

Erythema Multiforme

Clinical morphology · cytotoxic interface injury · diagnostic distinction

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Learning objectives

By the end of the lecture, learners should be able to:

- Recognize characteristic targetoid lesions and their distributions.
- Relate CD8⁺ T-cell-mediated keratinocyte damage to interface dermatitis.
- Interpret the main epidermal and dermal histologic changes.
- Distinguish erythema multiforme from SJS/TEN and other mimics.

Erythema multiforme: The core entity

An acute immune-mediated mucocutaneous reaction pattern

- Often associated with infection; Herpes simplex virus is a prominent trigger.
- Shows a polymorphic eruption with characteristic target lesions.
- Typical episodes are self-limited, but recurrence and mucosal disease matter.

“Multiforme” describes lesion diversity

Elementary lesion	Clinical appearance	Implication
Macule	Flat discoloration	Early or evolving lesion
Papule / plaque	Elevated solid lesion	Common precursor to a target
Vesicle / bulla	Fluid-containing lesion	More intense epidermal injury
Erosion	Superficial surface loss	After blister rupture / sloughing

A practical EM phenotype spectrum

Predominantly cutaneous

- Typical targets
- EM may involve oral mucosa

Mucosal-predominant / more severe

- Painful erosions
- Risk of impaired oral intake

EM and SJS/TEN: Distinguish the taxonomies

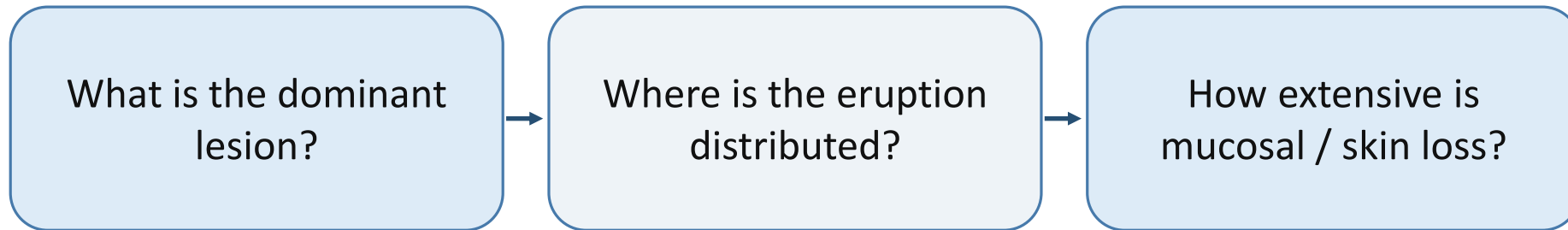
Historical Robbins passage

- Describes SJS and TEN alongside severe EM
- Highlights severe mucosal and epidermal loss

Contemporary classification

- EM is generally distinct from SJS/TEN
- Distribution, target type, detachment and illness distinguish them

Three questions anchor initial assessment



Pattern recognition must be paired with assessment for severe cutaneous adverse reactions.

Trigger categories in the Robbins account

Category	Examples reported
Infection	Herpes simplex; Mycoplasma; Fungal / bacterial infections
Medication	Sulfonamides, penicillin, hydantoins, others
Malignancy	Carcinomas and lymphomas (reported association)
Systemic inflammatory disease	Lupus, dermatomyositis, polyarteritis nodosa

Herpes simplex is a leading precipitant

Clinical history should interrogate recurrent HSV infection.

- EM may follow clinically evident oral or genital herpes.
- HSV-associated EM can recur with subsequent episodes of infection.
- Absence of reported cold sores does not eliminate an HSV association.

Other infectious associations require context

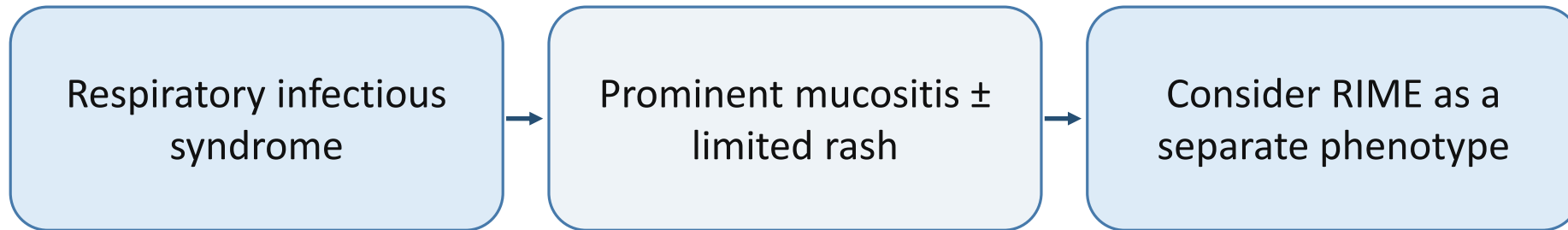
Key Diagnostic Features

- Mycoplasma
- Histoplasmosis and coccidioidomycosis
- Typhoid and leprosy

Interpretation

- The list is historical and broad
- Association $\neq$ established trigger in an individual
- Use clinical evidence for microbiologic attribution

Mycoplasma-related mucositis: Current terminology



RIME = reactive infectious mucocutaneous eruption.

Drug attribution is a differential diagnosis problem

A medication history is necessary, but the pattern matters.

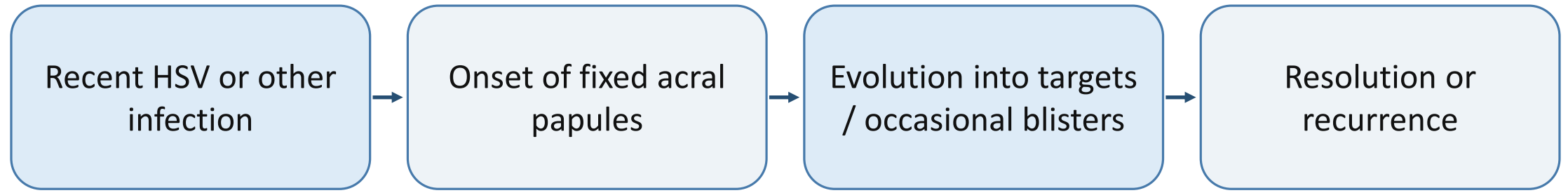
- Multiple drug associations with erythema multiforme.
- Drug-triggered SJS/TEN and fixed drug eruption can mimic targetoid EM.
- Record agent, start/stop dates, systemic features, and prior exposures.

Associated neoplastic and connective-tissue disease

Additional clinical associations.

- Carcinomas and lymphomas appear association list.
- Lupus erythematosus, dermatomyositis and polyarteritis nodosa are also listed.
- An isolated typical eruption does not justify assuming occult cancer or systemic autoimmunity.

Reconstruct the clinical chronology



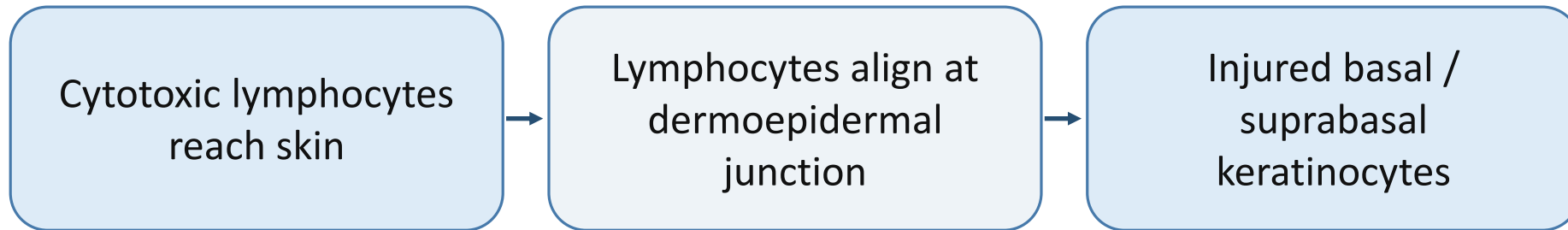
Schematic typical sequence; Individual patients vary.

CD8⁺ cytotoxic T cells drive epidermal injury

A cell-mediated cytotoxic mechanism.

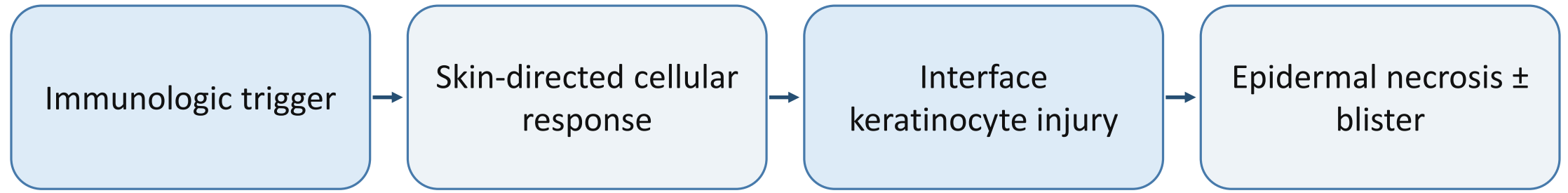
- Skin-homing CD8⁺ cytotoxic T lymphocytes interact with epidermal cells.
- Keratinocyte degeneration and death result at the epidermal–dermal interface.
- The same general pattern may arise in other cytotoxic interface reactions.

Why the basal epidermis is vulnerable



Conceptual schematic. Molecular effector molecules not specified excerpt.

The cytotoxic-interface injury sequence



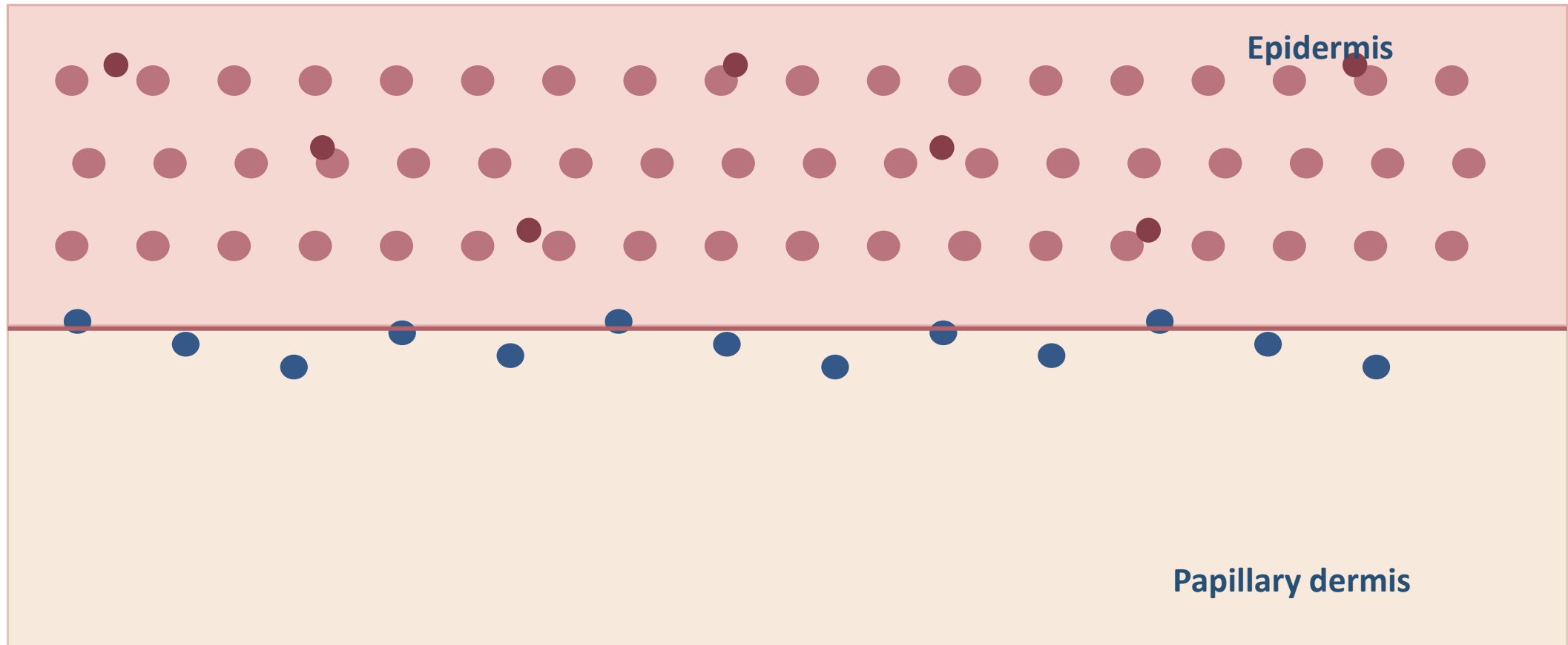
The causal arrows are conceptual; Antigenic recognition is incompletely defined.

The recognized epidermal antigens remain uncertain

Do not over-specify molecular targets.

- The epidermal antigens targeted in EM remain unknown.
- Known association with HSV does not identify a single universal EM antigen.
- Clinical trigger, immune mechanism and microscopic pattern are distinct levels of evidence.

Interface dermatitis is a reaction pattern

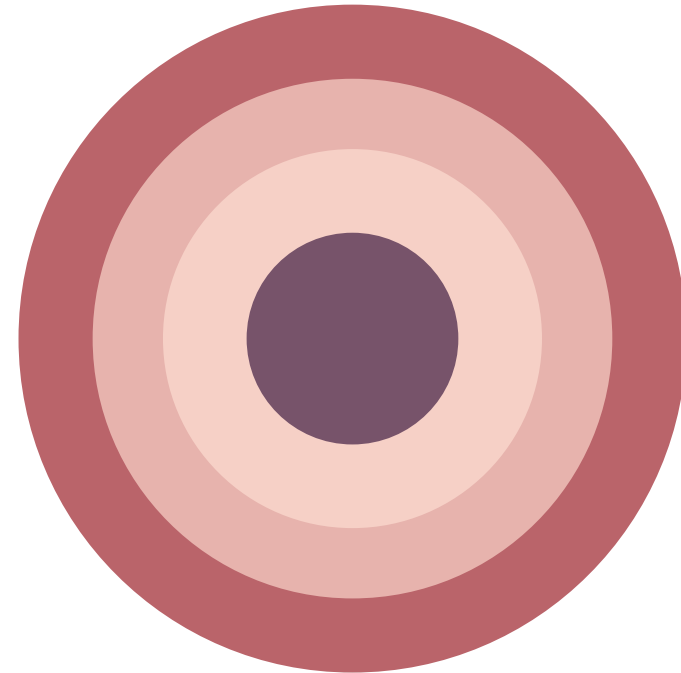


Schematic interface reaction: Lymphocytes at the junction and injured keratinocytes

Why the characteristic target forms

Concentric color is a clinical clue

- Color zones coexist in a single lesion
- The central dusky region may blister
- Not every lesion becomes a perfect target



Schematic lesion

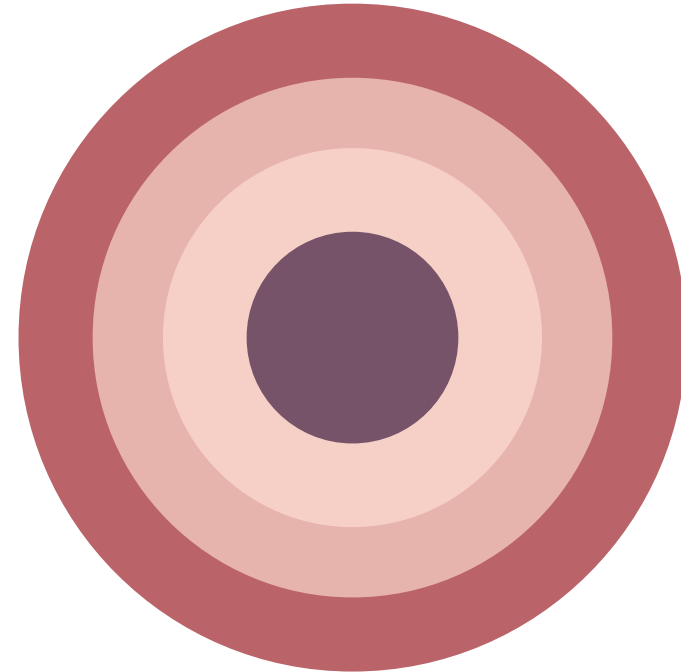
Individual lesions can have different forms

Observed structure	Microscopic correlate
Erythematous papule	Inflammatory cells / dermal edema
Central dusky area	Keratinocyte damage / epidermal necrosis
Vesicle or bulla	Epidermal injury with cleavage
Shallow erosion	Loss of damaged superficial epithelium

Classic targets have concentric zones

Concentric architecture

- Outer inflammatory erythematous ring
- Paler, edematous intermediate zone
- Dusky or blistered center reflects injury



Schematic target lesion — not a clinical photograph

An atypical target is not a unique diagnosis

Typical EM targets

- Often raised and sharply outlined
- Usually three color zones
- Common on acral / extensor sites

Alternative targetoid lesions

- May have only two indistinct zones
- Flat dusky macules raise SJS/TEN concern
- History and distribution remain decisive

Targets appear different across skin tones

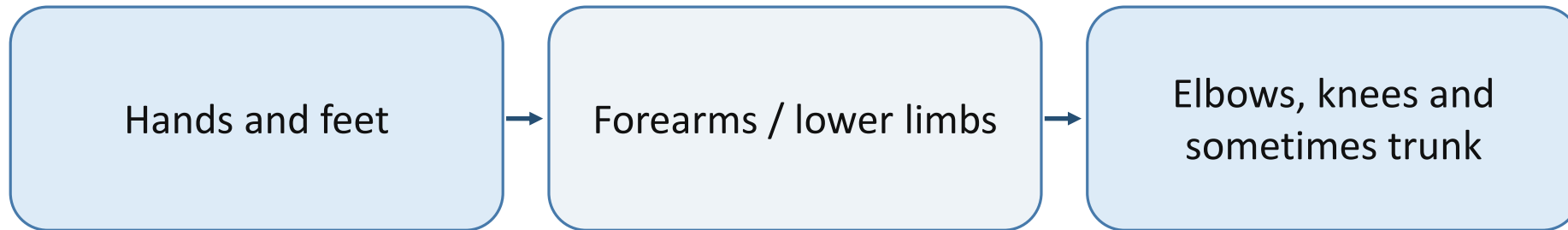
Lighter skin

- Erythematous outer rims often obvious
- Central dusky or blistered zone

Darker skin

- Areas may appear violaceous or hyperpigmented
- Gray-silver central zones
- Look for surface relief, edema and central injury

Acral and extensor distribution is characteristic



Typical distribution pattern, not an absolute rule.

Symmetry strengthens the EM pattern

Distribution adds specificity to morphology.

- Limited EM often affects the extremities symmetrically.
- A full examination may reveal more diagnostic targets than the index lesion.
- Atypical patterns require an expanded differential.

Evolution is dynamic, but lesions remain fixed

The timeline can distinguish EM from transient eruptions.

- Macules or papules can evolve into characteristic targets.
- Lesions may remain in the same location for several days.
- Individual wheals disappearing within hours instead suggest urticaria.

Constitutional symptoms are variable

Interpret systemic symptoms together with the skin phenotype.

- Malaise or fever may reflect the preceding infection.
- Disproportionate systemic illness suggests reconsideration of the diagnosis.
- Rapid diffuse epidermal loss is a major warning sign for SJS/TEN.

Mucosal involvement modifies disease severity

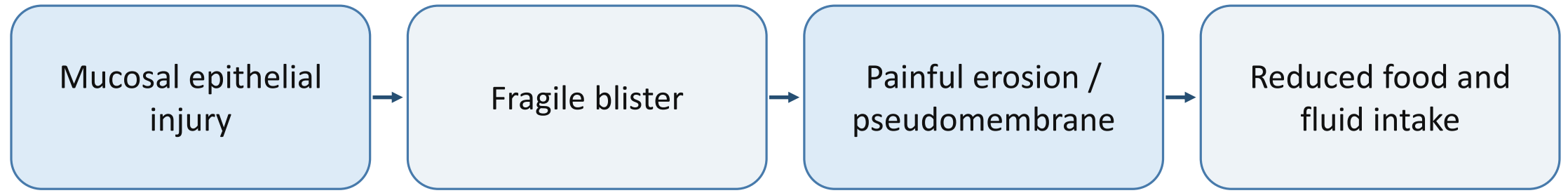
Possible mucosal sites

- Oral cavity and lips
- Urogenital mucosa
- Eyes, less often

Functional impact

- Erosions may be painful
- Oral intake may become difficult
- Ocular findings require immediate attention

Oral EM: Erosion follows blister rupture



Conceptual progression, not a literal time course for every lesion.

Ocular symptoms are clinically consequential

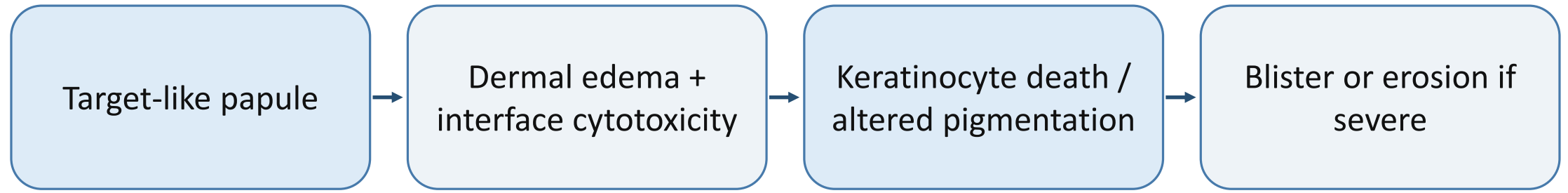
Eye involvement changes triage.

- Conjunctival injury may coexist with oral or cutaneous disease.
- Potential sequelae include keratitis and conjunctival scarring.
- Suspected ocular involvement warrants ophthalmology assessment.

EM minor versus EM major

Feature	EM minor	EM major
Cutaneous targets	Characteristic	Characteristic, sometimes widespread
Mucosal involvement	None or limited	Prominent / significant
Systemic threat	Usually limited	May impair oral intake; Assess eyes
Classification caution	Not SJS	Not synonymous with SJS

Bridge the visible lesion to the microscope



Relationship is mechanistic interpretation rather than a specimen-specific observation.

Histologic pattern: The core triad

Compartment	Recognizable finding
Superficial dermis	Perivascular lymphocytic infiltrate and edema
Dermoepidermal junction	Lymphocytic interface activity
Epidermis	Scattered apoptotic / necrotic keratinocytes

Superficial perivascular lymphocytes

Read the dermal infiltrate in anatomic context.

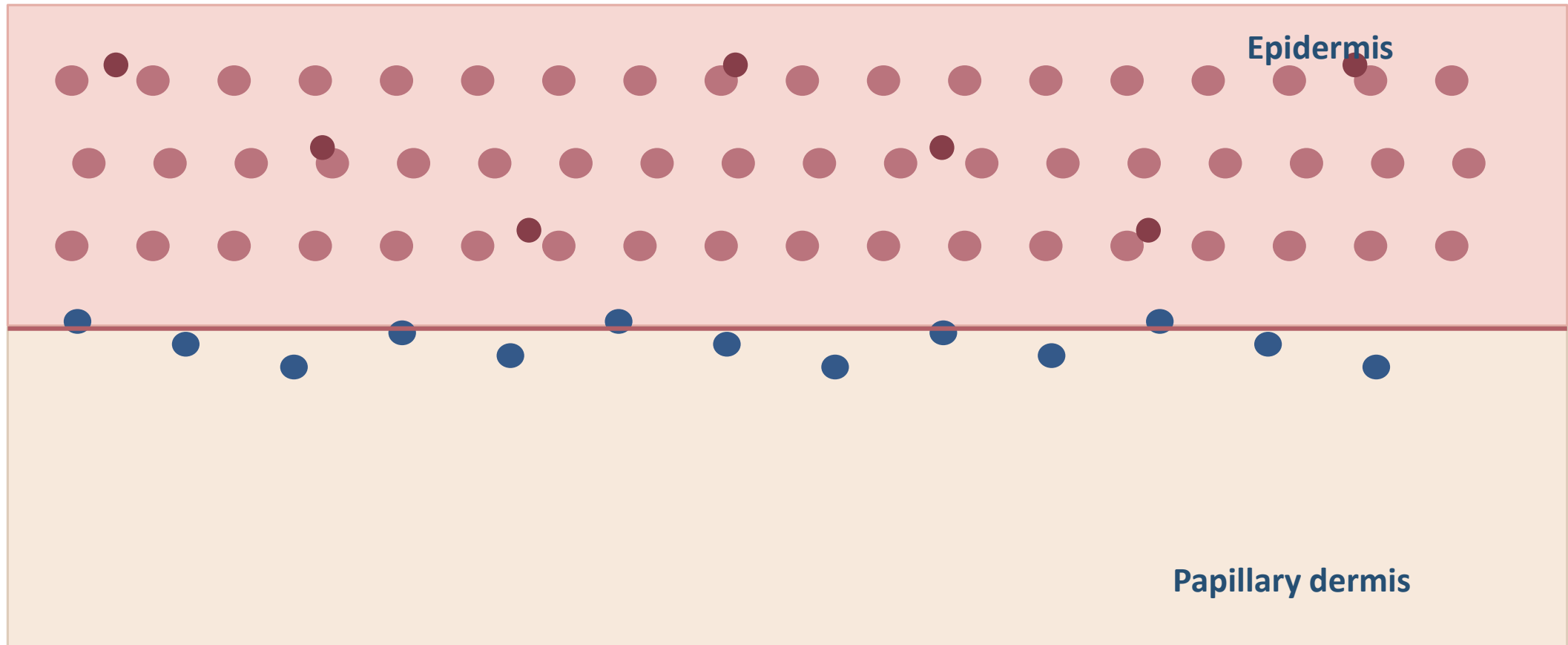
- A superficial perivascular lymphocytic infiltrate is.
- The infiltrate is part of the interface reaction pattern.
- Lymphocytes around vessels alone are not diagnostic of EM.

Papillary dermal edema accompanies inflammation

Interstitial fluid provides a morphologic correlate for raised lesions.

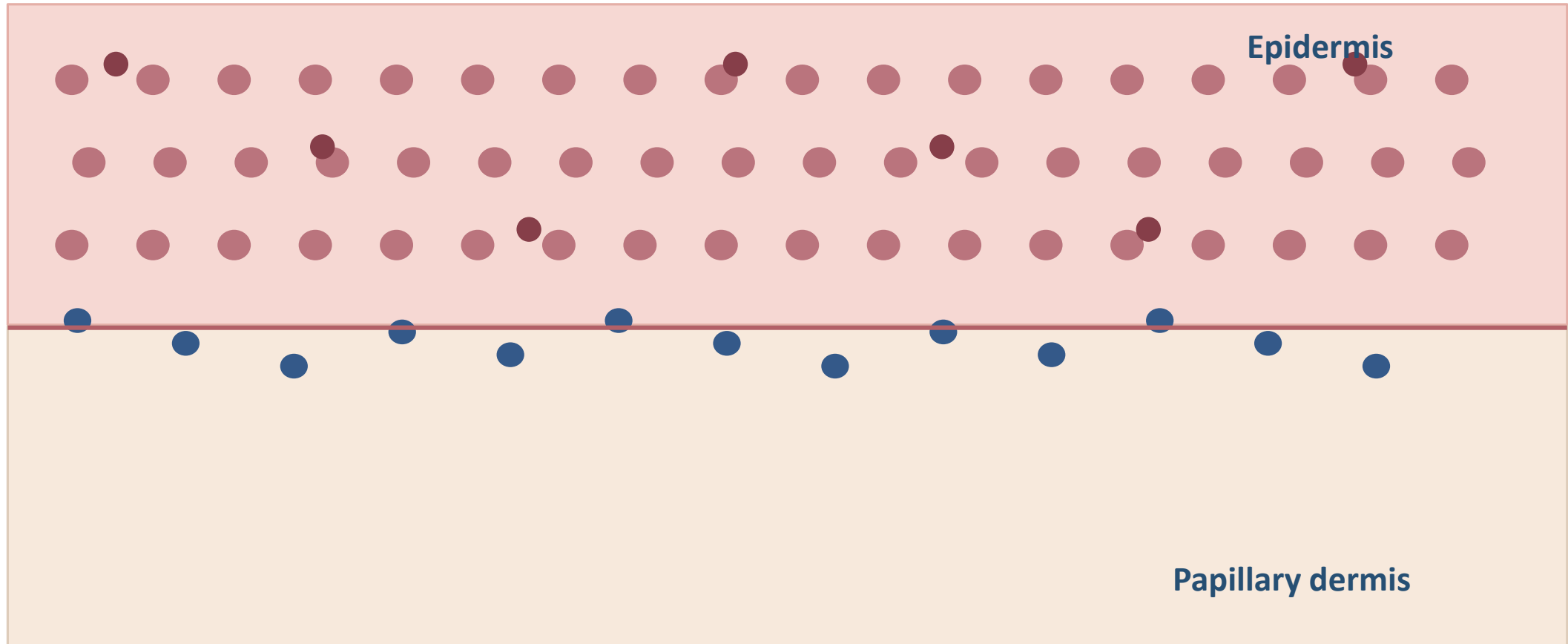
- Dermal edema in early targetoid lesions.
- Edema contributes to a swollen or pale zone of the clinical target.
- Edema is nonspecific and must be interpreted with keratinocyte injury.

Lymphocytes concentrate at the junction



Schematic: Basal-junction lymphocytic accumulation

Scattered apoptotic keratinocytes are central



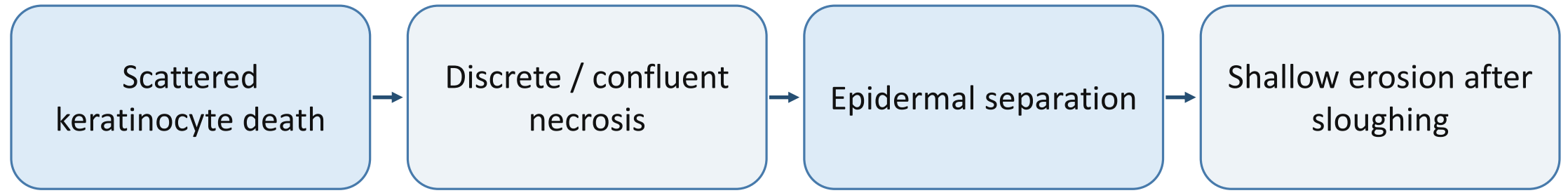
Schematic: Red compact circles mark keratinocyte injury

The intraepidermal response may intensify

Temporal progression in lymphocyte location.

- Initially, lymphocytes cluster at the dermoepidermal junction.
- Later, lymphocytes migrate upward into the epidermis.
- Progression may accompany more extensive epithelial cell damage.

Confluent necrosis produces blistering and erosion



More diffuse denudation requires consideration of severe alternative diagnoses.

Morphologic evolution across an EM lesion

Relative stage	Pathologic emphasis	Possible appearance
Early	Interface lymphocytes; Basal injury	Erythematous / edematous papule
Established	Apoptotic keratinocytes; Edema	Dusky central target
More injured	Necrosis and blister formation	Vesicle / bulla / erosion

When a skin biopsy is useful

Histology is ancillary to the clinical pattern.

- Consider biopsy if lesions are atypical or severe.
- Use it to investigate mimics, particularly blistering disease.
- Request clinical distribution, lesion timing and medication history for interpretation.

Interface change is not pathognomonic

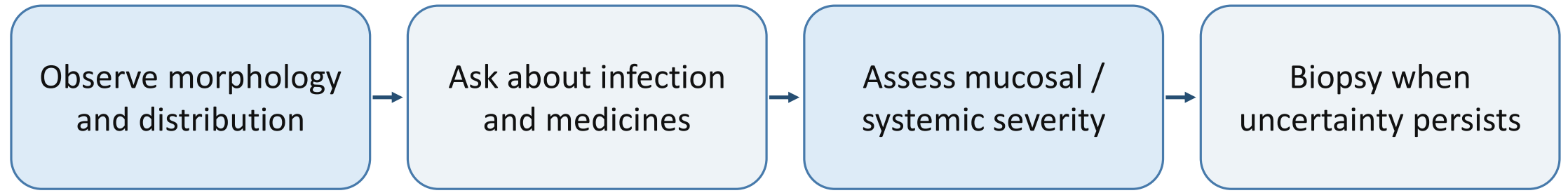
Findings supporting EM

- Scattered apoptotic keratinocytes
- Vacuolar interface change
- Superficial inflammation and edema

Important caveats

- Fixed drug eruption can show interface injury
- Lupus and other interface disorders overlap
- Clinical phenotype often decides the differential

EM is usually a clinicopathologic diagnosis



No single blood test or histologic feature confirms all cases.

Differential: EM versus urticaria

Feature	EM	Urticaria
Lesion persistence	Fixed for days	Wheals often resolve within hours
Typical surface	Target with dusky / injured center	Edematous wheal
Mucosal erosions	Possible	Not typical of uncomplicated urticaria
Histologic emphasis	Interface damage	Dermal edema ± sparse infiltrate

Differential: Fixed drug eruption

Erythema multiforme

- Symmetric acral targets common
- Often linked to preceding infection
- Lesions arise in multiple sites

Fixed drug eruption

- Recurs in the same location after exposure
- Can have dusky or bullous center
- Medication re-exposure history is decisive

Differential: EM versus SJS/TEN

Axis	Erythema multiforme	SJS/TEN
Typical lesion	Raised, well-demarcated targets	Flat atypical targets / purpuric macules
Predominant site	Acral / extensor	Often truncal onset
Skin detachment	Limited / uncommon	Can be extensive
Systemic illness	Often limited	Potentially severe / life-threatening

RIME is a key mucosal-predominant mimic

Reactive infectious mucocutaneous eruption (RIME)

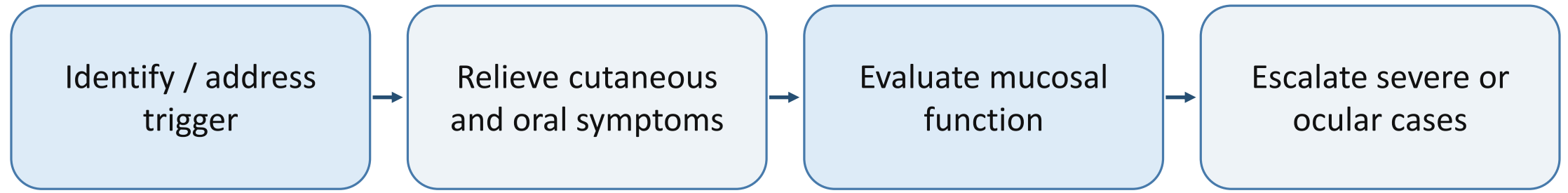
- Often follows a respiratory infectious episode.
- Mucositis may dominate, sometimes with relatively sparse skin lesions.
- Modern classifications distinguish RIME from classic EM and SJS/TEN.

Severe skin or mucosal disease changes urgency

Immediate specialist or emergency assessment is appropriate for:

- Rapidly progressive widespread blistering or detachment.
- Marked systemic illness with severe oral or genital erosions.
- Painful red eyes, photophobia, or visual symptoms.

Management follows trigger, symptoms and severity



Teaching overview only; Not a dosing protocol.

Recurrent HSV-associated EM: Evidence and strategy

Recurrence is a clinically distinct management problem.

- Review overt or possible recurrent HSV and medication exposures.
- Suppressive oral antiviral treatment may reduce recurrent attacks.
- The intervention evidence remains limited; One small randomized trial supports continuous acyclovir.

Prognosis: Most episodes resolve

Expected outcome varies with phenotype.

- Uncomplicated EM is commonly self-limited.
- Transient postinflammatory pigment changes may persist.
- Recurrent attacks and significant mucosal or ocular disease require follow-up.

Clinical application: Symmetric acral targets

A young adult develops well-circumscribed, concentric lesions on both hands several days after an episode of herpes labialis. There is no skin detachment or marked systemic illness.

What is the leading diagnosis, and which trigger is most plausible?

Clinical application: Fixed dark plaque

A patient develops a sharply demarcated dusky plaque at precisely the same site after repeatedly taking the same medication. A previous attack left residual pigmentation.

Which targetoid mimic should be prioritized?

Clinical application: Severe mucocutaneous illness

A recently medicated patient becomes systemically unwell with widespread dusky macules, painful mucosal erosions and sheets of skin detachment.

What is the urgent diagnostic alternative to uncomplicated EM?

Case answer: HSV-associated EM

Most likely: Erythema multiforme following herpes labialis.

- Concentric target lesions and symmetric acral distribution favor EM.
- The recent herpes simplex episode is a plausible precipitant.
- Absence of marked illness or detachment argues against SJS/TEN in this vignette.

Case answer: Fixed drug eruption

Most likely: Fixed drug eruption rather than recurrent EM.

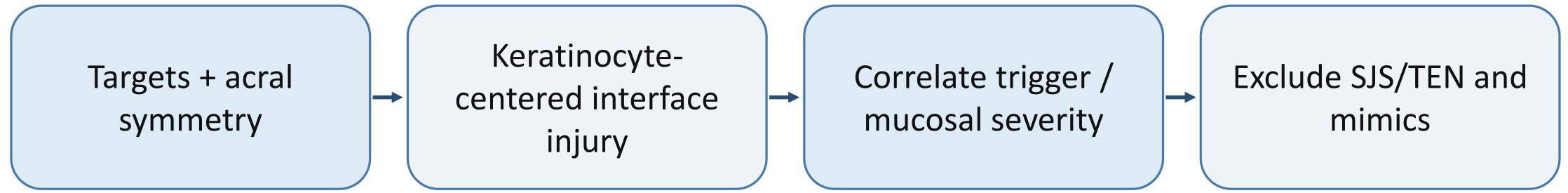
- Repeat occurrence at precisely the same site is the decisive clue.
- Drug-associated dusky plaques may simulate EM targets.
- Prior residual pigment supports the longitudinal clinical pattern.

Case answer: Suspect SJS/TEN

Urgently evaluate for Stevens–Johnson syndrome / toxic epidermal necrolysis.

- Widespread dusky macules and epidermal detachment are critical clues.
- Severe mucosal injury and systemic illness support this alternative.
- Emergency specialist assessment takes priority over routine EM follow-up.

Integrated diagnostic synthesis



Integrate morphology, histology, severity and modern disease taxonomy.

Selected references

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