

### boards fodder

## Darier and Hailey-Hailey diseases

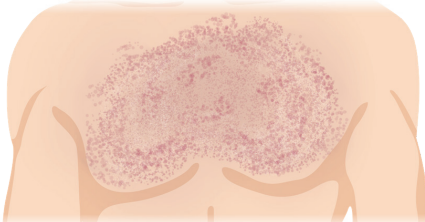
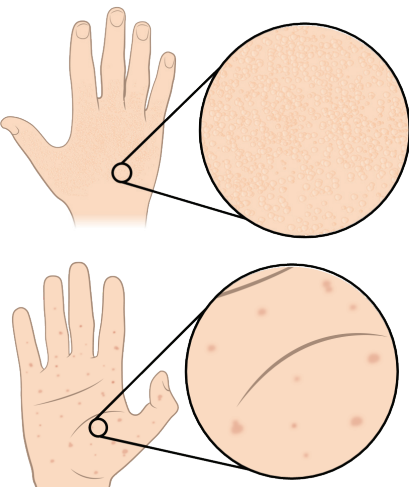

By Abdulhadi Jfri, MD, MSc, FRCPC, FAAD, and Oyetewa Oyerinde, MD



**Abdulhadi Jfri, MD, MSc, FRCPC, FAAD,** is a Complex Medical Dermatology Fellow at Brigham and Women's Hospital Dana-Farber Cancer Institute at Harvard Medical School.






**Oyetewa Oyerinde, MD,** is a dermatology resident, PGY-4, at Harvard Combined Dermatology Residency Training Program.

	Darier (Keratosis follicularis)	Hailey Hailey (Familial benign chronic pemphigus)
<b>Inh.</b>	AD complete penetrance, variable expressivity	AD complete penetrance, variable expressivity
<b>Etiology</b>	<b>ATP2A2</b> → endoplasmatic reticulum, Ca <sup>2+</sup> ATPase pump ( <b>SERCA2</b> )	<b>ATP2C1</b> → Golgi apparatus, Ca <sup>2+</sup> ATPase ( <b>hSPCA1</b> )
<b>Pathogenesis</b>	↓ Ca <sup>2+</sup> ER + cellular stress → impaired binding and trafficking of junctional proteins (desmoplakin and E-cadherin) → <b>acantholysis</b> Accumulation of unfolded proteins induce apoptosis → <b>dyskeratosis</b>	Impaired Ca <sup>2+</sup> sequestration → depleted Ca <sup>2+</sup> within golgi lumen → loss of cell-cell adhesion in stratum spinosum → <b>acantholysis</b>
<b>Ep.</b>	Age 6-20 with peak during puberty (11-15) M=F	2nd or 3rd decade (occasionally 4 <sup>th</sup> or 5 <sup>th</sup> ) → later onset compared to Darier
<b>Clinical manifestations:</b>	<b>Skin</b>	
	<p>Keratotic, crusted, red-brown papules</p>  <p><b>Seb derm</b> distribution (trunk, scalp, face, lateral neck) → becomes confluent</p> <p><b>Malodor</b> (due to bacterial colonization)</p> <p>Brown flat-topped papules on dorsal hands and feet (50%)</p>  <p>PP keratotic papules Acral hemorrhagic vesicles</p>	<p><b>Intertriginous</b> (axilla, groin, inframammary, perianal and lateral neck)</p>  <p>Flaccid vesicles on erythematous base → rupture easily → macerated/crusted → spread peripherally with circinate borders</p> <p>Painful fissures, moist, malodorous, vegetated plaques.</p> <p>Heal without scarring but can lead to PIH</p>

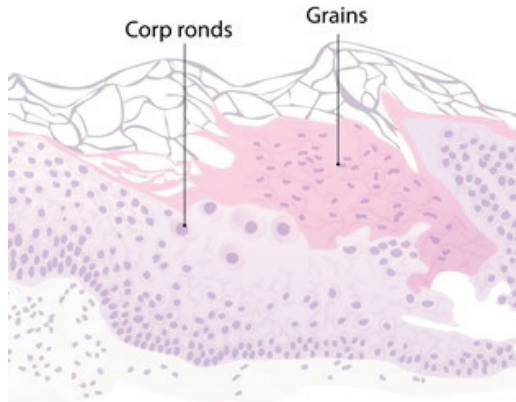
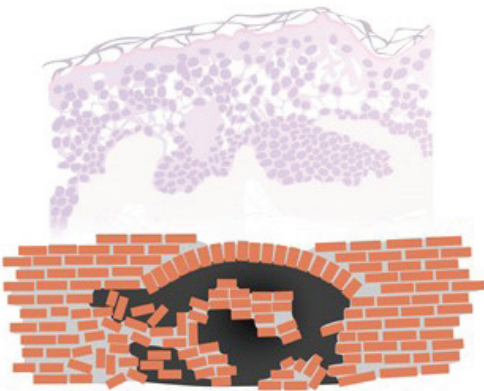
## Darier and Hailey-Hailey diseases

By Abdulhadi Jfri, MD, MSc, FRCPC, FAAD, and Oyetewa Oyerinde, MD

		Darier (Keratosi follicularis)	Hailey Hailey (Familial benign chronic pemphigus)
Clinical manifestations:	Nail	Longitudinal white/red lines Longitudinal ridging; fissuring Wedge-shape subungual hyperkeratosis V-shape notching 	Longitudinal leukonychia 
	Oral	15-50% Painless white papules/rugose plaques most common on hard palate, also gingiva, buccal and tongue 	Rare Can involve vaginal or conjunctival mucosa
Sympt.		Itch and odor	Pain, odor, pruritus
Aggravating factors		Heat, sweat, occlusion, friction, sun (UVB) → ↓ ATP2A2, lithium carbonate	Friction, heat, sweat *NOT SUN (vs. Darier) → although worse in summer due to heat and sweat UVB has been used in combination with an oral retinoid to treat Hailey Hailey.
Course		Chronic fluctuating	Complete remission vs. flares
DDx		<ul style="list-style-type: none"> <li>- Seborrhic:                             <ul style="list-style-type: none"> <li>• Seborrhic dermatitis (scalp and trunk)</li> <li>• Grover (trunk)</li> <li>• Acne</li> </ul> </li> <li>- Erosive/ vegetating flexural:                             <ul style="list-style-type: none"> <li>• Hailey-Hailey disease</li> <li>• Pemphigus vulgaris/vegetans</li> </ul> </li> <li>- Acral:                             <ul style="list-style-type: none"> <li>• Plane warts</li> <li>• Acrokeratosis verruciformis of Hopf</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>- Intertrigo</li> <li>- Inverse psoriasis</li> <li>- Vegetating lesions:                             <ul style="list-style-type: none"> <li>• Pemphigus vegetans</li> <li>• Lichen simplex chronicus</li> <li>• Botryomycosis like pyoderma (pyoderma vegetans)</li> </ul> </li> </ul>

## Darier and Hailey-Hailey diseases

By Abdulhadi Jfri, MD, MSc, FRCPC, FAAD, and Oyetewa Oyerinde, MD

	Darier (Keratosi follicularis)	Hailey Hailey (Familial benign chronic pemphigus)
Complications	<ol style="list-style-type: none"> <li>Infections → HPV, HSV (<b>kaposi varicelliform eruption</b>): Fever + malaise + ↑ lesion #. Generalized cowpox infection has been reported.</li> <li>Neuropsychiatric disorders including epilepsy, intellectual impairment, mood disorders (depression, bipolar), suicide, &amp; schizophrenia are associated with Darier, but their relationship is unclear.</li> </ol>	<ol style="list-style-type: none"> <li>Infections (bacterial, viral, fungal) – bacterial and fungal → ↑ vegetating lesions + odor; HSV → <b>Kaposi varicelliform eruption</b> → fever + ↑ vesicular lesion #.</li> <li><b>SCC</b> → in chronic anogenital lesions</li> </ol>
Pathology	 <p><b>Suprabasilar acantholysis &amp; dyskeratosis</b> (corps ronds, grains)</p> <p>vs. Grover: &gt; acantholysis &amp; &lt; dyskeratosis</p>	 <p><b>Acantholysis</b> &gt; widespread than Darier "Dilapidated brick wall" appearance Epidermal hyperplasia Uncommon dyskeratosis (corps ronds, grains) vs. Grover's → differentiate clinically vs. Pemphigus → +ve DIF and acantholysis of adnexal structures (hair follicles)</p>
Treatment	<ol style="list-style-type: none"> <li><b>General measures:</b> <ol style="list-style-type: none"> <li>Lightweight clothes</li> <li>Sun protection</li> <li>Daily antimicrobial cleanser (↓ colonization, ↓ smell)</li> <li>Keratolytic emollients</li> </ol> </li> <li><b>Topicals:</b> mid potency CS; calcineurin -; 5-FU, COX2 and diclofenac</li> <li><b>Systemic:</b> Retinoids: isotretinoin, acitretin, or alitretinoin. Cyclosporine, low-dose naltrexone 4.5 mg nightly + 200 mg once daily</li> <li><b>Surgical:</b> recalcitrant localized lesion → excision with STSG, dermabrasion or CO<sub>2</sub> ablative laser.</li> </ol>	<ol style="list-style-type: none"> <li><b>General measures:</b> Utilize lightweight clothes to avoid friction and sweating.</li> <li><b>Topicals:</b> Antimicrobial cleaners, topical steroids, calcineurin inhibitors, Vit D analogues, 5-FU, zinc paste (↓ moisture /maceration), Botox (↓ sweating)</li> <li><b>Systemic: Most options listed have anecdotal/case reports supporting them.</b> Intermittent doxycycline Retinoids: acitretin, isotretinoin, alitretinoin Cyclosporine, MTX, dapsone, afamelanotide Low-dose naltrexone 4.5 mg nightly</li> <li><b>Surgical:</b> recalcitrant localized lesion → excision with STSG, dermabrasion or CO<sub>2</sub> ablative laser.</li> </ol>

**References:**

- Fitzpatrick's dermatology* 9th edition
- Bolognia, Dermatology* 4th edition
- Jfri A, Litvinov I, Netchiporouk E. Naltrexone for the Treatment of Darier and Hailey-Hailey Diseases. *J Cutan Med Surg.* Jul/Aug 2019;23(4): 453-4. doi: 10.1177/1203475419843122