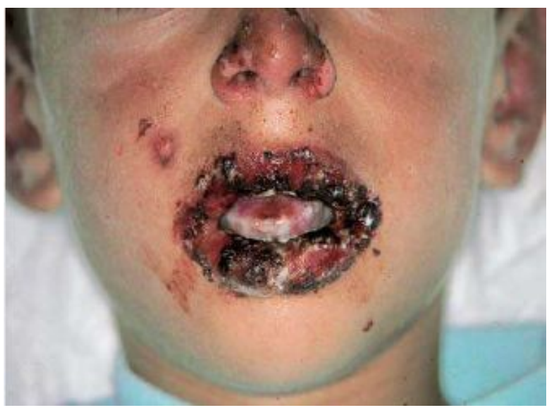
- History and Physical examination (skin, mucous membrane, nails)
- Investigation
- DIF: IgA autoantibodies directed against keratinocyte cell surface

Treatment:

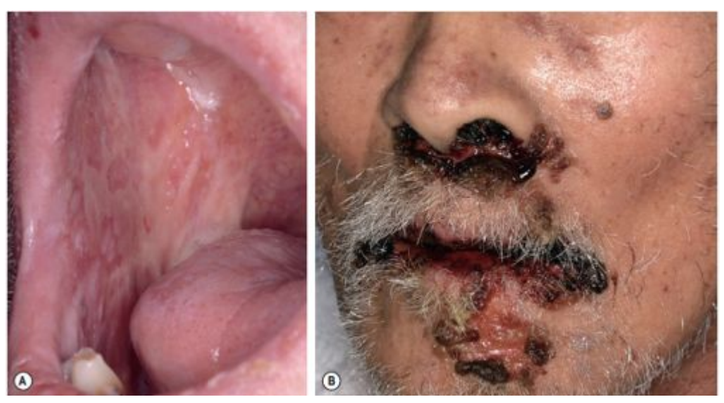
- Most cases are responsive to **dapsone** because of neutrophilic infiltration.
- If not: corticosteroids & other immunosuppressive agents.

5. Paraneoplastic Pemphigus

- The least common and most severe type of pemphigus is paraneoplastic (PNP).
- This disorder is a complication of cancer.
- Associated with underlying neoplasms, both benign and malignant
- **Most commonly associated neoplasms:** rare cancer types
  - Non-Hodgkin lymphoma
  - Chronic lymphocytic leukemia
  - Castleman's disease
  - Malignant and benign thymomas
  - Not associated with common tumors such as adenocarcinomas and SCC



- **Clinical features:** extensive, severe, hemorrhagic
  - The most constant clinical feature is the presence of **intractable stomatitis.**
  - The **Stomatitis** consists of erosions and ulcerations that affect all layers of the oropharynx and **characteristically** extend onto the **Vermilion lip**
  - **Stomatitis** is usually the **earliest** presenting sign, the one that **persists after treatment** and is extremely **resistant** to therapy.
  - Pseudomembranous **conjunctivitis**: scarring, blindness.
  - **Could also affect**: esophagus, nasopharynx, vagina, labia, penis.
  - Cutaneous findings are **polymorphic** always a hint for paraneoplastic:
    - Erythematous macules
    - Flaccid blisters and erosions (resembling pemphigus)
    - Tense blisters (resembling pemphigoid)
    - Erythema multiforme like lesions
    - Lichenoid eruptions
    - Histology is rarely helpful

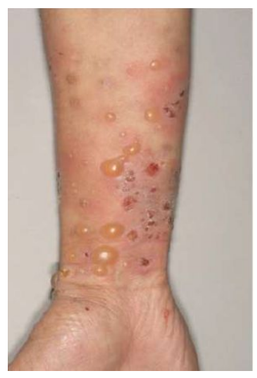


- **Treatment:**
  - Treat the underlying tumor
  - **Benign tumors:**
    - it may take 6-18 months to see complete resolution of lesions after excision of benign neoplasms
  - **Malignant tumors:**
    - No consensus on a standard effective therapeutic regimen
    - Cutaneous lesions respond more rapidly than the stomatitis, which is refractory to treatment
  - **Prognosis** of paraneoplastic pemphigus is **poor** due to its resistant nature to treatment
  - Important: desmoplakin is the targeted protein by autoantibody in paraneoplastic pemphigus

Pemphigoid Group

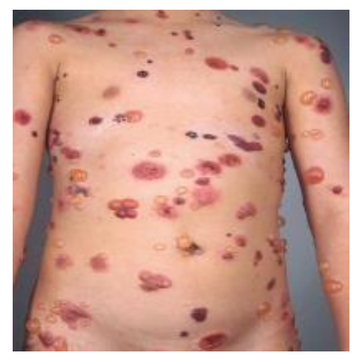
Bullous Pemphigoid (BP):

- The **most common** autoimmune **subepidermal** blistering disease, caused by autoantibodies against **hemidesmosomes** in the basement membrane zone (BMZ). The blisters are tense.
- Predominantly affects the **elderly.** **> 60 Y**
- May present as an erythematous base in the beginning and we do biopsy & IF , it will confirm pemphigoid
- **Pathogenesis:**
  - Tissue-bound and circulating **autoantibodies** directed against **two hemidesmosomal proteins:**
    - BPAG 1" BP230" (bullous pemphigoid antigen 1)
    - BPAG 2 "BP180" (bullous pemphigoid antigen 2) is most likely to be more involved in the initial immune response, since it is transmembrane.
- **Drug-induced bullous pemphigoid:**
  - Diuretics (furosemide), D-penicillamine, Antibiotics (amoxicillin, ciprofloxacin) Potassium iodide.

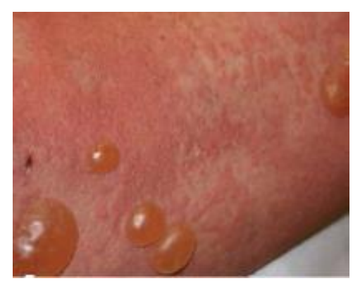


Clinical features:

- **Intensely pruritic** eruption with widespread blister formation, remember pemphigus was painful not pruritic.
- In **early** stages and atypical variant: excoriated, eczematous, **urticarial lesions,** can stay a long time without blistering.
- Always keep BP in mind when confronted with an elderly patient with persistent urticarial lesions.
- Mucosal involvement in < 20 %. Cicatricial: skin is 25% involved (opposite)

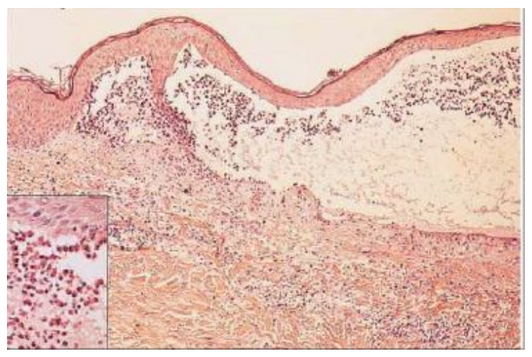


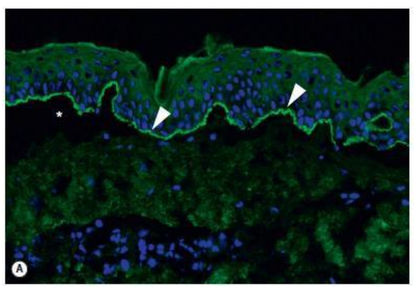
- **Non-bullous phase:** cutaneous manifestations are non-specific & polymorphic (pruritus, excoriations, eczematous, urticarial lesions) this phase can last years.
- **Bullous phase:** characterized by the development of vesicles and bullae on normal or erythematous skin along with urticarial lesions. Blisters are stable and **tense.**
- Bullae predominate on the flexural aspects of the limbs and the lower trunk (extremities)



- **Diagnostic Approach:**
  - The diagnosis of BP is based upon the clinical presentation, histological features and positive findings on direct and indirect immunofluorescence
  - **History and Physical examination**
  - **Investigations:** The following are elevated in 60% of patients with BP
    - Increased **eosinophils on CBC,** and **increased ESR** and **IgE.**
    - These also are increased in eczema or urticaria, that's why we do biopsy.
    - **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
    - **Indirect IF:** using salt-split human skin
    - **ELISA:** identifies antibodies against both BP 230 & 180 in 60-80% of patients

Fig. 30.10 Bullous pemphigoid – histologic features. Subepidermal blister which contains fibrin, eosinophils and mononuclear cells (see inset). Courtesy, Lorenzo Cerroni, MD.





Treatment:

Mild/localized Disease	Extensive/persistent Cutaneous Disease
• Superpotent topical corticosteroids • Dapsone • Topical immunomodulators (tacrolimus)	• Superpotent topical corticosteroids • Oral corticosteroids • Azathioprine • Methotrexate

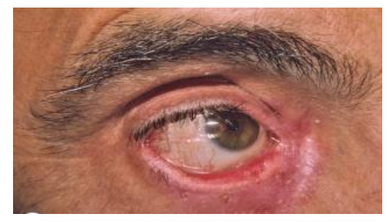
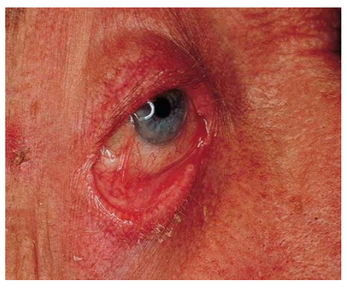
Remember to treat infected skin lesion to prevent sepsis.
If the patient does not respond to oral therapy we can use dapsone instead of oral steroid to prevent suppression of immunity

Cicatricial Pemphigoid: Cicatricial because it causes scarring.

- 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: most commonly present to ophtha, but usually more than 1 mucosa affected



- **Conjunctiva**:
  - affected in 75% of cases.
  - Starts unilaterally, within 2 years becomes bilateral
  - adhesions, ectropion, corneal damage
- **Oral mucosa:** lesions less painful than PV
- **Esophagus & larynx**: can develop strictures that may require surgery
- **Genitalia**: narrowing of vaginal orifice, adhesions between glans & foreskin
- **Skin**: only involved in 25% , face, scalp and upper trunk, atrophic scarring

Diagnostic Approach:

- **History and Physical examination**
- **Investigation**
  - DIF: IgG autoantibodies directed against the basement membrane of **mucosa** and/or skin. mucosa more than 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 corticosteroids, ophthalmology referral

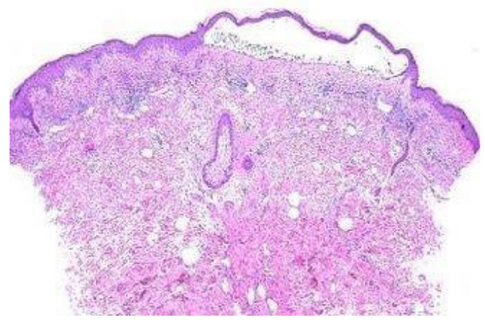
In severe disease:

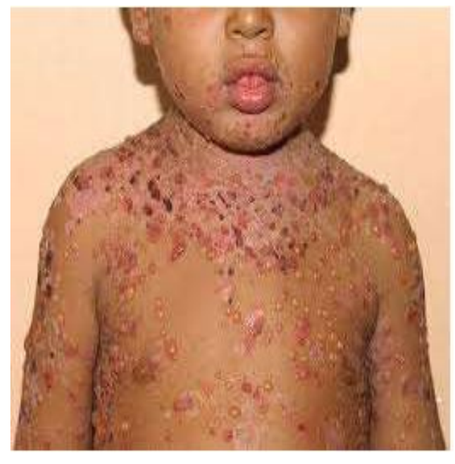
- Oral corticosteroids
- Dapsone
- Cyclophosphamide
- Azathioprine
- **Surgical therapy** to treat the ectropion and adhesions

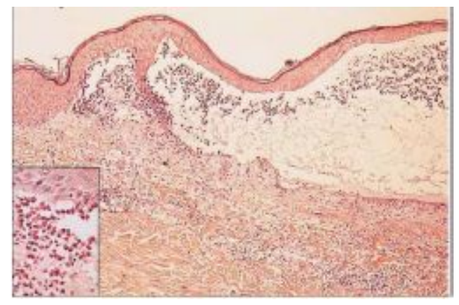
Pemphigoid Gestationis (Herpes gestationis):

Not herpes related disease (just similar looking lesions)

- **A form of BP occuring during pregnancy**
- Occurs in 1/10000-40000 pregnancies. Rare
- No maternal risk, no increase in birth defects.
- However, pregnancy complications and fetal death occurs in 15-30% mostly IUGR.
- **Clinical features:**
  - Erythematous urticarial plaques, alone or with papules, vesicles, blisters in sub-epidermal area, erosions. Tense vesicle/bullae on erythematous plaque or urticaria, annular shaped.
  - **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. If the mother got the disease early in her pregnancy, the chances of the newborn being affected is higher than if she got it later on.
- **Diagnostic Approach:**
  - **History and 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

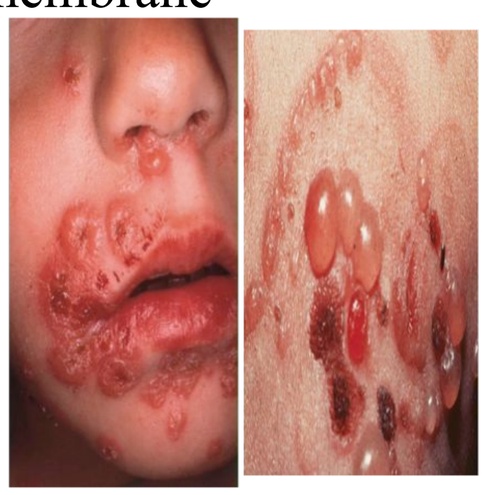


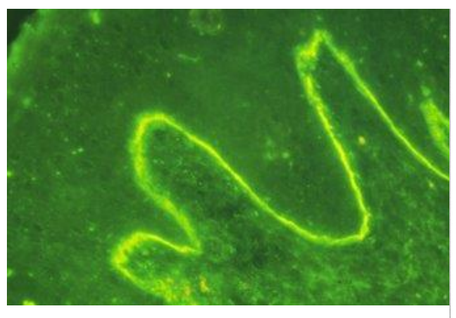




Linear IgA Disease:

- 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
- **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
- **Diagnostic approach :**
  - History
  - Physical examination
  - Investigation
    - DIF linear IgA deposits along the basement membrane
    - Indirect IF





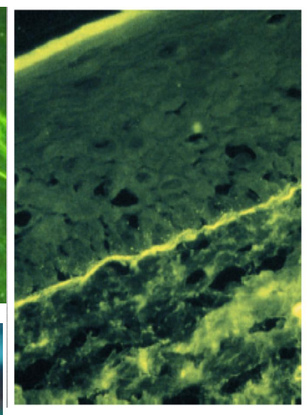
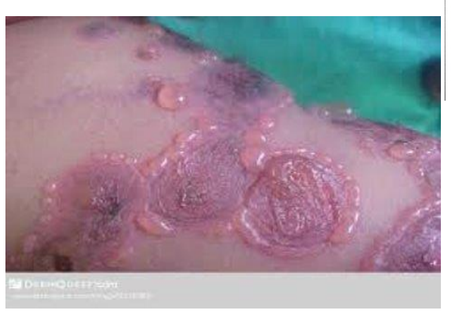


Fig. 31.8 Linear IgA bullous dermatosis – direct immunofluorescence. A linear pattern of IgA deposition is present within perilesional



Treatment:

- Oral dapsone 50-200mg daily (Ad/E) . Remember: igA and neutrophils we have to check G6PD level
  Dapsone is the drug of choice in adults, act as anti-neutrophilic (anti-inflammatory)
- Sulfapyridine and immunosuppressants.
- **Antibiotics:** Tetracycline first line treatment in children, erythromycin,dicloxoacillin
  In the childhood age group, They're a good treatment and were found to be better than dapsone.

Dermatitis Herpetiformis (DH):

Herpetiformis because its a group of vesicles.

- **Pruritic vesicular disease** caused by **IgA autoantibodies** directed against epidermal transglutaminase.
  It is a differential for any patient that complains of itching.
- Characterized by granular IgA deposition **at the basement membrane zone (**BMZ).
- It is also 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**)

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

- **Diagnostic Approach:**
  - **History and Physical examination**
  - **Investigations**
    - **Skin biopsy: subepidermal blister,** with **neutrophilic** micro-abscesses in the papillary dermis is the hallmark of the disease. bullous pemphigoid: eosinophils.
    - **DIF:** Granular deposits of **IgA** in the dermal papillae
    - **Indirect IF**
    - **ELISA:** 80% identifies IgA against transglutaminase.
    - **Jejunal Biopsy:** flattening of the villi

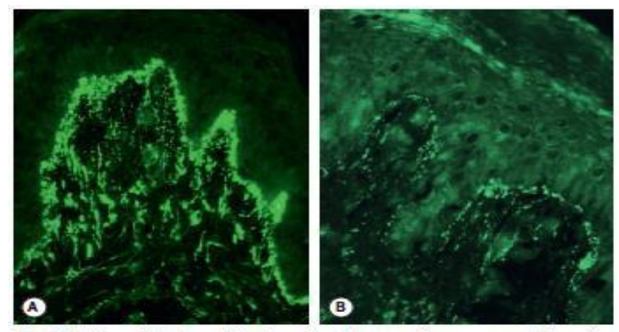
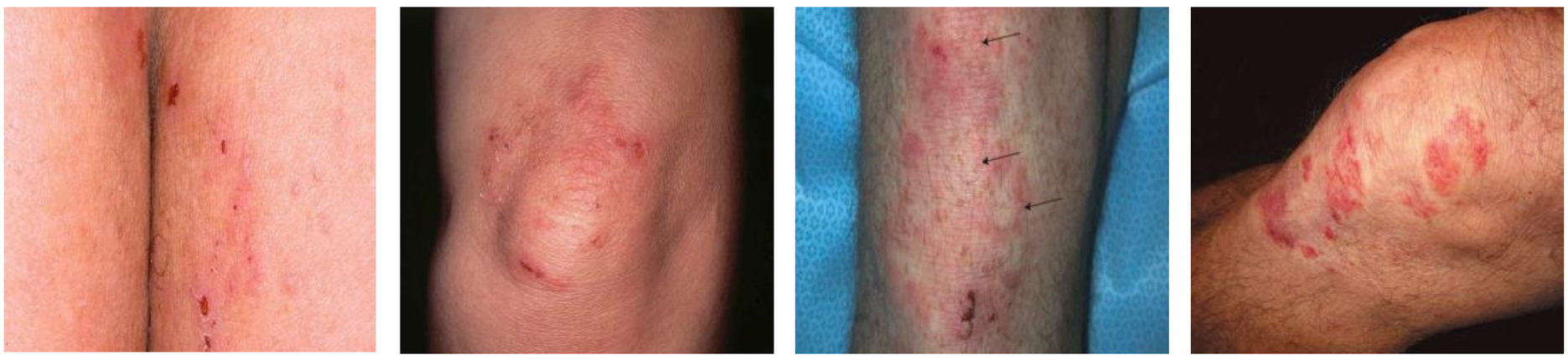


Fig. 31.5 Dermatitis herpetiformis – direct immunofluorescence. A Granular IgA deposition along the dermal–epidermal junction of normal-appearing skin adjacent to a lesion. **B** Granular deposition of epidermal transglutaminase (TG3) within the dermal papillae, which co-localizes with the IgA. *A, Courtesy, Kristin Leiferman, MD.*

- **Treatment**
  - **Gluten free diet**
  - **Dapsone**. IgA always comes with neutrophils.



Summary Table:

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

Questions:

1) From Where you will take a biopsy of Bullous pemphigoid?
A. Erythematous area at periphery
B. The blister itself
C. Normal Skin
D. Mucous Membranes

2) A case about pemphigus vulgaris then what drug cause this condition
A. Digoxin
B. Captopril
C. Ibuprofen D.

3) 30-year-old male present s with erosion and crust on lips. He was diagnosed with lymphoma a month ago. What is the most likely diagnosis?
A. Paraneoplastic pemphigus
B. Scurvy
C. Herpes labialis.

4) 12-year-old boy presented with vesicles and erosion look like cluster of jewels, what's the most likely diagnosis?
A. Linear IgA dermatosis
B. Bullous pemphigoid
C. Pemphigus vulgaris
D. Impetigo

5) Pt with erosions and vesicles, DIF was done and showes IgG & C3 deposition in the epidermis pattern, what's most likely diagnosis
A. Rosacea
B. Dermatitis herpetiformis
C. Pemphigus vulgaris
D. Bullous pemphigus

6) A pregnant female with papulovesicular eruption involving abdomen and extremities,
suspected to have herpes gestationis. Which of the following is a feature of Pemphigoid
gestationis?
A. It's a viral disease-
B. It's non itchy eruption-
C. It starts in first trimester-
D. It relapses with contraceptive pills-

7) A 30 year old lady referred urgently by the obstetrician with severe and extensive itching associated with widespread urticated plaques and two tense blisters on her left axilla, mucosal membranes are not involved- She is at 21 weeks of gestation with her second pregnancy- What is the most likely diagnosis?
A. Acute urticaria
B. Scabies infection
C. Erythema multiforme
D. Pemphigoid gestationis

8) A patient with pruritus (forgot the scenario) With neutrophilic microabscesses in the papillary dermis What's the management?
A. Topical steroid
B. Systemic steroid
C. A diet containing rice
D. A diet containing wheat

Dx: Dermatitis herpetiformis

9) 21 year old male complaining of grouped itchy vesicles at his extensors, immunofluorescent shows positive granular IgA deposition in dermal papilla. Which of the following is the most likely diagnosis?
A. Rosacea
B. Dermatitis herpetiformis
C. Pemphigus vulgaris
D. Bullous pemphigus

10) Direct immunofluorescence of skin biopsy from 54 years old patient with blistering disease revealed intracellular deposit of IgG and C3. In which one of the following blistering diseases this immunopathology finding is seen?
A. Bullous pemphigoid
B. Pemphigus vulgaris
C. Cicatricial pemphigoid
D. Dermatitis herpetiformis

1	2	3	4	5	6	7	8	9	10
A	B	A	A	C	D	D	C	B	B