

Bullous Pemphigoid

Clinical presentation • Immune pathogenesis • Morphology • Diagnosis

Autoimmune subepidermal blistering disease

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Learning objectives

- Localize bullous pemphigoid within the spectrum of blistering diseases.
- Connect hemidesmosomal autoantibodies to subepidermal cleavage.
- Recognize characteristic clinical, histologic and immunofluorescence patterns.
- Differentiate pemphigoid from pemphigus and dermatitis herpetiformis.
- Construct a rational confirmatory diagnostic approach.

A characteristic clinicopathologic pattern

Clinical findings

- Older individual with severe pruritus
- Tense, clear-fluid blisters
- Flexural or truncal involvement

Pathology findings

- Subepidermal, nonacantholytic bulla
- Eosinophil-rich inflammation
- Linear immunoreactants at the junction

Blistering diseases are classified by split level

Subcorneal

Very superficial

Pemphigus foliaceus

Roof includes superficial keratin

Suprabasal

Inside epidermis

Pemphigus vulgaris

Basal cells still attach to dermis

Subepidermal

Below epidermis

Bullous pemphigoid

Full epidermal thickness is lifted

Desmosomes and hemidesmosomes have different roles

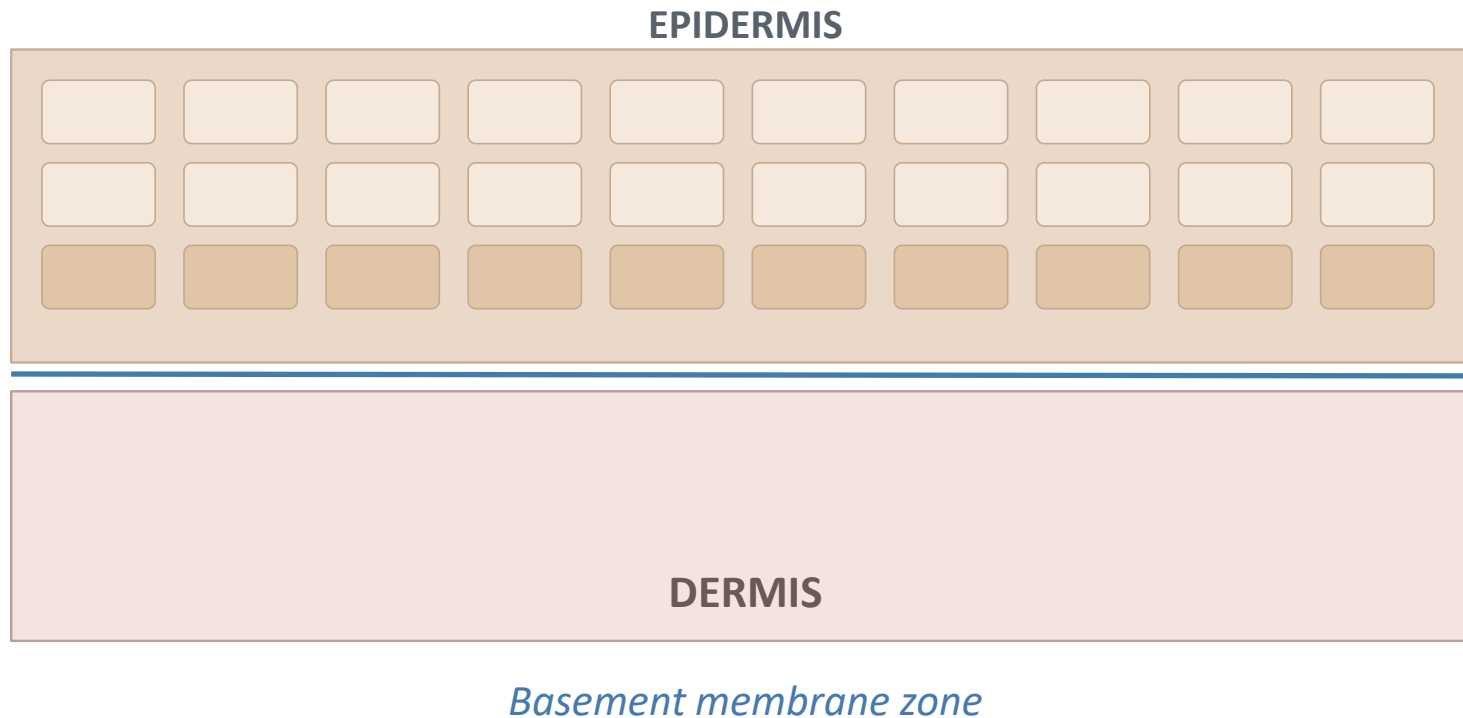
Desmosomes

- Attach adjacent keratinocytes
- Maintain cell-to-cell cohesion
- Disrupted in pemphigus

Hemidesmosomes

- Anchor basal keratinocytes
- Connect epidermis to basement membrane
- Targeted in bullous pemphigoid

Normal epidermis is anchored to the dermis



Morphologic interpretation

- Basal keratinocytes attach to the basement membrane zone.
- Hemidesmosomal complexes resist separation under mechanical stress.

Schematic (not a histologic image)

The level of cleavage determines blister robustness

Intraepidermal cleft

- Part of the epidermis remains below the blister.
- Thin roof tears more readily.
- Typical of pemphigus.

Subepidermal cleft

- The entire epidermis forms the roof.
- Relatively robust roof produces tense bullae.
- Typical of bullous pemphigoid.

Bullous pemphigoid is an acquired autoimmune disease

- Autoantibodies recognize proteins required for epidermal attachment.
- The target structure is the hemidesmosome–basement membrane interface.
- Inflammation progressively weakens dermoepidermal adhesion.
- Cleavage develops beneath an otherwise cohesive epidermis.

Bullous pemphigoid predominantly affects older adults

- An older age distribution.
- The disease may be clinically variable rather than uniformly bullous.
- Age is an important clue, not a sufficient diagnostic criterion.

The distribution favors flexural and truncal sites

Upper limb flexures

Flexor forearms, axillae

Trunk

Lower abdomen

Lower limb flexures

Inner thighs, groin

Severe pruritus may dominate the presentation

- Marked itching is a clinically important component.
- Pruritic lesions may be noticed before unequivocal blisters.
- Excoriations can obscure the primary eruption.
- Absence of a visible tense bulla does not exclude pemphigoid.

Urticarial plaques are a recognized presentation

Before blistering

- Pruritic, urticarial plaques
- Variable erythema
- No obvious epidermal separation

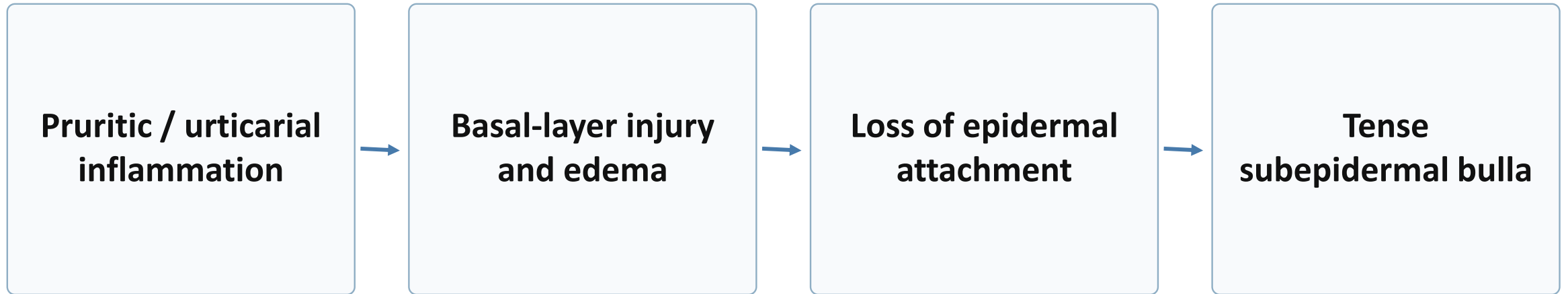
As blistering develops

- Tense fluid-filled bullae
- Normal-looking or erythematous surrounding skin
- Subepidermal cleft on tissue examination

Nonbullous pemphigoid requires diagnostic suspicion

- The contemporary guideline recognizes nonbullous presentations.
- Histology of early lesions can be nonspecific.
- Direct immunofluorescence and antibody studies are especially useful.
- A negative routine section alone is insufficient to dismiss the diagnosis.

The transition from inflammation to blistering



Inflammatory change can precede a fully developed blister.

A typical bulla is tense and filled with clear fluid

- Blisters arise on erythematous or normal-appearing skin.
- Intact epidermis constitutes the full blister roof.
- Bullae tend to remain intact longer than in pemphigus.

Bulla size varies considerably

- Most bullae are described as less than 2 cm in diameter.
- Robbins also describes occasional lesions measuring 4–8 cm.
- Size alone does not identify the disease; Cleavage level is decisive.

Blisters may occur without marked surrounding erythema

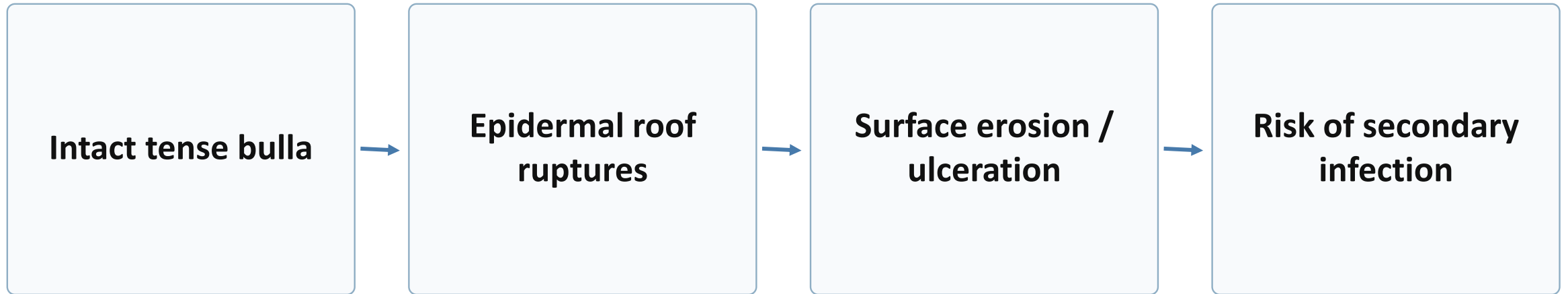
Erythematous background

- Visible inflammatory skin change
- Pruritus and urticarial plaques may coexist

Normal-appearing background

- Tense clear-fluid bulla
- Underlying immune injury may not be obvious clinically

Rupture produces erosions and possible secondary injury



Secondary infection can alter the expected pattern of healing.

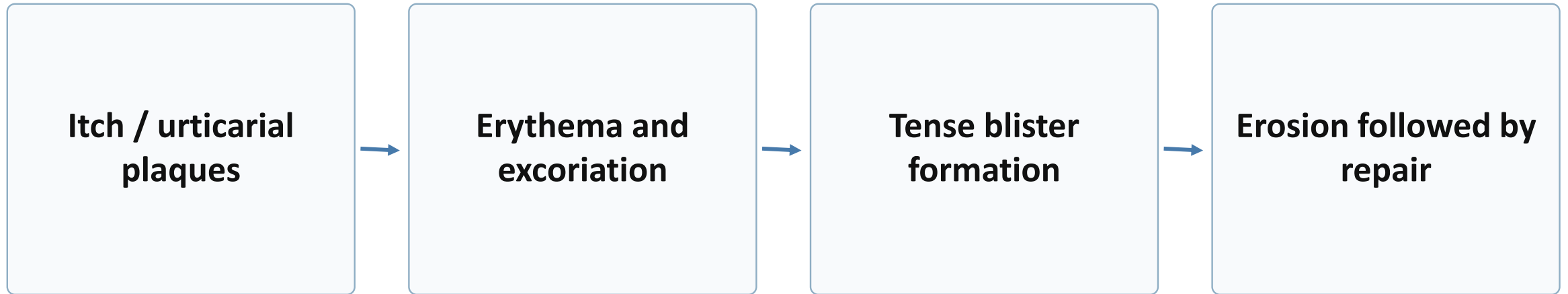
Healing is usually noncicatricial

- Uncomplicated lesions generally heal without scarring.
- Secondary infection can produce tissue damage and scars.
- Significant scarring should prompt reconsideration of the differential.

Mucosal involvement is less common than in pemphigus

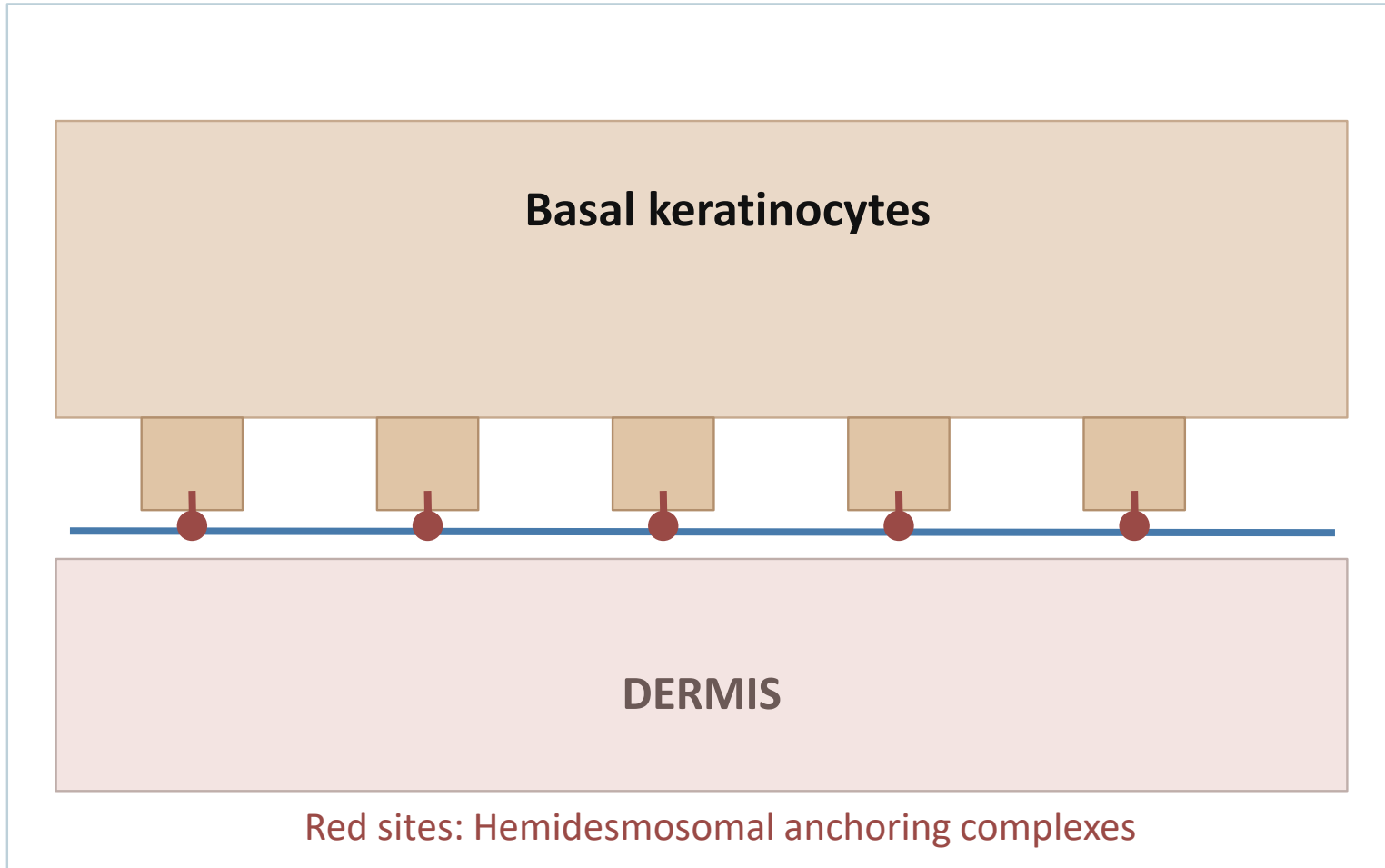
- Oral lesions in approximately 10–15% of affected individuals.
- Oral lesions usually appear after cutaneous lesions.
- Extensive mucosal disease invites evaluation for other pemphigoid phenotypes.

Clinical manifestations form a continuum



Not all patients show every stage, and lesions can coexist.

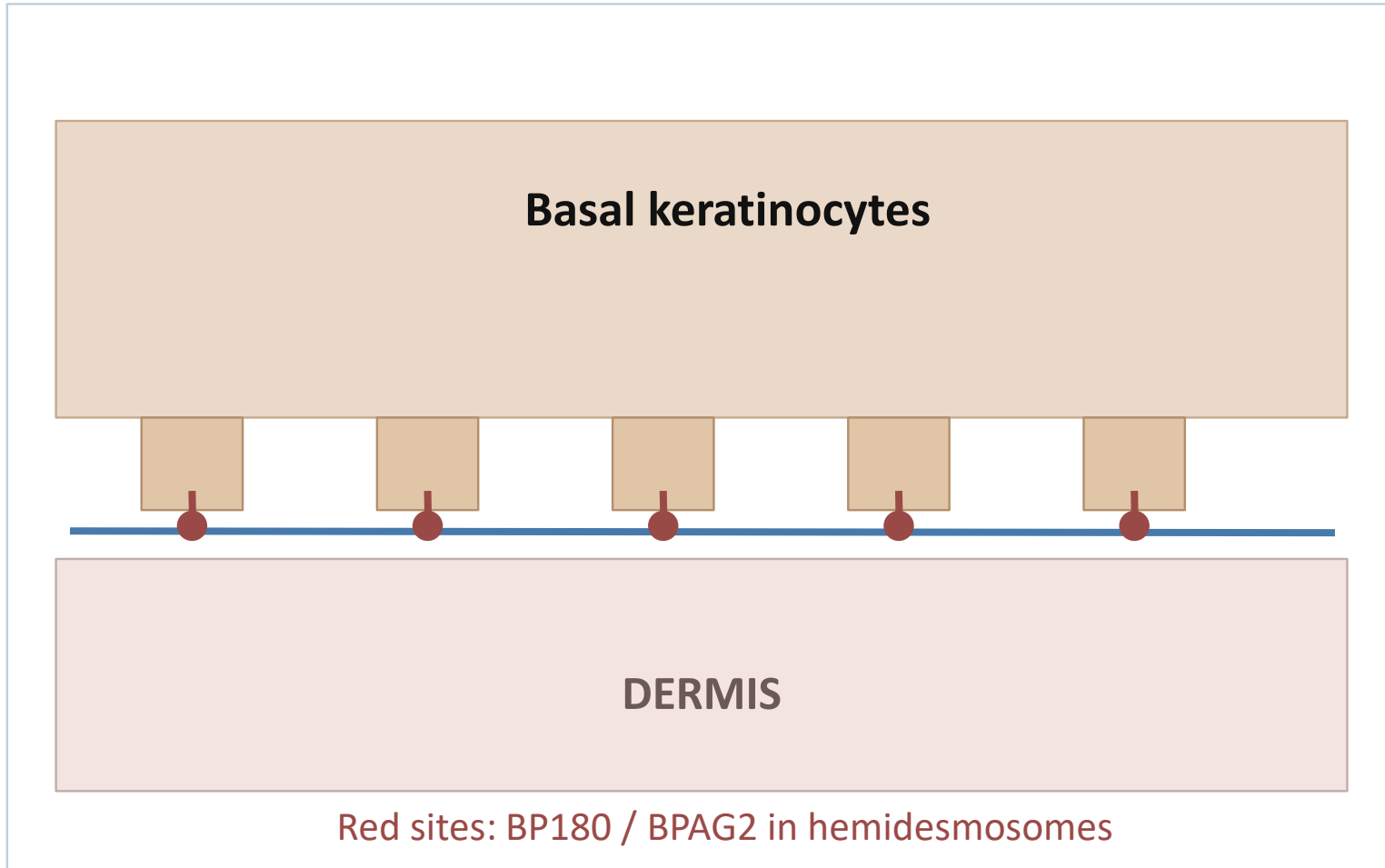
The autoantibody targets lie in hemidesmosomes



- Bullous pemphigoid antigens (BPAGs) are junctional proteins.
- Disrupted attachment occurs beneath basal keratinocytes.

Structural schematic

BPAG2 is a demonstrated pathogenic antigen



- Pathogenic antibodies directed against BPAG2.
- BPAG2 is termed BP180 / type XVII collagen in the EADV guideline.

Structural schematic

BP230 is another recognized autoantigen

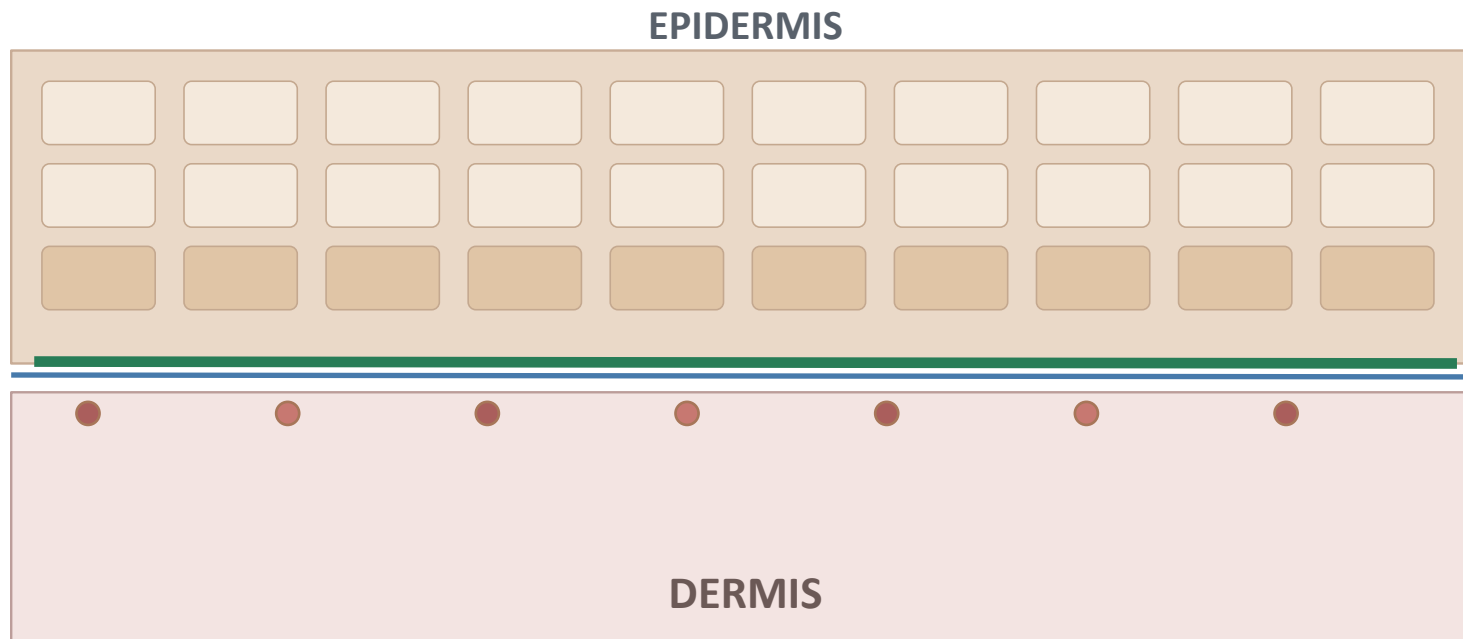
BP180 / BPAG2

- Transmembrane component of attachment machinery
- Pathogenic autoantibodies demonstrably induce blistering

BP230 / BPAG1e

- Hemidesmosomal plaque-associated antigen
- Serologic marker included in contemporary investigations

Immune targeting occurs at the basal cell interface



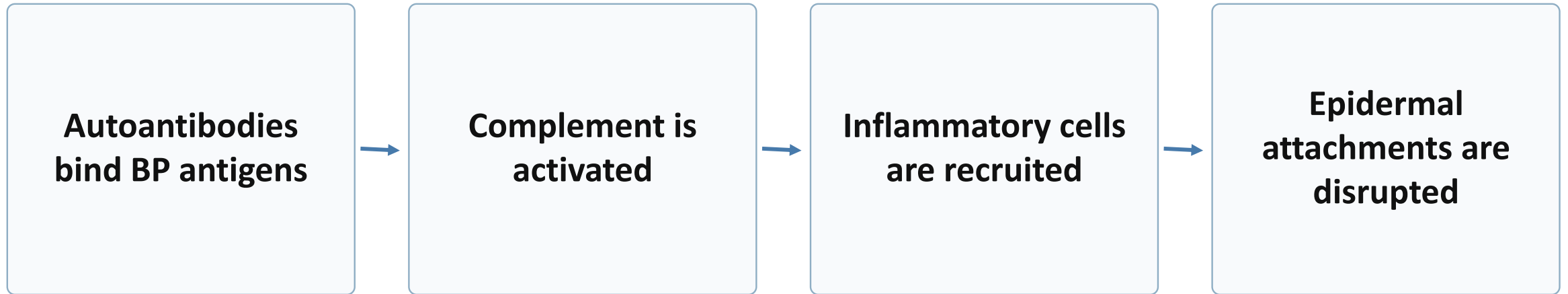
Antibody binding at basement membrane zone

Morphologic interpretation

- Immunoglobulin binds proteins at the hemidesmosomal zone.
- The immune signal localizes along the dermoepidermal interface.

Schematic (not a histologic image)

Complement activation amplifies tissue inflammation



Robbins explicitly describes complement-mediated inflammatory recruitment.

Eosinophils are a central morphologic clue

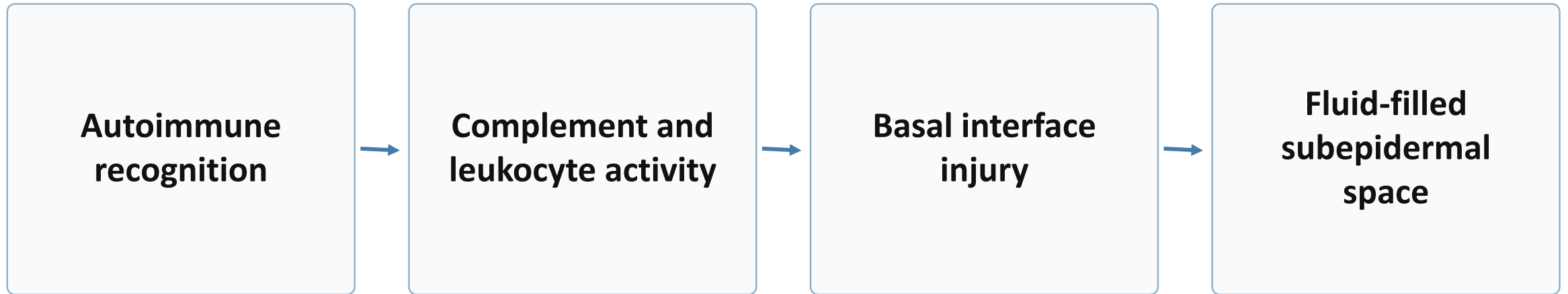
Inflammatory recruitment

- Eosinophils accumulate near basal keratinocytes
- Neutrophils may be present
- Lymphocytes populate perivascular sites

Morphologic consequence

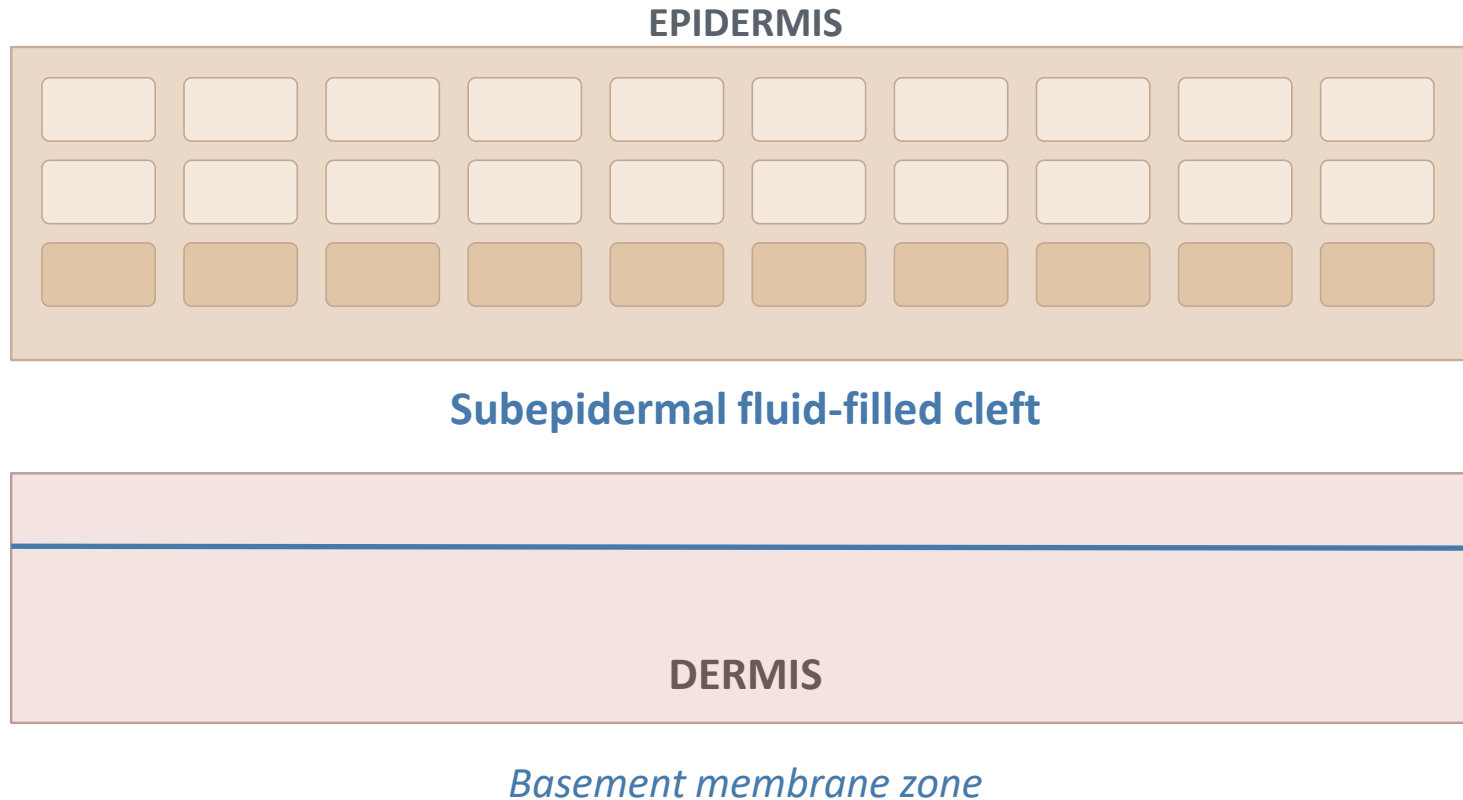
- Subepidermal inflammation
- Basal-cell vacuolization
- Progressive cleft formation

Inflammation translates antibody binding into cleavage



The pathway connects the immune lesion to the clinical tense bulla.

The plane of separation is subepidermal



Morphologic interpretation

- The entire epidermis remains on the blister roof.
- The separation occurs at the dermoepidermal interface.

Schematic (not a histologic image)

Bullous pemphigoid contrasts with pemphigus mechanistically

Bullous pemphigoid

- Hemidesmosomal / basement membrane targets
- Basal anchoring failure
- Subepidermal nonacantholytic cleft

Pemphigus

- Desmoglein targets in desmosomes
- Keratinocyte-to-keratinocyte failure
- Intraepidermal acantholytic cleft

Early lesions may be largely inflammatory

- Superficial and sometimes deeper perivascular lymphocytes are seen.
- Eosinophil numbers vary; Occasional neutrophils may be present.
- Dermal edema may precede an overt split.
- Basal-cell vacuolization is an important early change.

Perivascular inflammation is not disease-specific

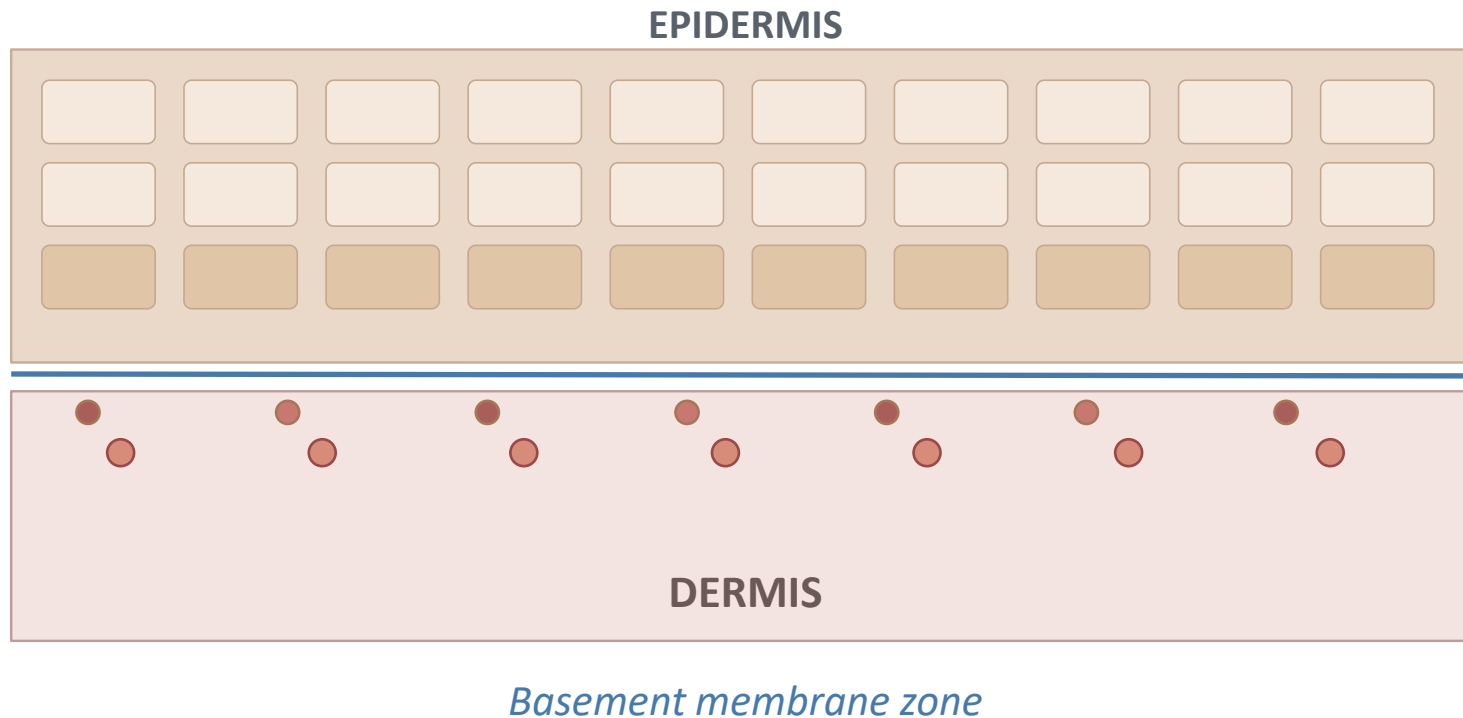
What it establishes

- A superficial or deeper inflammatory process
- Compatibility with an early inflammatory blistering lesion

What it does not establish

- The exact autoantibody specificity
- A confirmed bullous pemphigoid diagnosis
- An unequivocal split if no bulla is present

Eosinophils preferentially approach the basal layer

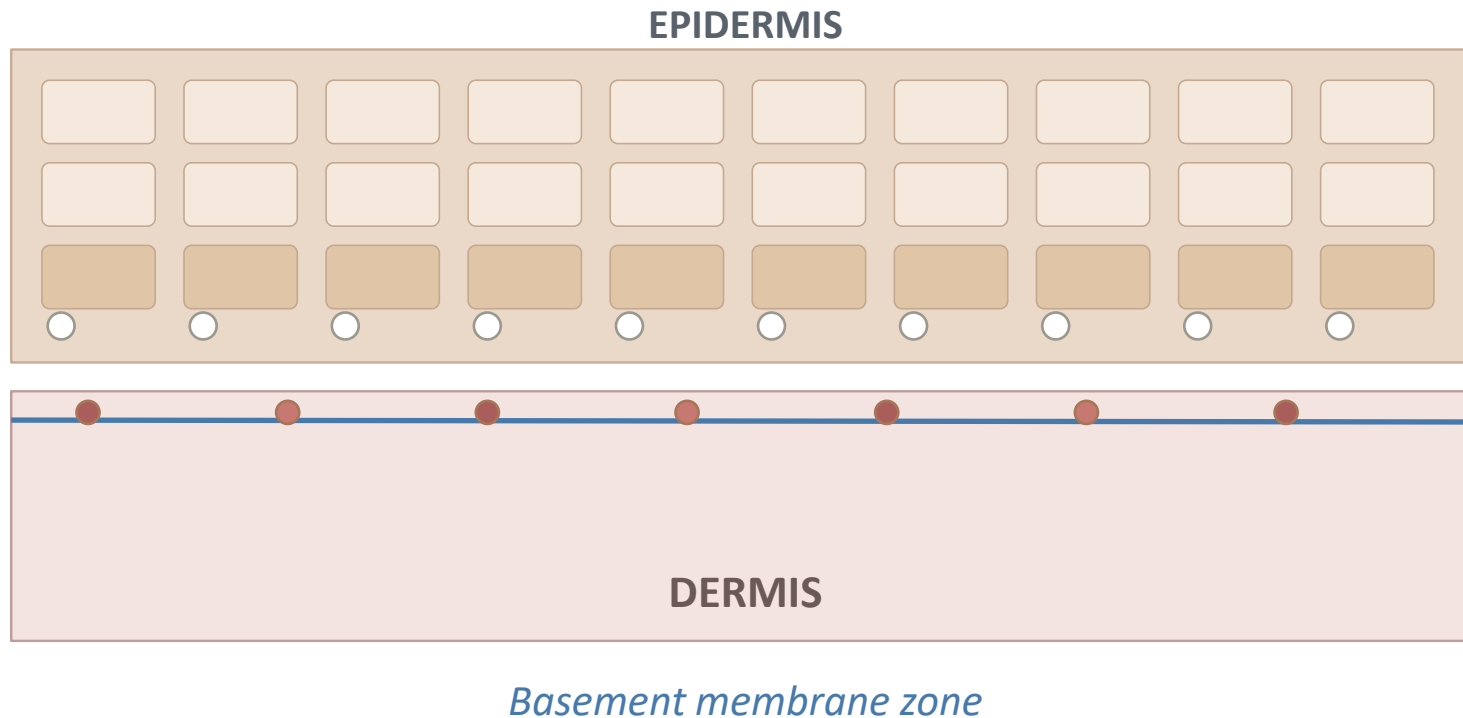


Morphologic interpretation

- Eosinophils frequently cluster beneath basal keratinocytes.
- The location connects inflammation to future epidermal detachment.

Schematic (not a histologic image)

Basal vacuolization is a precursor to separation

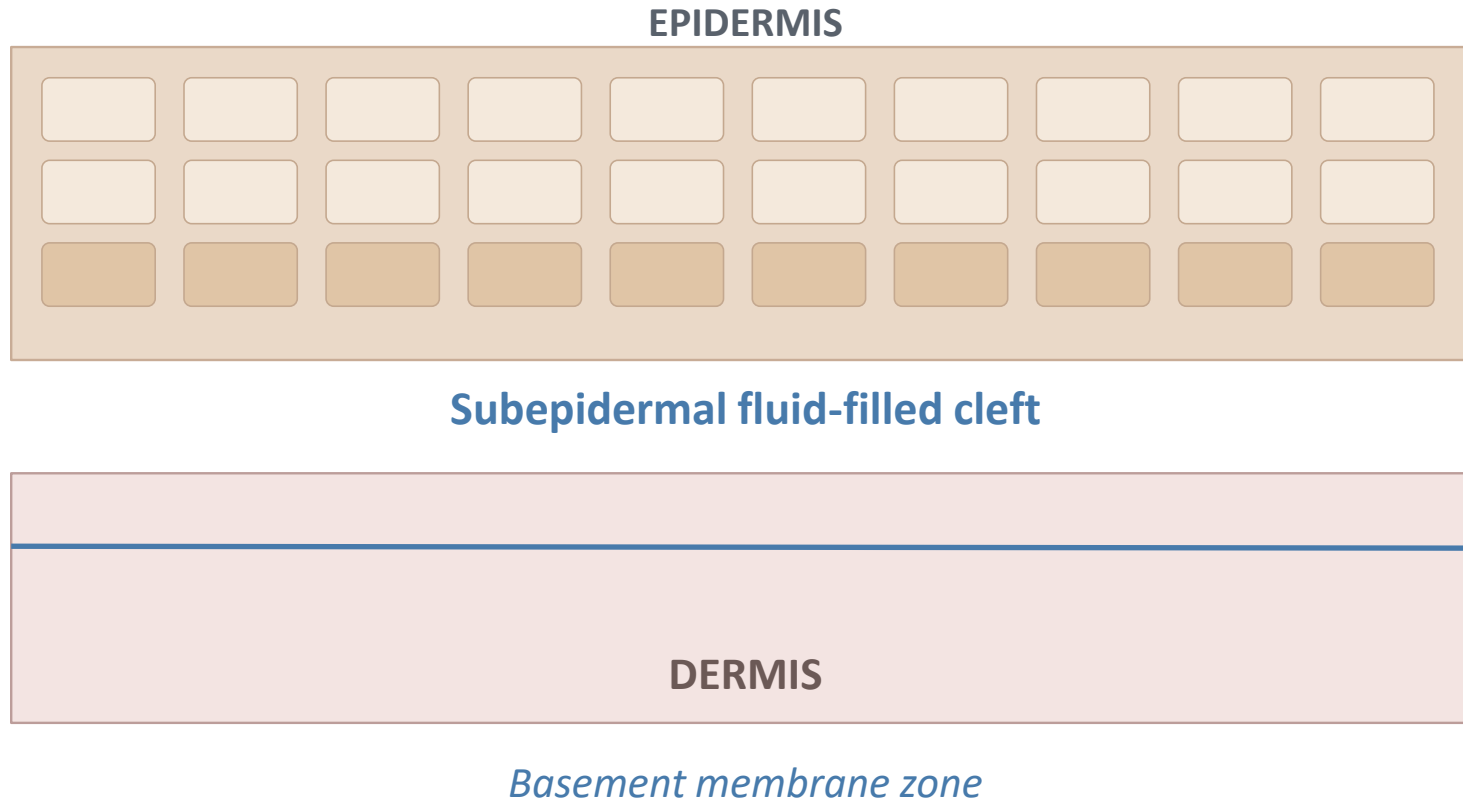


Morphologic interpretation

- The basal-cell layer develops vacuolar change.
- Injury permits lifting of the epidermis and formation of a cleft.

Schematic (not a histologic image)

A mature blister preserves the epidermal roof



Morphologic interpretation

- An intact, full-thickness epidermis roofs the bulla.
- Fluid accumulates in the subepidermal compartment.

Schematic (not a histologic image)

Routine histology shows a nonacantholytic blister

- The principal cleavage is beneath the epidermis.
- Keratinocytes retain their intercellular attachment.
- Inflammatory cells, particularly eosinophils, can accompany the bulla.
- This differs from suprabasal acantholysis in pemphigus.

Acantholysis is the pivotal negative finding

Acantholysis present

- Loss of intercellular bridges
- Rounded, dyscohesive keratinocytes
- Characteristic mechanism of pemphigus

Acantholysis absent

- Keratinocytes remain coherent
- Whole epidermis can lift as one roof
- Characteristic of bullous pemphigoid

Eosinophils are informative but not pathognomonic

- Eosinophils commonly appear in the dermis and blister cavity.
- Their presence supports an immune-inflammatory process.
- Interpret them with cleavage level and immunofluorescence.
- A cell type alone cannot confirm antibody specificity.

Light microscopy may be equivocal in nonbullous disease

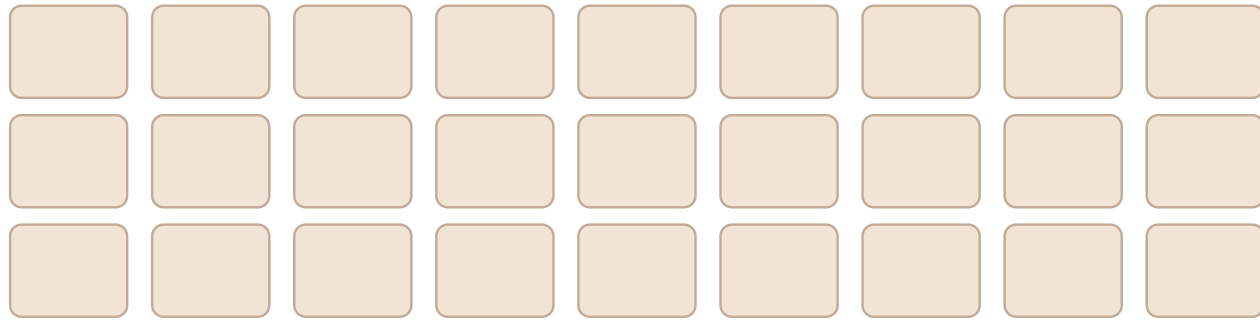
Typical developed bulla

- Clear subepidermal cleavage
- Supportive eosinophil-rich infiltrate

Early or nonbullous eruption

- Possible eosinophilic spongiosis
- Nonspecific dermal inflammation
- Confirm with immunopathology

Direct immunofluorescence localizes bound antibodies

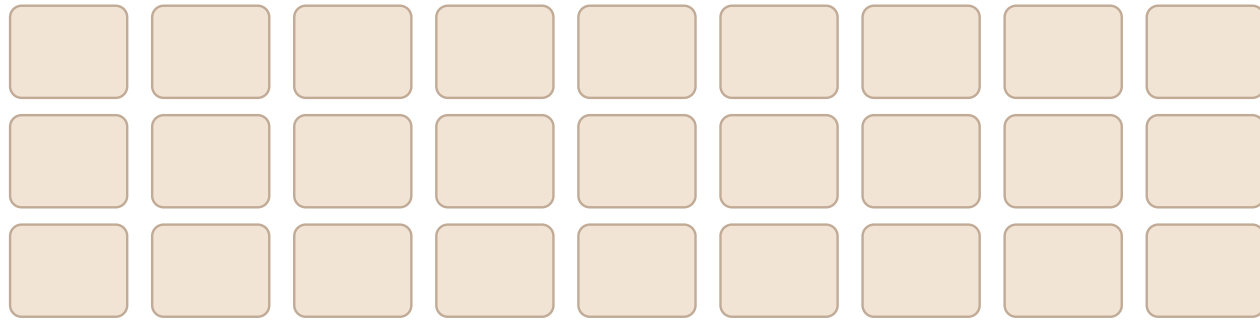


Schematic epidermis–dermis interface

**Continuous linear
junctional signal**

IgG and/or C3 outline the
basement membrane
zone.

The hallmark pattern is continuous and linear

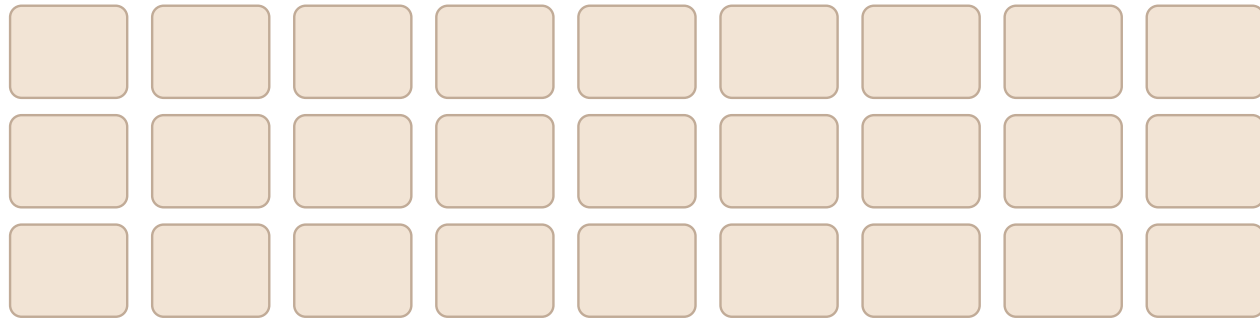


Schematic epidermis–dermis interface

**Continuous linear
junctional signal**

A continuous junctional
ribbon differs from
intercellular staining.

Complement deposits also line the junction

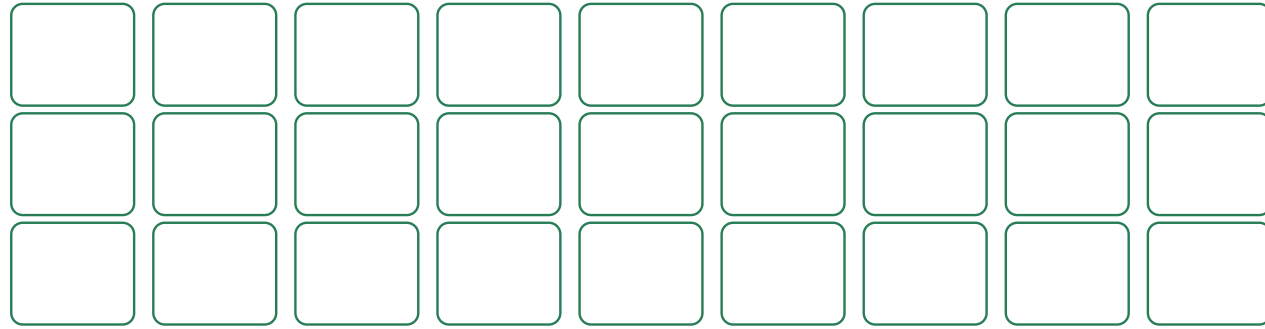


Schematic epidermis–dermis interface

**Linear complement
deposition**

Linear complement
deposition in bullous
pemphigoid.

Pemphigus shows an intercellular fishnet pattern



Schematic epidermis–dermis interface

**Intercellular
keratinocyte signal**

Intercellular IgG reflects
desmosomal rather than
basal-junction targeting.

Biopsy location matters for direct immunofluorescence

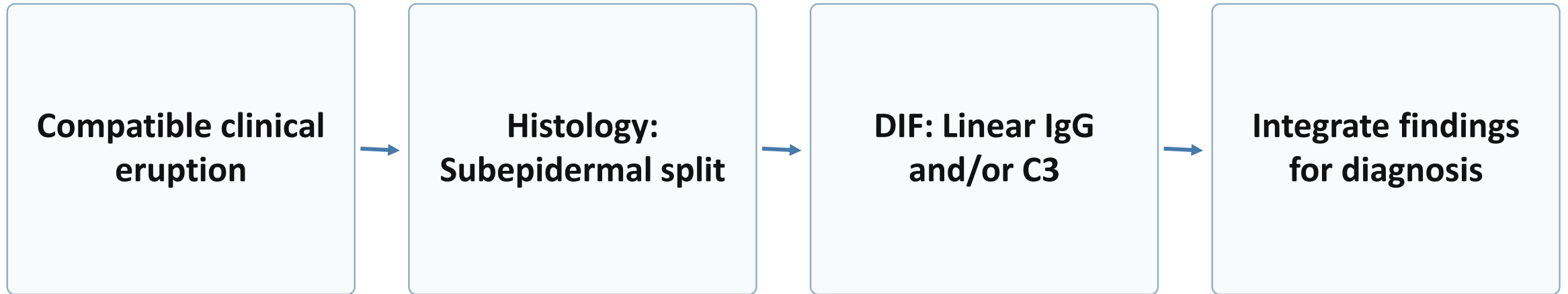
Routine H&E

- Choose a recent intact bulla.
- Identify the level of cleavage and inflammatory cells.

Direct immunofluorescence

- Sample perilesional nonbullous skin.
- Place tissue in a suitable IF transport medium.
- Avoid interpreting a poorly sampled negative test as exclusion.

Histology and immunofluorescence are complementary

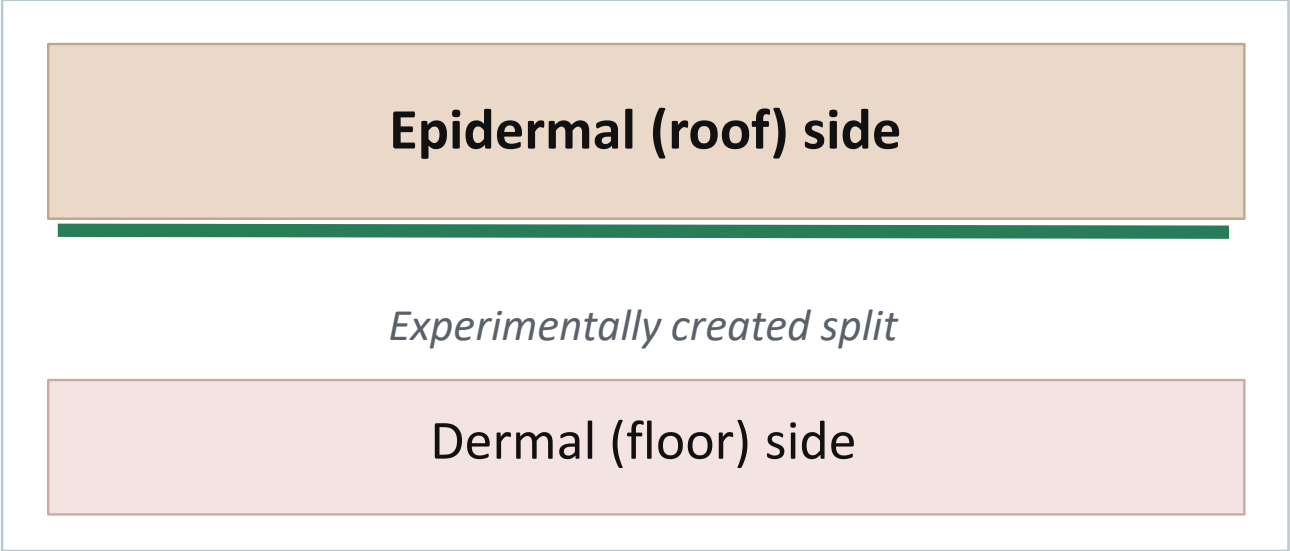


The 2022 guideline prioritizes DIF as a critical confirmation test.

Circulating autoantibodies refine classification

- Anti-BP180 and anti-BP230 serum antibodies can be measured.
- EADV describes ELISA and indirect immunofluorescence as complementary tests.
- A result requires interpretation in the clinical and tissue context.

Salt-split skin helps localize serum binding



The diagram illustrates a salt-split skin model. It consists of two horizontal rectangular blocks. The top block is light brown and labeled 'Epidermal (roof) side'. Below it is a thin, dark green horizontal line representing the split. The bottom block is light pink and labeled 'Dermal (floor) side'. The text 'Experimentally created split' is centered between the two blocks.

Epidermal (roof) side

Experimentally created split

Dermal (floor) side

Schematic; Not a patient photomicrograph

- For typical bullous pemphigoid, IgG binds the epidermal side of salt-split skin.
- The roof-versus-floor pattern helps distinguish some subepidermal blistering disorders.

Integrated diagnostic evidence is more reliable

1 • Clinical phenotype

Age, itch, distribution, tense bullae

2 • Histologic evidence

Subepidermal cleavage ± eosinophils

3 • Tissue immune pattern

Linear IgG and/or C3 on direct IF

4 • Circulating antibodies

BP180/BP230 and salt-split assays when indicated

Negative immunofluorescence warrants critical review

- Verify sampling site, transport, and tissue adequacy.
- Consider repeat biopsy if clinical suspicion remains high.
- Correlate with routine histology and circulating antibodies.
- Do not overrule consistent clinicopathologic evidence with an isolated technical failure.

Pemphigus typically differs in blister behavior

Feature	Bullous pemphigoid	Pemphigus vulgaris
Roof	Full-thickness epidermis	Partial epidermal roof
Blister	Typically tense	Often fragile / eroded
Mucosa	Less frequent	Common
Split	Subepidermal	Suprabasal

Pemphigus and pemphigoid differ microscopically

Feature	Bullous pemphigoid	Pemphigus
Cleft	Below epidermis	Within epidermis
Acantholysis	Absent	Present
Inflammation	Often eosinophil-rich	Variable
DIF	Linear junctional	Intercellular fishnet

Antibody targets explain both morphology and DIF

Pemphigoid

- Hemidesmosomal proteins at basal interface
- Linear immune deposits
- Whole-epidermis separation

Pemphigus

- Intercellular desmogleins
- Fishnet-pattern IgG
- Acantholytic intraepidermal blister

Dermatitis herpetiformis has a different clinical pattern

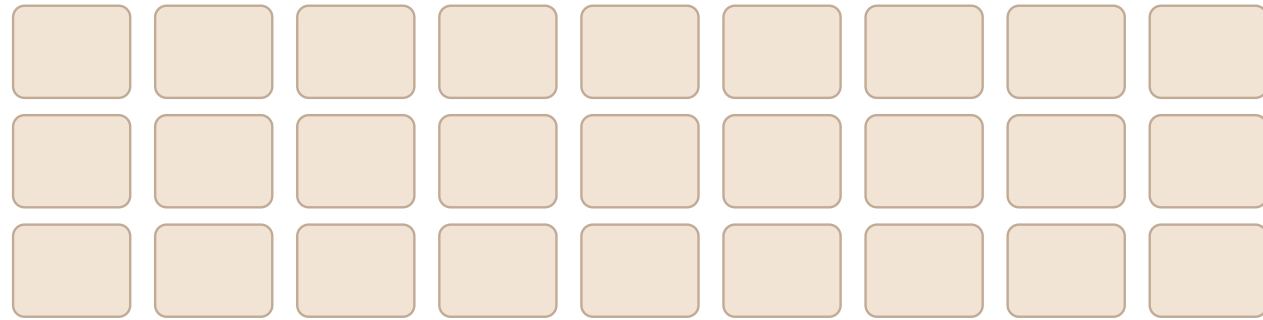
Bullous pemphigoid

- Often older individuals
- Tense bullae at flexural / truncal sites
- IgG / complement at basal junction

Dermatitis herpetiformis

- Grouped, intensely pruritic vesicles
- Extensor surfaces and buttocks
- Associated with gluten-sensitive enteropathy

Dermatitis herpetiformis is neutrophilic and IgA-rich



Schematic epidermis–dermis interface

**Granular signal at
papillary tips**

Granular IgA at dermal
papillae, not continuous
linear junctional
deposition.

The blistering differential requires multiple dimensions

Disorder	Cleft / lesion	Characteristic immune pattern
Bullous pemphigoid	Subepidermal, often eosinophils	Linear IgG/C3
Pemphigus vulgaris	Suprabasal acantholysis	Fishnet IgG
Dermatitis herpetiformis	Papillary neutrophil microabscesses	Granular papillary IgA
Epidermolysis bullosa	Inherited structural fragility	Not defined by BP antibodies

Inherited epidermolysis bullosa is a distinct mechanism

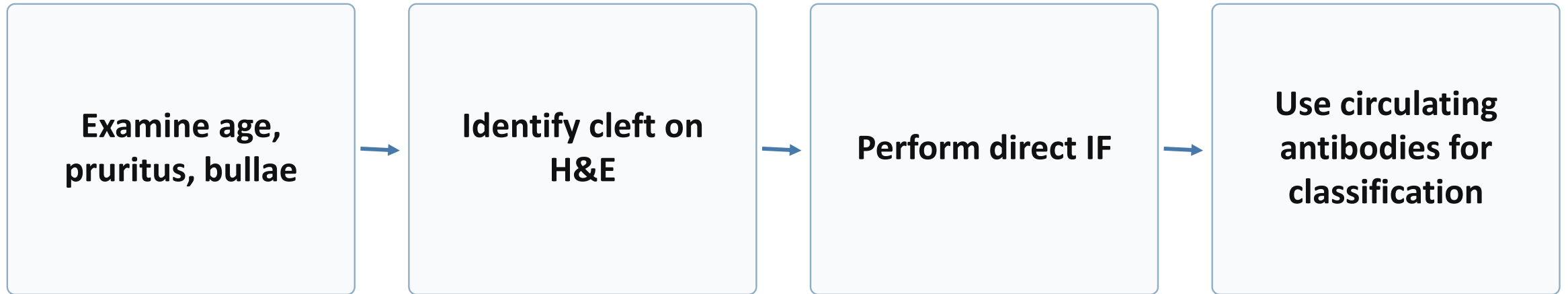
Bullous pemphigoid

- Acquired autoimmune injury
- Usually older age
- Inflammation and antibody deposition

Epidermolysis bullosa

- Inherited defects in structural skin proteins
- Often begins early in life
- Trauma-associated mechanical blistering

A rational diagnostic sequence begins with morphology



Exclude key mimics when morphology or antibody patterns do not agree.

Clinical context must remain part of interpretation

- Review how the eruption began and evolved.
- Record distribution, lesion integrity, mucosal symptoms and excoriations.
- Assess medication exposure and relevant comorbidities.
- Choose and interpret investigations in context.

Treatment focuses on controlling immune inflammation

- Contemporary EADV guidance emphasizes high-potency topical corticosteroids.
- Systemic approaches depend on extent, severity and treatment feasibility.
- Management must be adapted to frailty, comorbidity and treatment risks.
- Specific regimens require clinical judgment beyond this pathology lecture.

Follow-up tracks formation of new lesions

- Successful control means that new lesions or pruritic symptoms cease.
- Existing lesions should begin to heal.
- Disease activity and treatment toxicity both require monitoring.

Case study: Tense bullae in an older adult

An older patient reports weeks of pruritus followed by tense, clear bullae on the lower abdomen and inner thighs. Histology reveals a subepidermal blister with eosinophils.

Which direct immunofluorescence pattern would best support the diagnosis?

Case interpretation: Junctional immune deposition

Expected: Continuous linear IgG and/or C3 along the dermoepidermal junction.

- Tense roof corresponds to full-thickness epidermal separation.
- Eosinophils support the inflammatory phenotype.
- A fishnet IgG pattern would suggest pemphigus instead.

Case study: Pruritus without intact bullae

An older individual has persistent urticarial plaques and marked itch. A routine biopsy demonstrates eosinophilic inflammation but no definite cleft.

What important next step should be considered?

Case interpretation: Biopsy for direct IF

Consider properly sampled perilesional direct immunofluorescence, integrated with serologic studies.

- Nonbullous pemphigoid can precede typical blistering.
- Routine H&E may be nonspecific early.
- The clinical and immunopathologic evidence must be combined.

Case study: Granular papillary IgA

A patient has intensely itchy grouped vesicles on elbows and buttocks. Microscopy shows neutrophils near dermal papillae; DIF demonstrates granular papillary IgA.

Which disease is more likely than bullous pemphigoid?

Case interpretation: Dermatitis herpetiformis

Dermatitis herpetiformis.

- Grouped extensor lesions and papillary neutrophils favor DH.
- Granular papillary IgA contrasts with linear IgG/C3 in BP.
- The distribution and IF pattern outweigh the shared subepidermal split.

Core diagnostic synthesis

Clinical pattern

Older person • intense itch • tense blisters

Target and mechanism

BP antigens • complement • inflammatory recruitment

Morphology

Subepidermal, nonacantholytic bulla • eosinophils

Immunopathology

Linear basement membrane IgG/C3

Important differentials

Pemphigus • dermatitis herpetiformis • inherited blistering

Selected references

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition. Elsevier; 2026.

Borradori L et al. Updated S2k guidelines for the management of bullous pemphigoid initiated by the EADV. J Eur Acad Dermatol Venereol. 2022. doi:10.1111/jdv.18220.