Bullous Dermatosis

Supervised By: Prof. Khitam Al-Refu

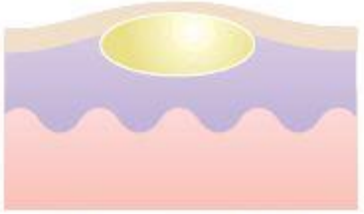
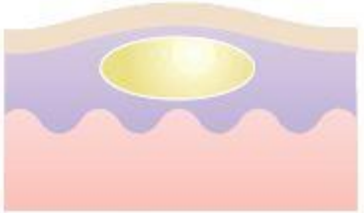
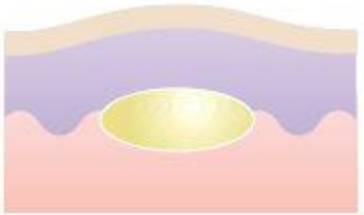
presented by:Zaid ALTarawneh
Mohammed Malkawi
Muns ALTarawneh

Mutah University

Definitions

- **Vesicles**:-fluid filled raised area 5mm or less across
- **Bulla**:-more than 5mm
- **Blister**:-common term used for vesicle or bulla.
- Although blisters occur as a secondary phenomenon in a number of unrelated conditions, there is a group of disorders in which blisters are the primary.

- **Subcorneal** blisters:
  - Just beneath the stratum corneum
  - Have the **thinner** roofs.
  - Rupture easily & leave an **oozing** denuded surface
- **Intra-epidermal** blisters:
  - Within the **prickle cell layer** of the epidermis
  - Have thin roofs
  - Rupture easily & leave an **oozing** denuded surface
- **Subepidermal** blisters:
  - Between the **dermis & epidermis**
  - Their roofs are relatively **thick**
  - Tend to be **tense**
  - May contain **blood**

Location of bullae	Diseases
 Subcorneal bulla	Bullous impetigo Miliaria crystallina Staphylococcal scalded skin syndrome
 Intra-epidermal bulla	Acute eczema Viral vesicles Pemphigus Miliaria rubra Incontinentia pigmenti
 Subepidermal bulla	Bullous pemphigoid Cicatricial pemphigoid Pemphigoid gestationis Dermatitis herpetiformis Linear IgA disease Bullous erythema multiforme Bullous lichen planus Bullous lupus erythematosus Porphyria cutanea tarda Toxic epidermal necrolysis Cold or thermal injury Epidermolysis bullosa

Different mechanism to form blisters.

- Spongiosis:

keratinocyte get separated by the accumulation of oedema fluid

- Epidermal cell necrosis:

When keratinocytes are invaded by a virus as varicella or herpes simplex .

The cells get swollen and vacuolated to produce an appearance called balloon degeneration.

Damage to intracellular cement.

- In pemphigus vulgaris, AB s against the int-cellular cement cause the keratinocytes to lose their cohesion and drift apart.

- This process is called **acantholysis** and the acantholytic cells can be recognized histologically because the are rounded and darkly stained.

Basal cell damage:

Epidermolysis bullosa simplex causes disruption of the basal cells following mild trauma.

Degeneration of basal cell layer also occurs in lupus erythematosus and lichen planus , and on rare occasions this can be so severe as to produce bullae.

Damage to the lamina lucida.

In bullous pemphigoid the split occurs at the level of the lamina lucida, presumably as a result of immunological damage caused by the IgG antibody binding with the bullous pemphigoid antigen at this site.

Dermal damage:

- **A.** in recessive dystrophic epidermolysis bullosa, the split occurs just below the basal lamina , and the anchoring fibrils are absent . In this condition there is increased collagenase activity.
- **B.** in dermatitis herpetiformis
- **C.** in porphyria cutanea tarda

According to histological level of the split, bullous dermatosis are classified into:

- Intra-epidermal (friction blisters, eczema, infections and pemphigus vulgaris).
- Sub-epidermal (burns, Dermatitis herpetiformis, erythema multiforme, pemphigoid).

Causes of bullous eruption

- Trauma Causes
  - Pressure sore/skin
- Electromagnetic, Physics, trauma, Radiation Causes
  - Burns/severe/extensive
- Infectious Disorders (Specific Agent)
  - Chickenpox/herpes zoster virus
- Infected organ, Abscesses
  - Infections
  - Bullous impetigo
- Neoplastic Disorders
  - Paraneoplastic Pemphigus
- Allergic, Collagen, Auto-Immune Disorders
- Metabolic, Storage Disorders
  - Porphyria cutanea tarda

- Deficiency Disorders
  - Pellagra/niacin deficiency
- Congenital, Developmental Disorders
  - Epidermolysis bullosa
- Hereditary, Familial, Genetic Disorders
  - Epidermolysis bullosa hered. letalis
  - Acrodermatitis enteropathica
- Usage, Degenerative, Necrosis, Age Related Disorders
  - Epidermolysis bullosa/hands and feet
  - Epidermolysis bullosa, localized
- Anatomic, Foreign Body, Structural Disorders
  - Decubitus ulcer
- Arteriosclerotic, Vascular, Venous Disorders
  - Gangrene, ischemic
  - Ischemic process
- Functional, Physiologic Variant Disorders
  - Bed rest, prolonged
- Drugs
  - Barbiturate overdose

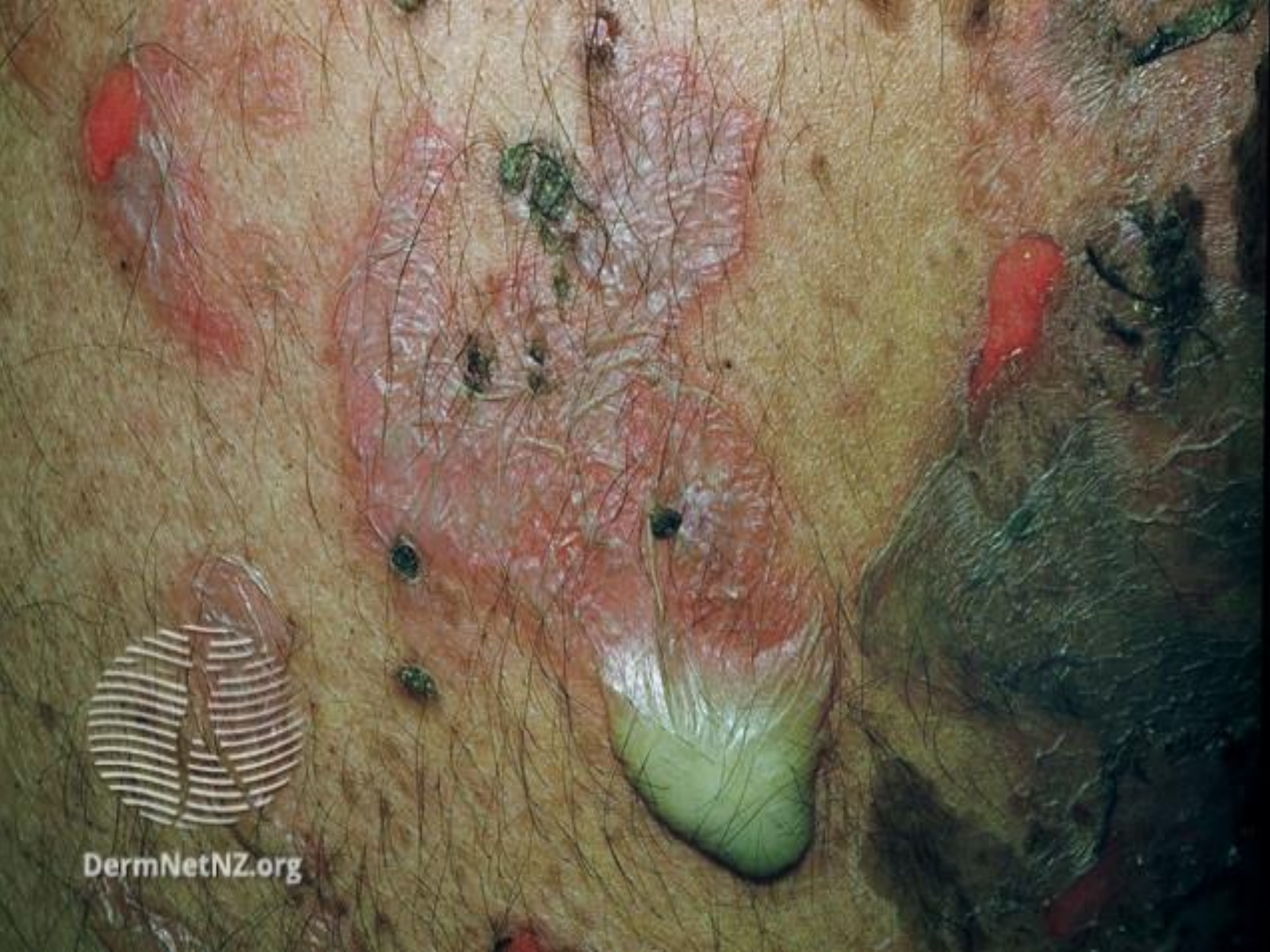
DIFFERENTIAL DIAGNOSIS OF AUTOIMMUNE BULLOUS DERMATOSES

1. Pemphigus vulgaris
2. Paraneoplastic pemphigus
3. Bullous pemphigoid
4. Cicatricial pemphigoid
5. Dermatitis herpetiformis

- The types can be distinguished clinically, because the thin roof of the intra-epidermal blister easily rupture.
- whereas the thicker roof of the sub epidermal blister allows the formation of a tense shiny dome shaped bulla.

Pemphigus vulgaris

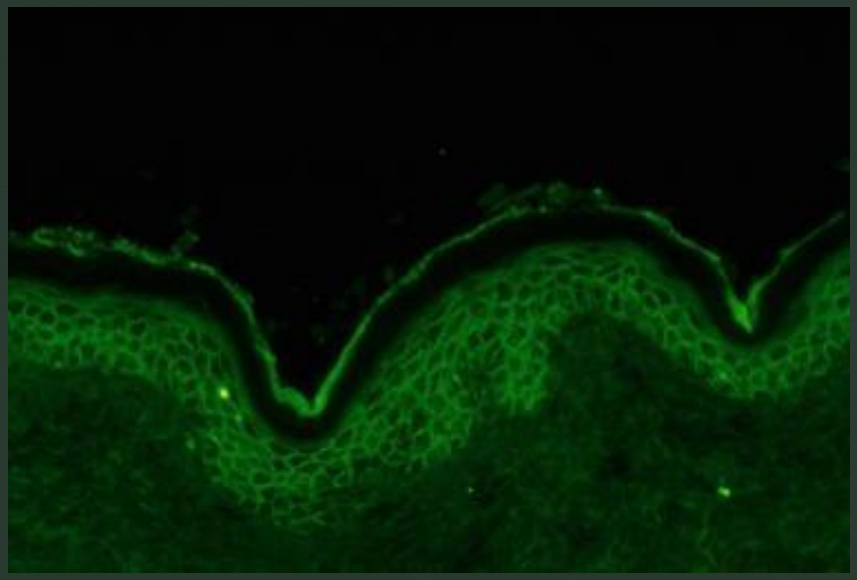
- Pemphigus vulgaris is a rare autoimmune disease that is characterized by painful blisters and erosions on the skin and mucous membranes, most commonly inside the mouth .
- Pemphigus vulgaris accounts for 70% of all pemphigus cases worldwide although it is extremely rare in New Zealand (about one case per million of the population).
- The other two main subtypes of pemphigus are pemphigusfoliaceus and paraneoplastic pemphigus .


DermNetNZ.org

- Pemphigus vulgaris affects people of all races, age, and sex.
- It most commonly appears between the ages of 30 and 60 years and is more common in Jews and Indians than in other races, presumably for genetic reasons.
- Drug-induced pemphigus is also recognized and is most often caused by penicillamine, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and cephalosporins.
- Pemphigus is sometimes triggered by cancer (paraneoplastic pemphigus), infection or trauma.

- Pemphigus vulgaris is an autoimmune blistering disease.
- The keratinocytes are cemented together at unique sticky spots called desmosomes.
- In pemphigus vulgaris, immunoglobulin type G (IgG) autoantibodies bind to a protein called desmoglein 3 (dsg3), which is found in desmosomes in the keratinocytes near the bottom of the epidermis.
- The result is the keratinocytes separate from each other, and are replaced by fluid (the blister).
- About 50% of patients with pemphigus vulgaris also have anti-dsg1 antibodies.

Intercellular deposits of IgG and/or C3 in the epidermis



Cutaneous manifestations.

- Most patients with pemphigus vulgaris first present with lesions on the mucous membranes such as the mouth and genitals. Blisters usually develop on the skin after a few weeks or months, although in some cases, mucosal lesions may be the only manifestation of the disease.
- Skin lesions appear as thin-walled flaccid blisters filled with clear fluid that easily rupture causing itchy and painful erosions.
- They most often arise on the upper chest, back, scalp, and face. Erosions in the skin folds may develop into vegetative lesions which are granular and crusted (pemphigus vegetans).
- The skin around the nails may be painful, red, and swollen.

- The inside of the mouth is commonly involved in pemphigus vulgaris. Involvement of the pharynx and larynx cause pain on swallowing and a hoarse voice.
- Nasal involvement causes congestion and bleeding.
- The conjunctiva, oesophagus, labia, vagina, cervix, penis, urethra and anus may also be affected.

Features of oral mucosal pemphigus include:

- Oral lesions in 50–70% of patients
- Superficial blistering and erosions
- Widespread involvement within the mouth
- Painful, slow-to-heal ulcers
- Spread to the larynx causing hoarseness when talking
- Difficulty eating and drinking.

Complications

Pemphigus vulgaris can cause very extensive, life-threatening erosions, especially if the diagnosis is delayed. Other potentially severe complications may include:

- Secondary bacterial infection
- Fungal infection, especially candida
- Viral infection, especially herpes simplex
- Nutritional deficiencies due to difficulty eating
- Complications of systemic steroids especially infections and osteoporosis
- Complications of immune suppressive treatments
- The psychological effects of severe skin disease and its treatment (anxiety and depression).

Diagnosis of pemphigus vulgaris

- generally requires a biopsy from the skin adjacent to a lesion. Histology typically shows rounded-up and separated keratinocytes (acantholytic cells) just above the basal layer of the epidermis. Suprabasal clefting may be reported. See pathology of pemphigus vulgaris.

- Pemphigus is confirmed by direct immunofluorescence staining of perilesional skin biopsy sections to reveal immunoglobulin (Ig)G antibodies or complement on the cell surfaces of keratinocytes.

- In most cases, circulating antibodies can be detected by a blood test (indirect immunofluorescence test). The level of antibodies fluctuates and may reflect the effectiveness of treatment. Specific anti-dsg1 and anti-dsg3 antibody titres can also be measured in blood or saliva by enzyme-linked immunosorbent assays (ELISAs).

- The primary aim of treatment of pemphigus vulgaris is to decrease blister formation, prevent infections and promote healing of blisters and erosions.
- Systemic corticosteroids are the mainstay of medical treatment for controlling the disease, usually in the form of moderate to high doses of oral prednisone or prednisolone, or as pulsed intravenous methylprednisolone.
- Since their use, many deaths from pemphigus vulgaris have been prevented (the mortality rate dropped from 99% to 5–15%).
- Corticosteroids are not a cure for the disease but improve the patient's quality of life by reducing disease activity.
- The doses of corticosteroids needed to control pemphigus vulgaris and the length of time on treatment may result in serious side effects and risks.

- Other immune suppressive drugs are used off-label to reduce the dose of steroids and may be required by patients with pemphigus vulgaris for years. These are most often:
- Azathioprine
- Mycophenolate mofetil
- Cyclophosphamide

Bullous pemphigoid

- Bullous pemphigoid is an autoimmune subepidermal blistering disease.
- Bullous pemphigoid often presents in people over 80 years of age, and mostly affects people over 50. It can occur in younger adults, but bullous pemphigoid in infants and children is rare.
- Bullous pemphigoid occurs equally in males and females.
- There is an association with human leukocyte antigen (HLA) indicating a genetic predisposition to the disease.

- It is more prevalent in elderly patients with neurological disease, particularly stroke, dementia and Parkinson disease.
- The risk of developing bullous pemphigoid is greater in people with psoriasis, and it can be precipitated by treatment of psoriasis with phototherapy.
- There may be an association with internal malignancy in some patients.
- A drug, an injury, or skin infection can trigger the onset of disease.

- The most common drugs associated with bullous pemphigoid are the PD1-inhibitor immunotherapies (such as pembrolizumab, nivolumab) used to treat metastatic melanoma and other cancers.
- Dipeptidyl peptidase four inhibitors (also called gliptins) used to treat diabetes (such as sitagliptin, saxagliptin, linagliptin and especially, vildagliptin) have also been reported to induce bullous pemphigoid. The median time to onset to bullous pemphigoid is 11 months after initiation of therapy.
- Other cases of bullous pemphigoid have been associated with antibiotics, penicillamine, potassium iodide, frusemide, captopril, gold, penicillin, sulfasalazine, and topical fluorouracil.

- Bullous pemphigoid is the result of an attack on the basement membrane of the epidermis by IgG +/- IgE immunoglobulins (antibodies) and activated T lymphocytes (white blood cells).
- The target is the protein BP180 (also called Type XVII collagen), or less frequently BP230 (a plakin).
- The binding of the autoantibodies to the proteins and release of cytokines from the T cells lead to complement activation, recruitment of neutrophils (acute inflammatory cells) and the release of proteolytic enzymes.
- These destroy the hemidesmosomes and cause the formation of subepidermal blisters.

- Bullous pemphigoid causes severe itch and (usually) large, tense bullae (fluid-filled blisters), which rupture forming crusted erosions.

Other variable features include:

- Nonspecific rash for several weeks before blisters appear
- Eczematous areas resembling nummular dermatitis
- Urticaria-like red skin
- Annular (ring-shaped) lesions
- Smaller blisters (vesicles)
- Prurigo nodules (pemphigoid nodularis)
- Clear or cloudy, yellowish or bloodstained blister fluid
- Postinflammatory pigmentation
- Milia in healed areas

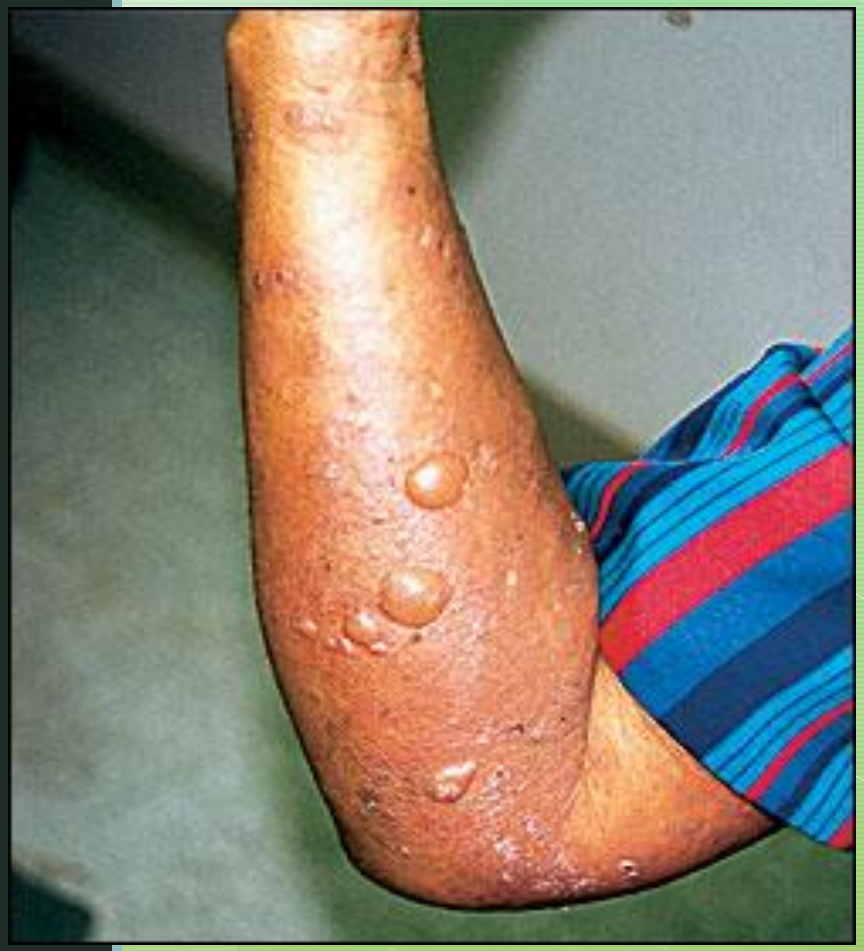
- Bullous pemphigoid can be a serious disease, particularly when widespread or resistant to treatment. Morbidity and mortality result from:
- Bacterial staphylococcal and streptococcal skin infection and sepsis
- Viral infection with herpes simplex, varicella or herpes zoster
- Complications of treatment
- Underlying and associated diseases.

- When typical bullae are present, the diagnosis is suspected clinically. In most cases, the diagnosis will be confirmed by a skin biopsy of an early blister. The diagnosis can also be made from non-blistered, inflamed skin.
- Pathological examination of bullous pemphigoid shows a split under the epidermis. A dermal neutrophilic infiltrate is usual but not always present. Eosinophils may be prominent.
- Direct immunofluorescence staining of a skin biopsy taken adjacent to a blister highlights antibodies along the basement membrane that lies between the epidermis and dermis.
- Blood tests include an indirect immunofluorescence test for circulating pemphigoid BP180 antibodies.
- Other tests will relate to planning and monitoring treatment.

Medical treatment involves:

- Ultrapotent topical steroids to treat limited disease < 10% of body surface (eg, clobetasol propionate cream)
- Moderate potency topical steroids and emollients to relieve itch and dryness
- Systemic steroids (eg, prednisone)
- Tetracycline antibiotics, usually doxycycline 200 mg/day; doxycycline has fewer adverse effects than oral corticosteroids and is effective on its own for mild disease
- Other steroid-sparing medications on their own or in combination with steroids
- Antibiotics for secondary bacterial infection
- Pain relief.

- Most patients with bullous pemphigoid are treated with steroid tablets, either prednisone or prednisolone at an initial dose of 0.5 mg/kg/day. The dose is adjusted until the blisters have stopped appearing, which usually takes several weeks. The dose of prednisone is then slowly reduced once there are fewer than 3 significant blisters, over many months or years. As systemic steroids have many undesirable side effects, other medications are added to ensure the lowest possible dose (aiming for 5–10 mg prednisone daily). These other medications may include doxycycline or:
- Dapsone
- Nicotinamide
- Methotrexate
- Azathioprine
- Mycophenolate
- Intravenous immunoglobulin



- Bullous pemphigoid. Tense bullae on erythematous skin.

Dermatitis herpetiformis

- **Rare, male to female ratio is 2:1, onset at 20 to 40 years of age, but also in children, whites, rare in blacks or Asians**

- **Clinical features:**
- **Grouped (herpetiform) excoriations or vesicles symmetrically located on extensor remission; watch for signs surfaces of elbows, knees, sacrum, buttocks, and shoulders with intense pruritus and burning sensation**

Diagosis

- **Light: neutrophilic abscesses in dermal papillae, dermal infiltrates of neutrophils and eosinophils with subepidermal vesicles**
- **DIF: granular IgA deposits in the tips of the dermal papillae**

treatment

- **Gluten-free diet; sulfones dermal infiltrates of neutrophils and eosinophils**

comment

- **Chronic with occasional remission; watch for signs of other autoimmune disorders; may coexist with gluten-sensitive enteropathy**

Diagnosis

- **Light: subepidermal blister with mixed superficial inflammation DIF: IgG and/or C3 at the basement membrane**

Treatment

- **Corticosteroids (prednisone) alone or with azathioprine, mycophenolate mofetil or a tetracycline**

Erythema multiforme

- Erythema multiforme is a type of hypsersensitivity reaction that occurs in response to medications, infections, or illness.
  - Medications include:
  - Barbiturates
  - Penicillins
  - Phenytoin
  - Sulfonamides

- Infections include:
- Herpes simplex
- Mycoplasma

- The exact cause is unknown. The disorder is believed to involve damage to the blood vessels of the skin, followed by damage to skin tissues.
- Some forms of this condition are more severe than others.

- **Erythema multiforme minor** is not very serious. Most erythema multiforme is caused by herpes simplex or mycoplasma infections.
- **Erythema multiforme major** is more severe, and is known as Stevens-Johnson syndrome. The more severe form is usually caused by reactions to medications, rather than infections.

- Erythema multiforme occurs primarily in children and young adults

- Multiple skin lesions:
  - Start quickly and may return and May spread
  - May appear as a nodule, papule, or macule and may look like hives
  - Central sore surrounded by pale red rings, also called a "target", "iris", or "bulls-eye"
  - May have vesicles and blisters

- Located on the upper body, legs, arms, palms, hands, or feet
- May involve the face or lips
- Usually even on both sides (symmetrical)

- **Other symptoms that may occur with this disease:**
- Bloodshot eyes
- Dry eyes
- Eye burning, itching, and discharge
- Eye pain
- Mouth sores
- Vision problems

Thank you