In the strict sense, blistering and pustular diseases do not include physical injuries (e.g., burns and frostbite) or infections (e.g., those by bacteria or by viruses such as herpes). Diseases that are associated with blistering are divided into inherited congenital ones and acquired ones. Congenital blistering diseases such as epidermolysis bullosa are caused by mutation in the gene that codes for epidermal basement membrane structural proteins. Ultrastructural molecular sites where the genetic mutation is expressed become fragile, which results in blistering. Since the causative gene of epidermolysis bullosa was identified, accurate diagnosis of disease subtypes, genetic consulting and prenatal diagnosis have become possible. Acquired blistering diseases such as pemphigus and bullous pemphigoid are autoimmune diseases. Autoantibodies against epidermal structural proteins are produced, which leads to fragility of the epidermis and blistering. Pustular diseases are those in which multiple sterile pustules are produced.

**A. Genetic blistering diseases**

**a. Epidermolysis bullosa (EB)** (Fig. 14.1)

*Synonym: Epidermolysis bullosa hereditaria*

- **Outline**
  - It is caused by a mutation in structural molecules of the epidermal basement membrane.
  - Shortly after birth, blisters, erosions and ulcers form at sites of friction in newborns, whose skin is congenitally fragile (Nikolsky’s sign).
  - It is divided by the ultrastructural site of cleavage into EB simplex (in the epidermis), junctional EB (in the lamina lucida junctions), and dystrophic EB (in the dermis). It is subdivided into 10 to 30 subtypes by clinical features, inheritance patterns and causative genes (Table 14.1, Fig. 14.2).
  - Identification of genetic mutation by immunofluorescence (IF) to determine protein levels, and electron microscopy of the cleavage site are important for diagnosis.
  - There are no effective treatments, only symptomatic treatments.

1. **Epidermolysis bullosa simplex (EBS)**

*Outline*

- The three main types of EBS are Dowling-Meara EBS
Table 14.1 Classification of epidermolysis bullosa (EB).

<table>
<thead>
<tr>
<th>3 major types</th>
<th>Main subtypes</th>
<th>Causative protein and gene</th>
<th>Inheritance pattern (autosomal chromosome)</th>
<th>Clinical features</th>
<th>Immunohistochemistry and immunoelectron microscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>EB simplex (EBS)</td>
<td>Dowling-Meara (severe)</td>
<td>Keratin 5/14</td>
<td>AD</td>
<td>Blistering on the whole body surface</td>
<td>Intraepidermal blisters, aggregation of keratin fibers</td>
</tr>
<tr>
<td></td>
<td>Köbner (moderate)</td>
<td>Keratin 5/14</td>
<td>AD</td>
<td>Blistering spread to sites other than the palms and soles</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weber-Cockayne (mild)</td>
<td>Keratin 5/14</td>
<td>AD</td>
<td>Blistering on the palms and soles</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EBS associated with muscular dystrophy</td>
<td>Plectin</td>
<td>AR</td>
<td>Late-onset muscular dystrophy as a complication</td>
<td></td>
</tr>
<tr>
<td>Junctional EB (JEB)</td>
<td>Herlitz JEB</td>
<td>Laminin-332</td>
<td>AR</td>
<td>Blistering and erosion on the whole body at birth. Death within 1 year after birth</td>
<td>Lamina lucida blister, absence of laminin 332</td>
</tr>
<tr>
<td></td>
<td>Non-Herlitz JEB</td>
<td>Laminin-332</td>
<td>AR</td>
<td>Poor development in teeth and nails. Alopecia. Good prognosis</td>
<td>Lamina lucida blister, reduced laminin 332 or complete absence of Type XVII collagen.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type XVII collagen</td>
<td>AR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>JEB associated with pyloric atresia</td>
<td>α6β4 integrin</td>
<td>AR</td>
<td>Blistering on the whole body. Congenital pyloric atresia. Poor prognosis</td>
<td>Lamina lucida blister. Absence or reduced α6β4 integrin.</td>
</tr>
<tr>
<td>Dystrophic EB (DEB)</td>
<td>Hallopeau-Siemens recessive DEB</td>
<td>Type VII collagen</td>
<td>AR</td>
<td>Recurrent blistering on the extremities and trunk. Fusion of fingers and toes in club-shape.</td>
<td>Intradermal blister. Hypoplastic anchoring fibrils</td>
</tr>
<tr>
<td></td>
<td>Non-Hallopeau-Siemens recessive DEB</td>
<td>Type VII collagen</td>
<td>AR</td>
<td>Milder than Hallopeau-Siemens recessive type</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autosomal dominant DEB</td>
<td>Type VII collagen</td>
<td>AD</td>
<td>Comparatively mild</td>
<td></td>
</tr>
</tbody>
</table>

(MEMO)

Are epidermolysis bullosa hereditaria and epidermolysis bullosa different?

Epidermolysis bullosa may be called “epidermolysis bullosa hereditaria” to distinguish it from epidermolysis bullosa acquisita; however, the name “epidermolysis bullosa” is now widely used for all hereditary bullous.

Fig. 14.2 The mechanism of epidermolysis bullosa.
(severe), Köbner EBS (moderate), and Weber-Cockayne EBS (mild). The disorder is caused by keratin gene mutation (K5 or K14). It is autosomal dominantly inherited.

- Blisters form at sites prone to friction, beginning at birth or early childhood.
- The prognosis is generally good. It subsides with age.
- EBS with muscular dystrophy (EBS-MD), a rare type of EBS, is caused by a plectin gene mutation. Inheritance is autosomal recessive.

**Clinical features**

Shortly after birth, blisters of various sizes form at sites that are prone to friction: hands, feet, elbows, knees and so on. Blistering is observed by rubbing a normal site on the skin of a patient with severe EBS (Nikolsky’s sign). EBS heals without scarring. It tends to aggravate in summer, from the high temperature. It subsides with age and generally has a good prognosis. EBS is dermatologically divided by severity into three subtypes; however, there are intermediate subtypes. EBS with muscular dystrophy (EBS-MD) is rare (MEMO).

1. **Dowling-Meara EBS**: Ring-shaped blisters form. When it occurs in newborns, systemic erosions and fatality may occur. This is the severest subtype (Fig. 14.3).
2. **Köbner EBS**: Blistering is present on the whole body surface. The severity is moderate (Figs. 14.4-1 and 14.4-2).
3. **Weber-Cockayne EBS**: Blister only on the hands and feet. It is the mildest subtype (Fig. 14.7).

**Pathogenesis**

Basal cells collapse from mutation of either the K5 or K14 gene, which codes for cytoskeletons of basal cells (intermediate filaments). Cleavage occurs, resulting in blistering. Epidermolysis bullosa simplex (EBS) is autosomal dominantly inherited. The severity depends on the type and location of the mutation in the K5 or K14 gene. The severity of clinical symptoms is measured by the location of genetic mutation and the amino acids produced.

**Pathology**

Separation occurs within the cytoplasm of the epidermal basal cells, which leads to intra-epidermal blistering (Fig. 14.5). Clumping of degenerated keratin fibers in severe Dowling-Meara EBS is clearly observable by electron microscopy (Fig. 14.6).

**Treatment**

Symptomatic therapies are the main treatments. Friction and warm temperatures should be avoided. Local therapies (e.g., drainage of blisters, application of antibiotic ointments) are helpful. The cutaneous symptoms subside with age.
Clinical images are available in hardcopy only.

**Fig. 14.7 Epidermolysis bullosa simplex, Weber-Cockayne type.**
Blistering is localized on the hands and feet. Blistering is induced by mechanical stimulation, such as from long walks.

**Epidermolysis bullosa simplex associated with muscular dystrophy**
This specific type of epidermolysis bullosa simplex is associated with late-onset muscular dystrophy, a disease caused by plectin gene mutation. Plectin is a protein found in the epidermal basement membrane, hemidesmosomes and sarcolemma of muscle fascia. The mutation is autosomal recessively inherited. Epidermolysis bullosa simplex is accompanied by muscular dystrophy in the fingers and toes, and muscle atrophy.

Clinical images are available in hardcopy only.

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**Fig. 14.4-2 Epidermolysis bullosa simplex, Köbner type on hands.**

**Fig. 14.5 Electron microscopic image of epidermolysis bullosa simplex.**
The arrows indicate lamina densa. The cytoplasm of the basal cells (indicated by stars) on the basement membrane is damaged, leading to blistering.

**Fig. 14.6 Aggregation of keratin fibers seen in Dowling-Meara type.**

Clinical images are available in hardcopy only.
Blistering occurs at dermo-epidermal junctions. The disease is caused by dissociation of the lamina lucida in the basal cells. All JEB subtypes are autosomal recessively inherited. The majority of patients with Herlitz JEB die within 1 year after birth. Non-Herlitz JEB has a better prognosis. JEB with pyloric atresia, an atypical type, is caused by genetic mutation in the integrin $\alpha_6$ or integrin $\beta_4$ gene. The prognosis is poor. Symptomatic therapies are the main treatments. In recent years, genetic counseling and prenatal diagnosis have been conducted.

In Herlitz JEB, there is systematic blistering, erosion and ulceration in newborns after birth. The lesions do not heal, but recur and enlarge. Mucosal lesions and growth insufficiency of teeth and nails are seen. Herlitz JEB is fatal, causing death within 1 year after birth in almost all cases (Fig. 14.8). Non-Herlitz JEB has a better prognosis, and patients may survive to reproductive age. Non-scaling alopecia, palmoplantar keratosis, nail deformity, and aplasia of dental enamel are present (Fig. 14.9). Nikolsky’s sign is positive.

Herlitz JEB and non-Herlitz JEB are the two main subtypes of JEB. They differ in prognosis. Herlitz JEB is caused by the complete absence of laminin 332 (laminin 5). Non-Herlitz JEB is caused by reduction of laminin 332 or complete absence of type XVII collagen (BP180). It has a better prognosis.

JEB with pyloric atresia is caused by a genetic mutation in integrin $\alpha_6$ or integrin $\beta_4$ in the membrane ligands of hemidesmosomes. Complications associated with the disease are systemic junctional bullosa and congenital pyloric atresia. It is fatal soon after birth in many cases (Fig. 14.10).

JEB presents as subepidermal blistering under light microscopy. Blister formation is observed between the basal cell plasma membrane and the lamina densa. Electron microscopy shows the separation more clearly (Figs. 14.2 and 14.11).

Symptomatic therapies are the main treatments for JEB. Friction should be avoided. Local therapies and symptomatic therapies including nutrition management, topical application of ointments and antibiotic administration are conducted. Prenatal diagnosis is also made in severe cases, such as Herlitz JEB.
Fig. 14.9 Junctional epidermolysis bullosa, non-Herlitz type.
Blistering and pigmentation occur on the whole body surface. Nonscarring alopecia also occurs on the scalp.

Fig. 14.10 Junctional epidermolysis bullosa associated with pyloric atresia.
Aplasia cutis congenita-like ulcer of skin and congenital pyloric atresia occur as complications.

Fig. 14.11 Electron microscopic image of junctional epidermolysis bullosa.
A blister (star) forms in the lamina lucida, between the plasma membrane of the basal keratinocytes (purple arrows) and the lamina densa (black arrows).
3. Dystrophic epidermolysis bullosa (DEB)

**Outline**
- There are several subtypes; however, all are caused by a mutation in the gene that codes for type VII collagen, a structural component of anchoring fibrils. Subepidermal blistering is present over the entire body.
- DEB can be autosomal dominantly inherited or recessively inherited. Nikolsky’s sign is positive.

1. Hallopeau-Siemens recessive DEB (HS-RDEB)
   Hallopeau-Siemens recessive DEB is the severest DEB. At birth or shortly thereafter, blisters and erosions appear recurrently on the extremities and trunk, with or without external influences. They heal, leaving milium and scarring, which results in the club-shaped coalescence of fingers and toes (Fig. 14.12). Lesions are mostly seen in nails, oral mucosa and esophageal mucous membranes, and there is a tendency for esophageal atresia and dysphagia to occur. The symptoms do not subside with age. When patients reach adolescence or older, a malignant tumor (squamous cell carcinoma, in particular) often occurs. Expression of type VII collagen is completely absent. Recessive Hallopeau-Siemens is extremely serious and may cause death in young patients.

2. Non-Hallopeau-Siemens recessive DEB (non-HS-RDEB)
   Type VII collagen is reduced, but not completely absent. The clinical symptoms are less severe than those of Hallopeau-Siemens (Fig. 14.13).

3. Autosomal dominant DEB
   This DEB occurs in newborns and infants. Multiple blisters form on the extensor surfaces of the extremities. The disease may cause esophageal atresia, or papules on the trunk. It heals with scarring (Fig. 14.14). Deformation of nails is present. It tends to subside over time.

**Pathogenesis**
Dystrophic epidermolysis bullosa (DEB) is caused by a mutation in the gene that codes for the type VII collagen, a main component of anchoring fibrils that is essential in connecting the dermis and the epidermis. Subepidermal blistering occurs from hypoplasia of anchoring fibrils (Fig. 14.2).

**Pathology**
Subepidermal blistering (dermolysis) is present. Dissociation is observed immediately below the lamina densa by electron microscopy (Figs. 14.15 and 14.16). It is characterized by hypoplasia of anchoring fibrils.

**Laboratory findings, Differential diagnosis**
DEB is diagnosed by findings obtained by clinical examination, electron microscopy and immunofluorescence (IF). DNA tests are conducted to determine whether it is autosomal...
Fig. 14.13 Dystrophic epidermolysis bullosa, non-Hallopeau-Siemens type.
Scarring blisters, crusts and adhesion occur in the fingers; however, these are milder than in the Hallopeau-Siemens type. Expression of collagen type VII remains.

Fig. 14.14 Dominant dystrophic epidermolysis bullosa.
a: Blistering and scarring occur on areas subjected to friction, such as knees. b: Deformity in the toenails.

Fig. 14.15 Light microscopic image of dystrophic epidermolysis bullosa.
Typical subcutaneous blistering and slight inflammatory cellular infiltration are present.

Fig. 14.16 Electron microscopic image of dystrophic epidermolysis bullosa.
Blistering is observed immediately beneath the lamina densa (arrows).
dominant or recessive. For Hallopeau-Siemens recessive DEB with severe clinical symptoms, prenatal diagnosis is made by fetal skin biopsy, amniocentesis and chorionic villis biopsy.

**Treatment**

Synthetic type VII collagen therapy has been attempted on DEB patients in recent years. Friction is avoided and topical therapies are applied. Fluid therapies, nutritional management and genetic counseling are conducted for recessive DEB.

**b. Other genetic blistering diseases**

1. **Skin fragility syndrome**

Skin fragility syndrome, an autosomal recessive inherited disease, is caused by abnormality in the gene that codes for plakophilin 1, a desmosomal structural protein. Epidermal fragility, painful hyperkeratosis in the hands and soles, and abnormalities of hair, nails and perspiration are found.

**2. Hailey-Hailey disease**

Synonym: Familial benign chronic pemphigus

**Outline**

- Vesicles aggregate on an erythematous base in areas exposed to friction. The appearance resembles that of impetigo.
- It is autosomal dominantly inherited and occurs in adults in their 30s.
- It is caused by a mutation in the ATP2C1 gene that codes for a calcium pump in the Golgi apparatus within keratinocytes.
- The pathology is acantholysis and villi formation. It is somewhat similar to Darier’s disease.
- Topical steroid application is the main treatment.

**Clinical features**

Hailey-Hailey disease is inherited. It tends to manifest in adults in their 30s, appearing as aggregated erythema and blistering in areas that are exposed to friction, such as the cervical regions, axillary fossa, inguinal regions and anus. On an erythematous blistering base there are crusts, pustule formation and pigmentation, and secondary infection produces impetigo-like lesions (Fig. 14.17). Itching is usually present. Although it heals without scarring, it leaves abnormal pigmentation and is recurrent. The disease worsens in summer, and subsides in winter. It is worsened by external friction, perspiration, infection and UV radiation.

**Pathology**

Acantholysis of the epidermis leads to intradermal lacunae

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**Fig. 14.17 Hailey-Hailey disease.**

a, b: Vesicles, erosion, impetigo and pustules form in the groin. c: Blisters may appear, although only rarely.

**Fig. 14.18 Histopathology of Hailey-Hailey disease.**

Intraepidermal acantholysis.