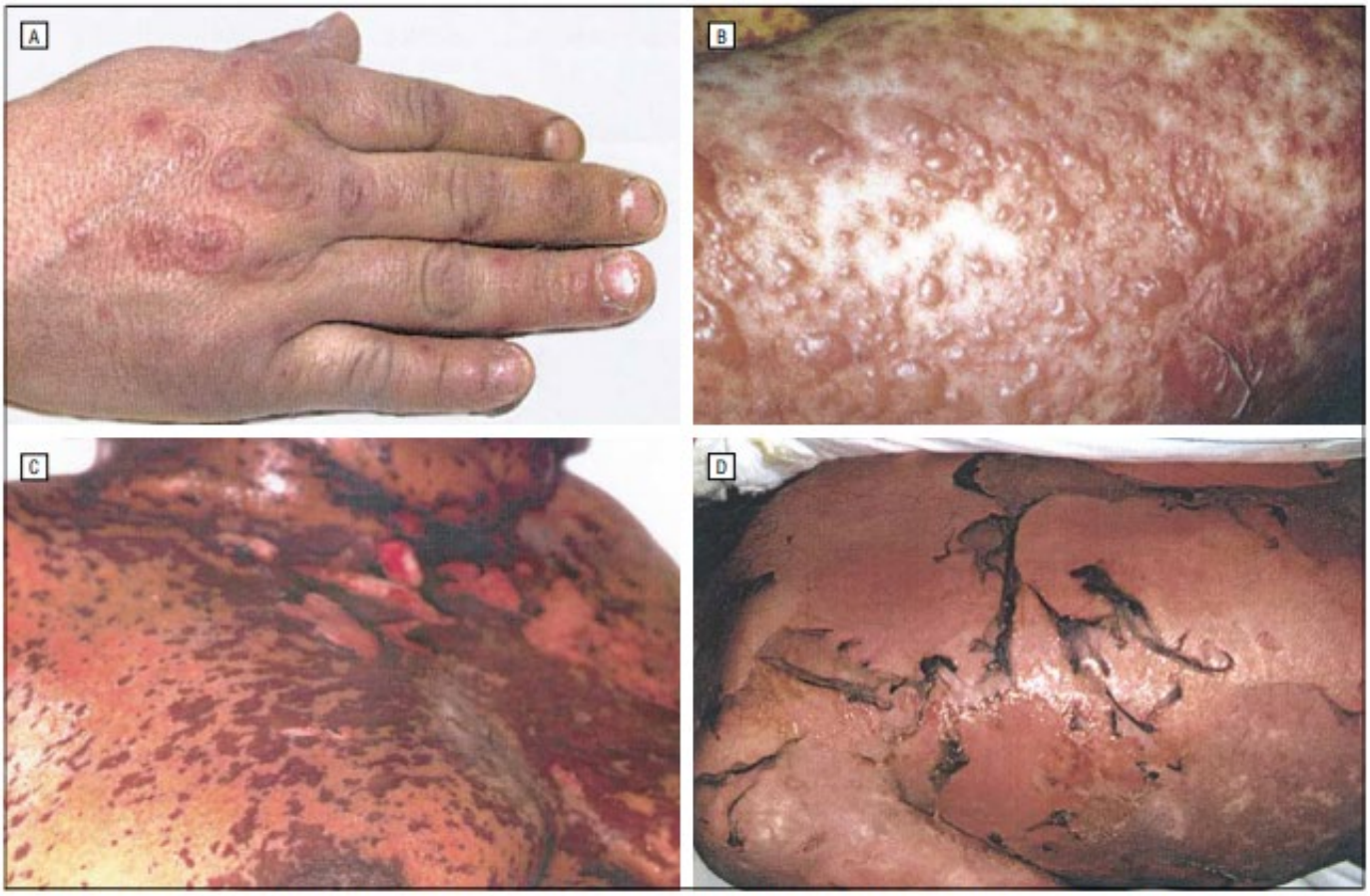
# Clinical Pharmacology & Toxicology Pearl of the Week

## ~ Severe Cutaneous Adverse Reactions (SCARs): Epidermal Necrolysis ~

- ✓ **Case:**
  - A 70-year-old male with a history of diabetes is started on lamotrigine for management of seizures after it was discovered that he was developing mood changes on levetiracetam
  - Approximately 1 week after starting the lamotrigine, he developed a pruritic rash on his anterior neck. Continued this medication as he thought rash was diabetes related
  - The rash became progressively generalized and he presented to the Emergency Department
    - Temp 37.8. Macular/papular rash, blanchable, diffuse, skin edema prominent to anterior knees. Rash not tender, no desquamation. 50% BSA involved
  - Admitted to Internal Medicine
    - Lamotrigine stopped, switched back to levetiracetam. All other outpatient meds continued
    - IV methylprednisolone and topical betamethasone started
    - Nikolsky's sign positive
    - Rash progresses to desquamation and skin sloughing, 95-99% BSA involved
    - Clin Pharm consulted for review of culprit drug(s)

- ✓ **Introduction:**
  - Epidermal necrolysis (EN) can be classified into SJS, SJS-TEN overlap, and TEN
    - SJS = skin involvement of <10%
    - SJS-TEN overlap = 10-30% skin involvement
    - TEN = skin involvement of >30%
  - Pathophysiology: type 4c non-immediate hypersensitivity, mediated by cytotoxic T cells
  - Several medications have been implicated in causing SJS/TEN
    - Main culprits = anticonvulsants (carbamazepine, phenytoin, phenobarbital, lamotrigine), antibiotics (sulfonamides, cephalosporins, cyclines, fluoroquinolones), allopurinol, and NSAIDs

- ✓ **Clinical features:**
  - Fever, influenza like illness, eye pain, sore throat, runny nose, and skin pain frequently precede dermatological manifestations
  - Skin lesions:
    - Initially on the face, upper trunk, and proximal extremities, whereas distal portions of upper and lower limbs are relatively spared
    - Initial lesions are characterized as erythematous, irregularly shaped, dusky-red macules
    - Atypical target lesions with dark centres can often be observed without the typical three concentric rings of erythema multiforme major
    - Necrotic lesion confluence leads to extensive erythema, flaccid blisters, and large epidermal sheets, revealing areas of red dermis
    - Nikolsky's sign = epidermis sloughs off under lateral pressure (present but not specific for TEN)
  - Accompanying acute organ failure is rare (transient rise in renal or liver tests may be seen)




Clinical patterns and classification of the diseases included in the study. A, Erythema multiforme: typical targets, with regular round shape, well-defined borders, 3 different zones, predominant on the extremities. B, Stevens-Johnson syndrome: erythematous or purpuric macules with irregular shape and size. Blisters often occur on all or part of the macule. Lesions are widespread. Confluence of individual lesions remains limited, involving less than 10% of the body surface area. C, Overlap Stevens-Johnson syndrome–toxic epidermal necrolysis: confluent blisters result in detachment of the epidermis and erosions on 10% to 29% of the body surface area. D, Toxic epidermal necrolysis: widespread detachment of epidermis on more than 30% of the body surface area. All photographs were printed from digital records of the original color photographs with no other change than magnification.

Arch Dermatol 2002:138: 1019-1024

- ✓ **Causality Assessment Tools**
  - ALDEN
    - Algorithm of Drug Causality for Epidermal Necrolysis
    - Grades causality for drug-induced SJS/TEN in five levels: “very probable,” “probable,” “possible,” “unlikely,” or “very unlikely”
    - ALDEN considers a drug initiated 56 days or more prior to the onset of SJS/TEN as unlikely to be causal

**Table 1.** ALDEN algorithm criteria and scoring for drug causality.

| Criteria | Possible score |
|---|---|
| Time lag between initial drug intake to onset of reaction (index day) | −3 to +3 |
| Presence of drug in the body on index day | 0 to −3 |
| Prechallenge/rechallenge outcome with the suspect drug | −2 to +4 |
| Outcome of rechallenge | 0 to −2 |
| Drug notoriety for causing SJS/TEN | −1 to +3 |
| Other possible etiologic alternatives | −1, if applicable |

The total ALDEN is based on the six criteria listed. A total score of ⩾6 is categorized as very probable, 4–5 as probable, 2–3 as possible, 0–1 as unlikely, and <0 as very unlikely. Specifics of the scoring system for each criterion is not described here but can be found in Sassolas and colleagues.[4]
ALDEN, algorithm of drug causality for epidermal necrolysis; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.

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- ✓ **Management**
  - Discontinue:
    - the causative drug, OR
    - all non-essential and suspected medications if the causative drug cannot be specifically identified
  - Intensive care unit or specialized burn unit
  - Resuscitation, hydration, control of electrolyte imbalances, and adequate nutrition
  - Obtain multidisciplinary input for evaluation and management of care, including dermatology, plastic surgery, ophthalmology
  - Skin: Reconstitution of skin barrier function with nonadherent dressings such as paraffin gauze, petrolatum impregnated gauze, xenografts, allografts, or with newer skin substitutes
  - Ophth: lubrication, topical antibiotics to start, amniotic membrane transplant if eye involvement
  - Systemic immunomodulatory medications have been used as treatment, but their efficacy is variable
    - IV corticosteroids, IV cyclosporine, IVIG, or etanercept

✓ **Prognosis:**

**SCORTEN**

**Table III. Mortality rates and relative risks according to the SCORTEN level (development sample of 165 patients)**

| SCORTEN | No. of patients | Mortality rate | | Odds ratio (95% CI[a]) |
|---|---|---|---|---|
| | | Percent | 95% CI | |
| 0–1 | 31 | 3.2 | (0.1–16.7) | 1 |
| 2 | 66 | 12.1 | (5.4–22.5) | 4.1 (0.5–35.2) |
| 3 | 34 | 35.3 | (19.8–53.5) | 14.6 (2.0–138.0) |
| 4 | 24 | 58.3 | (36.6–77.9) | 42.0 (4.8–367.0) |
| ⩾5 | 10 | 90.0 | (55.5–99.8) | 270.0 (15.0–487.0) |

[a]Confidence interval, SCORTEN represents the number of abnormal parameters among the seven independent prognosis factors (a weight of 1 was assigned to each independent parameter).

*J Invest Dermatol 115:149–153, 2000*

✓ **Case resolution:**

- Patient was admitted to ICU
- Daily dressing changes under guidance of Plastics and Dermatology
- Etanercept given
- Amniotic membrane transplant because of bilateral eye involvement
- Some skin recovery noted
- Developed systemic fungemia secondary to extensive skin breakdown
- Died one month after presentation to ED

**The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.**

**The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.**

**More CPT Pearls of the Week can be found HERE.**

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