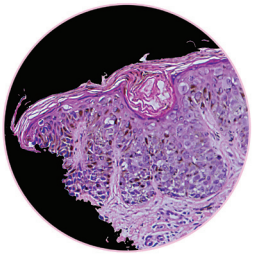
DERMATOLOGY FOR THE USMLE®



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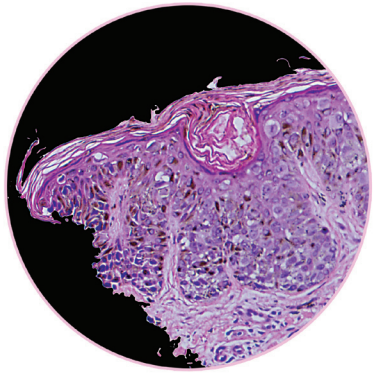

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To my parents, Wanda and Andres—for always believing in me.
Thank you for preparing me to persevere through adversity
and encouraging me to follow my dreams.

To my family, without whom none of my success would have been possible.

To my furry companions, for their unconditional love and support.

To the contributing residents and consultants,
for showing the true meaning of teamwork
and doing such a fantastic job. You were all incredible!

To the Department of Dermatology at Mayo Clinic Rochester,
my profound gratitude for the opportunity to be part
of this wonderful program. Thank you for providing the resources
and environment to fully develop my potential.

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CONTENTS

INTRODUCTION

As medical students, we constantly try to find ways to make our USMLE studying experience as effective as possible, while learning all the necessary information to become great physicians. This book contains the information you need to excel in the dermatology portion of the **USMLE Step 1, 2 and 3.** The goal of this book is to facilitate your USMLE studying experience by *summarizing* selected dermatology topics in the most precise, convenient and effective format possible. For every skin disease presented, this book provides general background, basic clinical presentation, diagnostic tests and treatments. Also included are high-yield images for almost every skin condition you may encounter during your USMLE preparation. Histological patterns are rarely covered in the USMLE exams but are incorporated for those who want a more comprehensive understanding of the skin pathology presented.

The information and images provided are also very useful for residents, physicians and other allied healthcare staff interested in dermatologic conditions. This review book summarizes the most common diseases seen by dermatologist and diseases frequently seen by other specialists that present with skin manifestations. This is by no means a complete and comprehensive dermatology textbook —it only reviews basic dermatology concepts and pathologies.

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HOW TO USE THIS BOOK

Start reading this book early in your medical career. Being familiar with the key concepts and images provided will ease your USMLE preparation and clerkship experience. Associating a medical condition with its clinical appearance will improve memory retention and enhance recall. **Bold** or *italic* text and USMLE Pearls emphasize important and most tested information or distinctions between differential diagnoses. One way or another I came across almost every skin pathology discussed in this book during my USMLE preparation and clerkships. Dermatologic manifestations of disease are seen in almost every specialty and recognizing them will help you tackle difficult exam questions. For example, when you recognize *Pyoderma gangrenosum* or *Erythema nodosum*, you should be thinking of underlying *inflammatory bowel disease* (IBD) as a possible diagnosis. Studying this book will help you answer the majority of dermatology questions in your board exams. It is my honor to provide this valuable tool for your development as a professional health provider.

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Chapter 1

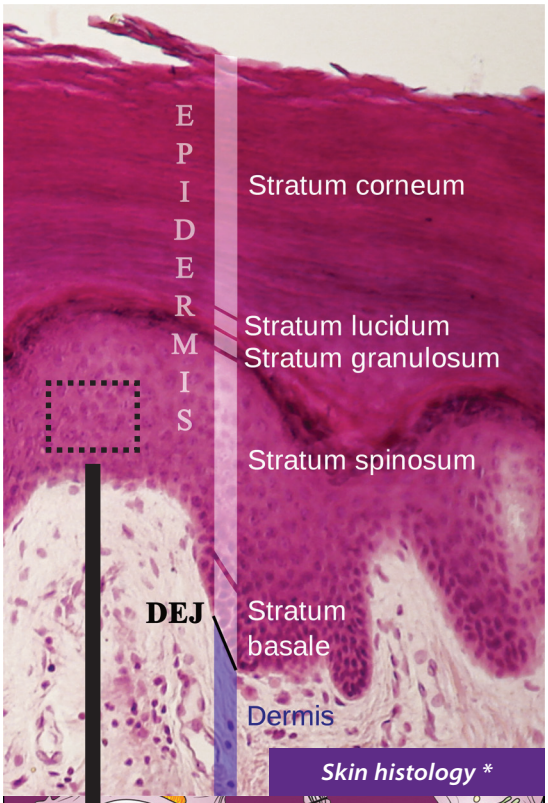
BASICS OF DERMATOLOGY

Skin: Largest and fastest growing organ in the human body. The skin is divided into **four layers,** beginning from superficial to deep: **Epidermis → Dermal-epidermal junction** (DEJ) **→ Dermis** (subepidermal) **→ Subcutaneous tissue.**

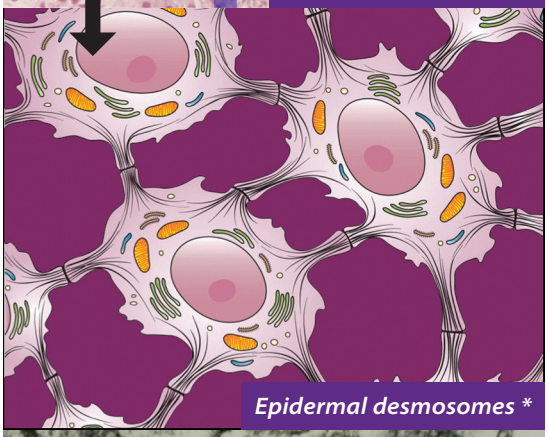
1. **EPIDERMIS:** Outermost and avascular portion of the skin. This **semipermeable barrier** is mainly composed of **stratified squamous epithelium.** The predominant cell type is the **keratinocyte.** Embryonic origin is the **surface ectoderm.**

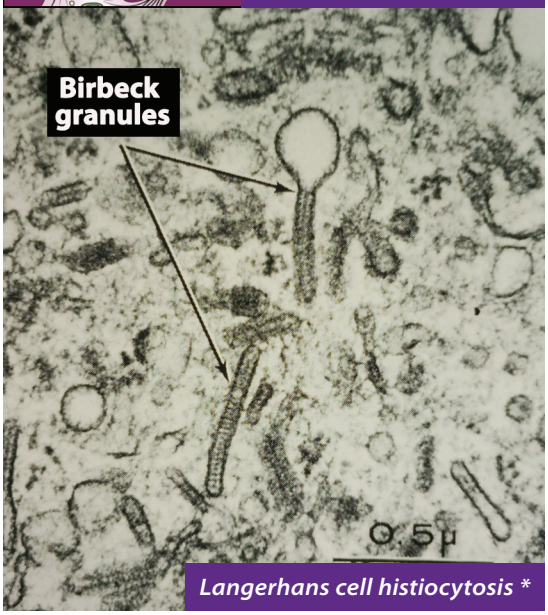
- **Functions of the Epidermis**
  - **Absorption and secretion:** Exchange of *toxins, medications* and *sweat* through direct interaction with glands and vessels in the dermis.
  - **Immunosurveillance:** Epidermal antigen presenting cells (Langerhans cells) activate the immune system after encountering foreign antigens. Faulty cutaneous immunosurveillance may result in **autoimmune diseases, skin infections** and **cancer.**
  - **Pigmentation:** Skin pigment **(melanin) protects** against UV-light damage and **provides pigmentation** to skin, hair and eyes. Disorders of pigmentation may result in photosensitive, light skin **(eg, vitiligo** and **albinism).**
  - **Protection and repair:** Specialized barrier protecting against: *Infections, mechanical and chemical injuries, loss of fluids* and *temperature changes*. Provides skin **regeneration** and **repair** following damage. Faulty regeneration and repair system may result in **xeroderma pigmentosum** and **keloid** formation.

- **Layers of the Epidermis**
  - **Stratum corneum (horny layer):** Outermost superficial layer of the epidermis; mainly composed of multiple layers of dead, anucleated keratinocytes. Contains a **superficial layer** of amino acids, fatty acids, sebum and hormones that protects against the environment and external pathogens.
    - **USMLE Pearls:** Dermatophytes are fungi that cause superficial infection of the *skin, hair* and *nails*. They **obtain nutrients from keratin** in the stratum corneum, thus infection is mainly limited to this cornified layer. Dermatophytes produce metabolic byproducts that lead to skin inflammation; neutrophils can accumulate *beneath* the stratum corneum and clinically present as **pustules.**
  - **Stratum lucidum:** Thin layer of anucleated keratinocytes found in thick parts of the skin, such as the **palms** and **soles.**
  - **Stratum granulosum (granular layer):** Three to five layers of keratinocytes containing prominent keratohyalin granules which appear dark on histology. This layer may be absent in **psoriasis** and certain types of **ichthyosis.**
  - **Stratum spinosum (prickly layer):** This layer contains prominent:
    - **Langerhans cells:** Bone marrow-derived dendritic cells; contain **Birbeck granules** which have a characteristic **"tennis racket"** shape under electron microscopy. Langerhans cells are **CD1a** positive and the primary cells involved in **Langerhans cell histiocytosis** (LCH).

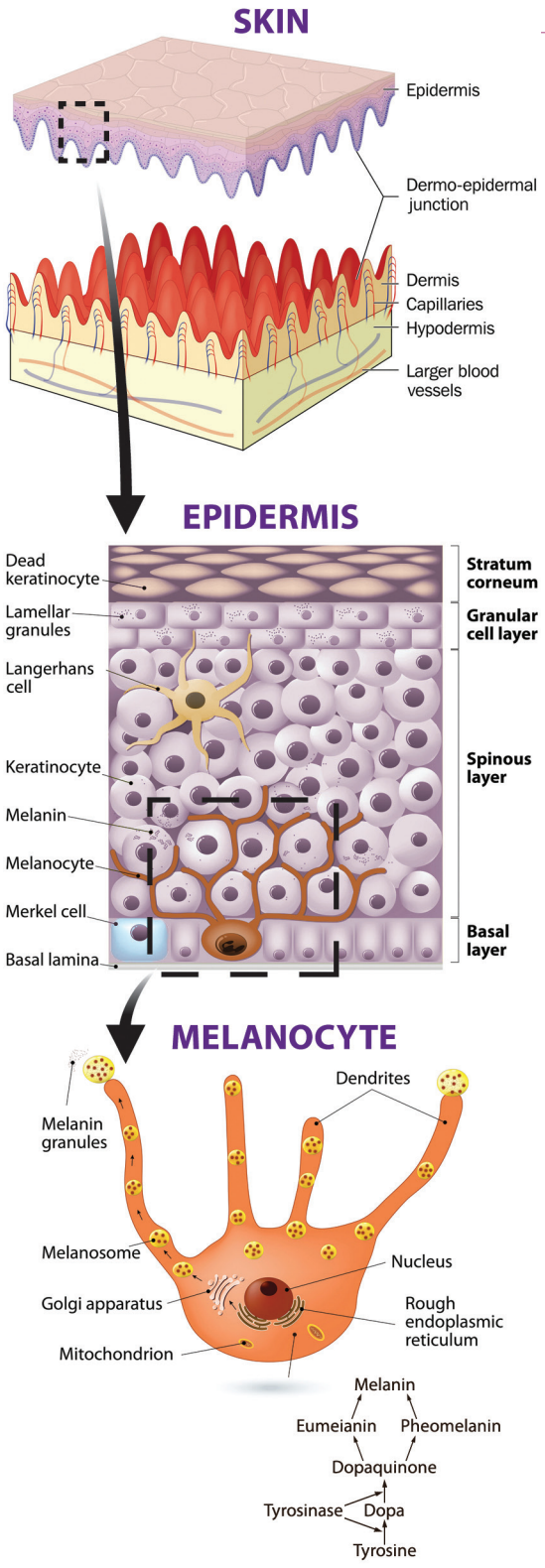


*Skin histology **


*Epidermal desmosomes **



*Langerhans cell histiocytosis **



*Skin, Epidermis and Melanocyte **

- **Desmosomes:** Structure that provide **connection** between keratinocytes. Destruction of desmosomes by **toxins** (eg, staphylococcal scalded skin syndrome) or **autoantibodies** (eg, pemphigus vulgaris) may result in dyscohesion of keratinocytes and **intraepidermal blisters.**

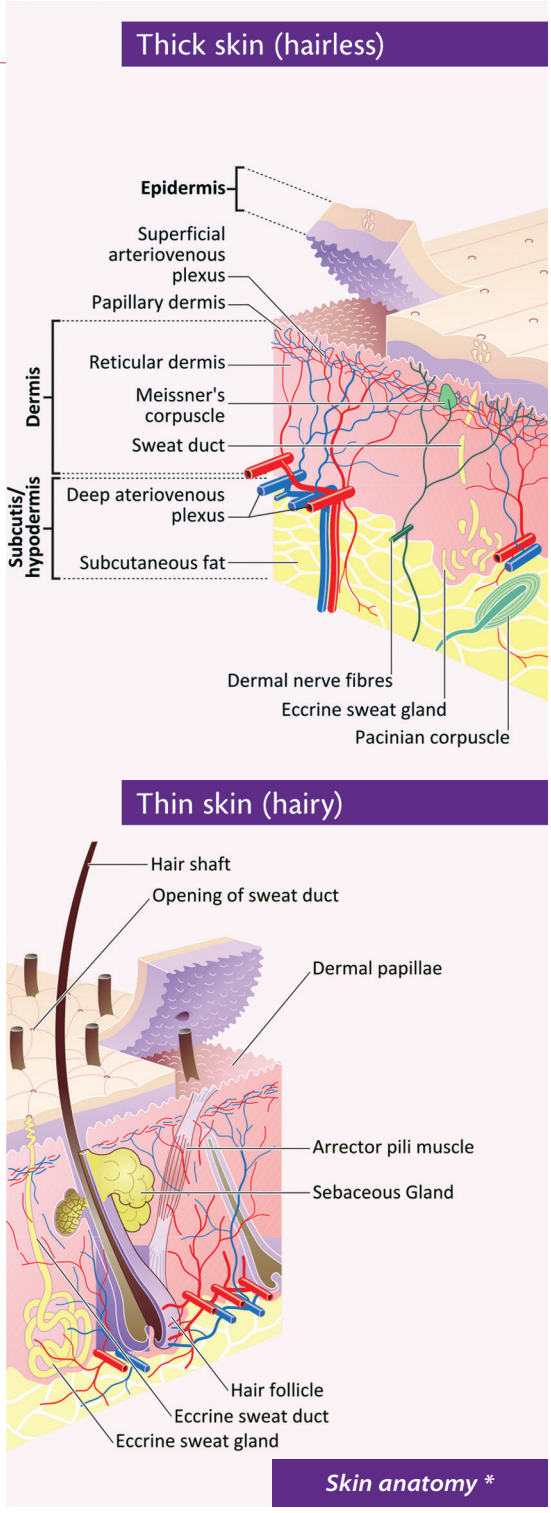
- **Stratum basalis (basal layer):** Innermost layer of the epidermis located *above* the dermal-epidermal junction (DEJ). Composed of a single row of **columnar basal cells** attached to the DEJ by **hemidesmosomes.** Keratinocytes are produced in this layer and move up as they mature to form the other four epidermal layers. The basal layer contains **melanocytes** and actively dividing **stem cells** responsible for **skin regeneration.**
  - **Melanocytes:** Neural crest-derived cells primarily present in the **skin basal layer, retina, uveal tract** and **leptomeninges.** In the skin, their main function is to **produce pigment** (melanin) and store it in melanosomes for transfer to neighboring keratinocytes. **Melanin synthesis** (melanogenesis) is stimulated by **UV-light, inflammation, melanin stimulating hormone** (MSH) and **adrenocorticotropic hormone** (ACTH), a precursor of MSH. The main steps in melanin *synthesis, storage* and *transfer* are summarized below:
    - **First step:** Conversion of **tyrosine → DOPA,** followed by **DOPA → dopaquinone;** both reactions are mediated by the enzyme **tyrosinase.**
    - **Second step:** Conversion of **dopaquinone → eumelanin** and **pheomelanin,** the two major types of **melanin** in the skin.
    - **Third step:** Melanin is **stored in melanosomes** and **transferred** to neighboring keratinocytes by melanocyte dendritic processes. Melanin remains permanently inside keratinocytes as pigmented granules.
    - **USMLE Pearls:** The number of melanocytes is essentially the same in all races. Melanocytes in darker skin types are larger and melanin is degraded slower. Skin complexion is generally classified using the **Fitzpatrick skin type scale,** which ranges from **skin type I** (lightest skin) to **skin type VI** (darkest skin).

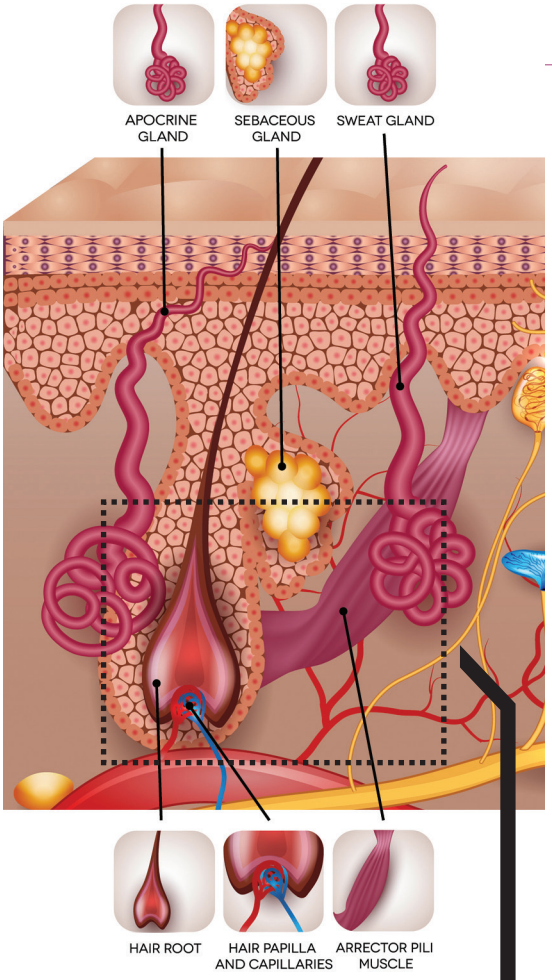
2. **DERMAL-EPIDERMAL JUNCTION (DEJ):** Also known as **dermoepidermal junction** or **basement membrane zone** (BMZ), functions to provide **attachment** and **communication** between the epidermis and dermis. The DEJ is connected to the overlying epidermis by **hemidesmosomes** and to the dermis by **anchoring fibrils** (composed of type VII collagen). Other important BMZ structures include the **lamina lucida** and **lamina densa.**
   - **USMLE Pearls:** Destruction of DEJ structures may result in subepidermal blistering disorders. Common examples include **bullous pemphigoid** (BP) and **epidermolysis bullosa acquisita** (EBA), which produce autoantibodies against **hemidesmosomes** and **type VII collagen,** respectively.

3. **DERMIS:** Embryonic origin is the **mesoderm.** The dermis provides **structural** and **nutritional support** for the epidermis. Composed mostly of mucopolysaccharide gel, collagen and elastic fibers. Main cell type is the **fibroblast,** responsible for synthesis of collagen and elastin. The dermis may be predominantly infiltrated by different cell types during pathological processes. Common examples are:
   - **Allergic reactions:** Lymphocytes and eosinophils.
   - **Acute inflammatory reactions:** Neutrophils (< 24 hours) and lymphocytes (> 24 hours).
   - **Chronic diseases and infections:** Lymphocytes and plasma cells.

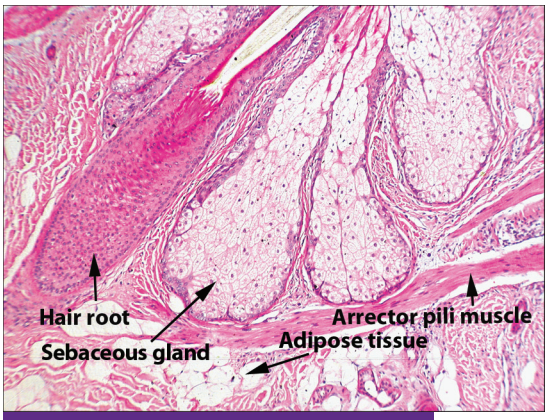
- **Functions of the Dermis**
  - **Communication:** Specialized nerve fibers provide *touch, pressure, pain* and *temperature sensation* to communicate and interact with the external environment. Patients with **syringomyelia, diabetes** and **leprosy** lose cutaneous sensation and often suffer from recurrent skin trauma or burns.
  - **Nutrients and waste exchange:** Blood vessels and capillaries provide *nutrients* to the epidermis and *exchange toxins, medications* and *waste products*. Blood circulation disorders may result in skin ulcers and necrosis; common examples include **vasculitis** and **embolic occlusion.**
  - **Support:** Dense collagen and elastic fibers provide *structural support* to overlying epidermis. Collagen production disorders such as **Ehlers-Danlos syndrome** may result in loose, lax skin.
  - **Thermoregulation:** Adaptation to different temperatures by regulating *vasodilation* and *vasoconstriction* of dermal vessels. Faulty thermoregulation may result in **hyperthermia** or **hypothermia.**
  - **USMLE Pearls:** In **nutritional deficiencies,** the skin is often the first to show signs. Common clinical manifestations are:
    - **Angular stomatitis:** Riboflavin (vitamin B2), cobalamin, zinc and niacin (vitamin B3) deficiency.
    - **Glossitis:** Folate, cobalamin (vitamin B12) and iron deficiency.
    - **Non-healing wounds:** Zinc and ascorbic acid (vitamin C) deficiency.
    - **Hair loss, dry skin and pruritus:** Protein and calorie deficiency.
    - **Pale skin:** Iron-deficiency anemia.

- **Layers of the Dermis**
  - **Papillary dermis:** Superficial dermal layer located *below* the epidermis. Mainly composed of loose and thin collagen, elastic fibers and capillaries.
  - **Reticular dermis:** Deep dermal layer *beneath* the papillary dermis made up 90% of dense collagen and elastic fibers. Contains *pilosebaceous units, glands, sensory nerve fibers, blood vessels* and *lymphatics*.





*Skin glands and pilosebaceous unit **



Pilosebaceous unit histology

4. **SUBCUTANEOUS TISSUE:** Also known as **subcutis** or **hypodermis;** embryonic origin is the **mesoderm.** Located *below* the dermis and provides *insulation, shock absorption, energy storage* and *structure* to the skin. The subcutis is composed of mature **white adipocytes** and contains large blood vessels, lymphatics and nerves.
    - **USMLE Pearls:** Adipose inflammation in this layer is known as **panniculitis.** The classic example of panniculitis is **erythema nodosum,** which most commonly presents as painful, red nodules over the pretibial area.

5. SKIN GLANDS

- **Apocrine sweat glands:** Present at birth but become functional during puberty secondary to hormonal stimulation. Continuously secrete minute quantities of oily fluid of unclear function; oil degradation by skin commensals produce a **malodorous smell.** Mainly located in the **axillae, areola, external ear canal, eyelids** and **anogenital region.**

- **Eccrine sweat glands:** Also called **merocrine sweat glands,** main function is **thermoregulation.** Located throughout the body, with the highest density in the palms, soles and axillae. Eccrine sweat glands are **not** present in the lips, external ear, penis glans or vaginal labia.
    - **USMLE Pearls:** Patients with **cystic fibrosis** secrete *hypertonic* sweat due to **defective chloride channels** in sweat glands. When exposed to hot climate or strenuous exercise, they can rapidly become **dehydrated** and **hypotensive.**

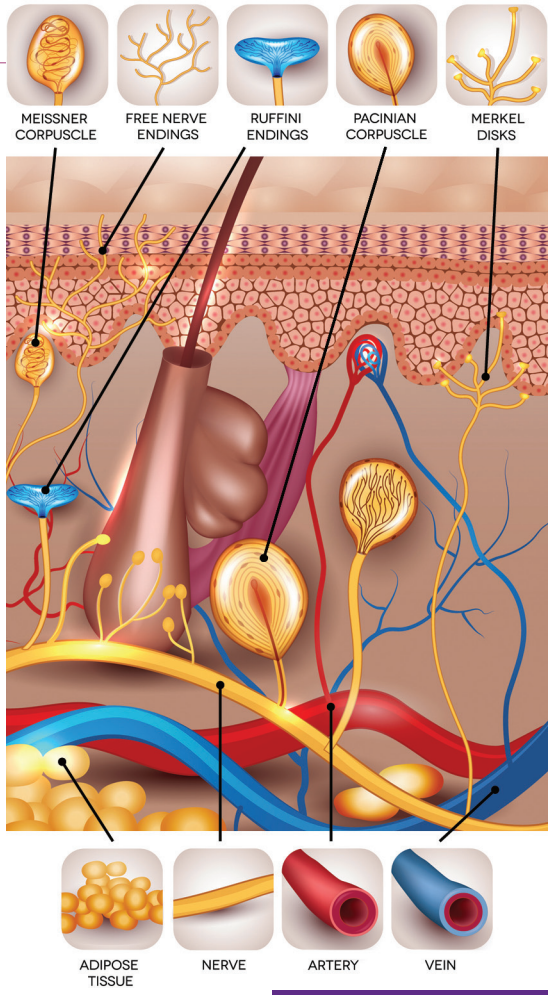
- **Sebaceous glands:** Produce sebum via **holocrine secretion;** these glands are under androgenic hormonal regulation and enlarge during puberty. Found throughout the body **except** on palms and soles. Highest density on the **face, scalp, ears** and **upper trunk,** hence pathologies affecting sebaceous glands will mainly affect these areas **(seborrheic distribution).** Sebaceous glands play a major role in the pathogenesis of **acne vulgaris.**

6. SKIN NERVE FIBERS

- **Free nerve endings:** Most common type of sensory receptor in the skin, located throughout the epidermis and superficial dermis. Provide **touch, pain** and **temperature** sensation. Common types of free nerve ending fibers are:
    - **C-type fiber:** Small, slow and unmyelinated.
    - **Aδ-type fiber:** Small, fast and myelinated.

- **Meissner corpuscles:** Mainly located in the superficial dermis of glabrous (hairless) skin such as fingertips, palms, soles, genitalia, lips and tongue. Rapidly adapting mechanoreceptors that provide **light touch, vibration** and **position** sensation.

- **Pacinian corpuscles:** Mainly located in deep dermis and subcutaneous tissue. Lamellar or onion-shaped, rapidly adapting mechanoreceptors that provide **vibration** and **pressure** sensation.
- **Ruffini corpuscles:** Mainly located in deep dermis and subcutaneous tissue. Slowly adapting mechanoreceptors that provide **stretching, continuous pressure** and **proprioception** sensation.
- **Merkel disks:** Mainly located in the basal layer of epidermis and hair follicles. Slowly adapting mechanoreceptor that provides **sustained pressure** and **deep static touch** sensation.



*Skin nerve fibers **

7. SKIN COLOR CHANGES

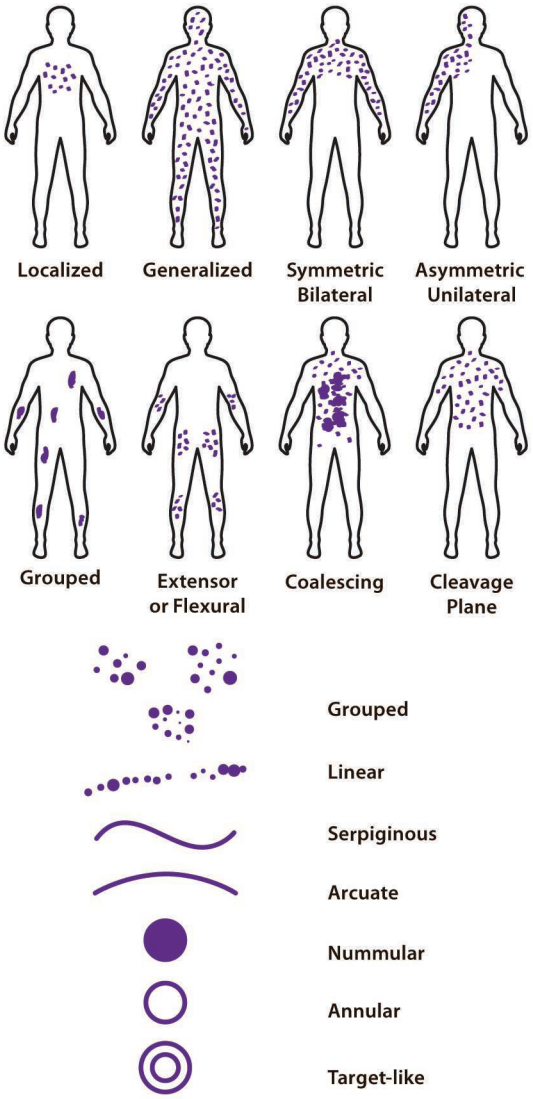
- The skin color may provide quick clues to the underlying pathological process.

Table 1.1. Skin Color Changes

Red Skin	Hyperpigmented Skin (Blue-Gray or Brown)	Purple/Black Skin
• **Acute sunburn** • **Carbon monoxide and cyanide poisoning** • **Carcinoid syndrome and VIPoma** • **Cutaneous lymphoma** • **Dermatomyositis and Lupus Erythematosus** • **Drug eruptions** » Beta-lactams, sulfonamides, tetracyclines and vancomycin ("red man" syndrome) • **Drugs side effects** » Calcium channel blockers (CCBs) » Nicotinic acid • **Eczema** (eg, atopic dermatitis) • **Fever** • **Hemangioma, angiosarcoma and Kaposi sarcoma** • **Hemorrhagic lesions** (eg, petechiae) • **Hot flashes** (menopause) • **Polycythemia** • **Raynaud disease** • **Scabies** • **Urticaria** • **Vasculitis** (eg, Henoch-Schönlein purpura) • **Viral and bacterial exanthems** (eg, measles)	• **Acanthosis nigricans** • **Addison disease** • **Arsenic and mercury exposure** • **Chronic stasis dermatitis** • **Chronic UV-light exposure** • **Dermal melanosis (Mongolian spot)** • **Drugs** » Antiarrhythmics (eg, amiodarone) » Antimalarials (eg, hydroxychloroquine) » Antipsychotics (eg, chlorpromazine) » Chemotherapy (eg, bleomycin, busulfan and daunorubicin) » Estrogens (eg, oral contraceptive pills) » Tetracyclines (also brown teeth) • **Hemochromatosis and Wilson disease** • **McCune-Albright syndrome** • **Melanocytic disorders** (eg, freckles, melasma, lentigines and nevi) • **Melanoma** • **Nelson syndrome** • **Ochronosis** (alkaptonuria) • **Peutz-Jeghers syndrome** • **Post-inflammatory hyperpigmentation** • **Silver intoxication** (argyria)	• **Bruises** (ecchymosis) • **Infections** » Cutaneous anthrax » Ecthyma gangrenosum (pseudomonas) » Mucormycosis » Necrotizing fasciitis • **Ischemic skin necrosis** (embolic occlusion) » Antiphospholipid syndrome (APL) » Antithrombin III deficiency » Factor V Leiden » Heparin-induced thrombocytopenia (HIT) » Protein C and S deficiency » Warfarin-induced skin necrosis • **Severe vasospasm** (frostbite) • **Tattoos** • **Vasculitis** » Buerger disease (thromboangiitis obliterans) » Cryoglobulinemia » Eosinophilic granulomatosis with polyangiitis (Churg Strauss) » Granulomatosis with polyangiitis (Wegener) » Henoch-Schönlein purpura » Polyarteritis nodosa (PAN) » Takayasu arteritis

Table 1.1. Skin Color Changes *(continued)*

Yellow Skin	Blue Skin (Cyanosis)	Hypopigmented Skin (White)
• **Beta-carotenemia** (excessive consumption of orange vegetables such as carrots, sweet potato and squash) • **Chronic renal failure** (CRF) • **Excessive circulating bilirubin** (jaundice) » Biliary cirrhosis » Bilirubin metabolism disorders (eg, Gilberts and Crigler-Najjar syndromes) » Hemolytic and microangiopathic anemia » Hepatitis (eg, infectious, toxic, autoimmune or drug-induced) • **Hypothyroidism** • **Necrobiosis lipoidica** • **Sepsis** • **Xanthomas**	• **Cardiovascular disease** » Congenital heart disease » Congestive heart failure and cardiac arrest • **Pulmonary disease** » Chronic obstructive pulmonary disease (COPD) » Pulmonary embolism (PE) » Respiratory foreign body » Restrictive lung disease (RLD) » Pneumonia, croup and epiglottitis • **Vasospasm** » Hypothermia » Raynaud disease • **Ventilatory depression** » Drug overdose (eg, heroin, benzodiazepines) » Prolonged seizures (eg, tonic clonic seizure)	• **Albinism** (eg, Hermansky-Pudlak syndrome) • **Iatrogenic** (eg, laser, bleaching agents) • **Leprosy** • **Lichen sclerosus** • **Pityriasis alba** • **Post-inflammatory hypopigmentation** • **Raynaud disease** (blanching) • **Scleroderma** • **Tinea versicolor** • **Tuberous sclerosis** ("ash leaf" spots) • **Vitiligo** (depigmented skin)



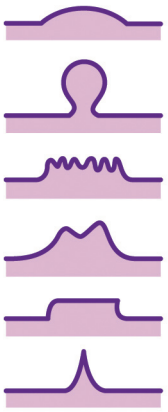
Skin lesions

8. COMMON TERMS IN DERMATOLOGY

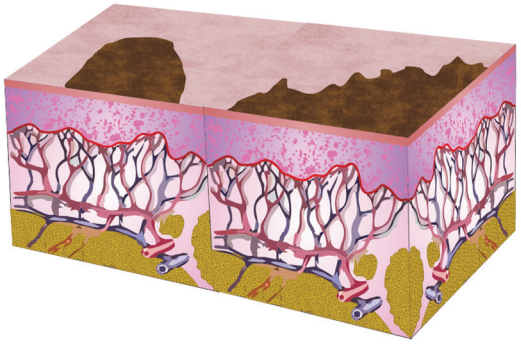
- **General Terms**
  - **Dermatosis:** Synonym for skin disease.
  - **Dermatitis:** Inflammation of the skin. Often used to refer to **eczema.**
  - **Eczematoid:** A lesion that resembles eczema (inflamed, oozing and crusted).
  - **Erythema:** Pink-red discoloration of skin secondary to blood vessel dilation or increased blood flow.
  - **Erythroderma:** Erythema that affects > 90% of the body surface.
  - **Rash:** Sudden or gradual widespread eruption of skin lesions. Rashes can be acute, subacute or chronic.
  - **Exanthem:** Widespread rash often associated to an infectious agent and accompanied by systemic symptoms (eg, headache, myalgias, fever). If the rash occurs inside the body on mucous membranes, it is called an **enanthem** (eg, Koplik spots).
  - **Koebner phenomenon:** Appearance of the underlying dermatosis on previously uninvolved skin due to trauma.
  - **Lesion:** Area of altered skin. Lesions can vary in:
    - **Color**
      - Hyper- or hypopigmented, red, purple, black, yellow, blue and white skin (see Table 1.1).

- **Configuration and topography**
  - Grouped, linear, serpiginous, arcuate, nummular, annular or target-like.
  - Dome-shaped, pedunculated, verrucous, umbilicated, flat-topped or acuminate.
- **Distribution**
  - Localized or generalized
  - Symmetric or asymmetric
  - Unilateral or bilateral
  - Flexural or extensor
  - Acral (hand, foot and nails)
  - Cleavage plane
  - Photodistributed, dermatomal or seborrheic
- **Texture and consistency**
  - Smooth or rough
  - Firm or soft
  - Mobile or fixed
  - Compressible, fluctuant or sclerotic
- **Morphology:** Basic and representative appearance of a skin lesion; **primary** and **secondary lesions** are described below.

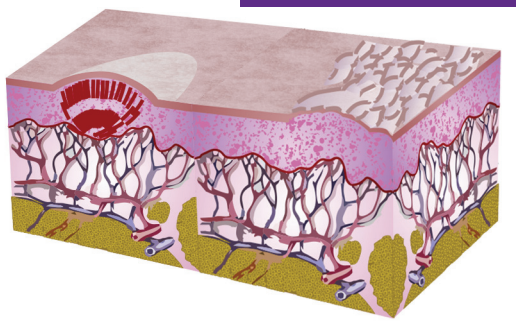
- **Primary Lesions**
  - The basic initial lesion of a skin disease. Primary lesions have **not been altered** by temporal changes or exogenous factors such as trauma, scratching or infections. Specific descriptive terms are:
    - **Macule:** Discolored area **≤ 1 cm** in diameter. *Nonpalpable;* when a finger is run over the skin, no lesion is felt (eg, tinea versicolor).
    - **Patch:** Discolored area **> 1 cm** in diameter, *nonpalpable* (eg, vitiligo).
    - **Papule:** **≤ 1 cm** in diameter. *Palpable* (raised), commonly called "a bump." Papules can be flat-topped, pedunculated, sessile, umbilicated, acuminate, dome-shaped or verrucous (eg, molluscum contagiosum).
    - **Plaque:** **> 1 cm** in diameter. Thickened and elevated *palpable* skin, often formed by confluence of papules (eg, psoriasis).
    - **Nodule:** **≥ 1 cm** in diameter. Elevated and circumscribed solid lesion, usually located within the dermis or subcutaneous tissue (eg, lipoma).
    - **Cyst:** Enclosed cavity containing liquid or semisolid substance (eg, epidermoid cyst).
    - **Vesicle:** **≤ 1 cm** in diameter. Circumscribed and elevated serum or blood-filled blister (eg, herpes simplex).
    - **Bulla:** **> 1 cm** in diameter. Fluid or blood-filled blister (eg, bullous pemphigoid).



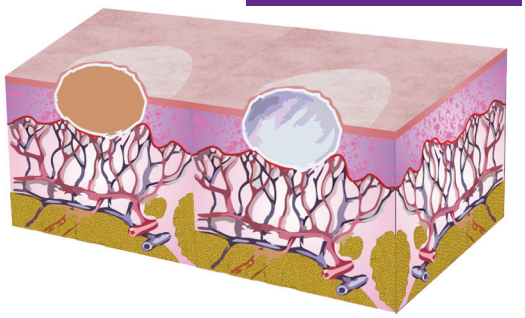
Skin lesions



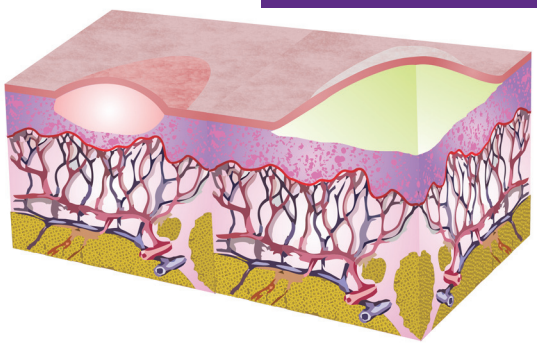
Macule and Patch



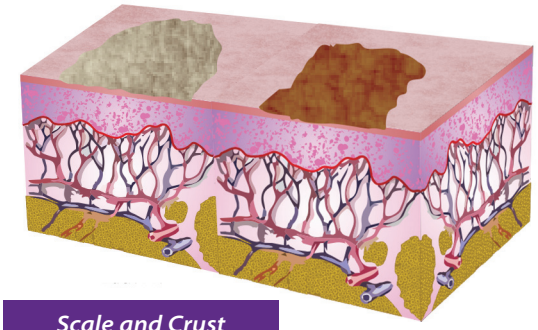
Papule and Plaque



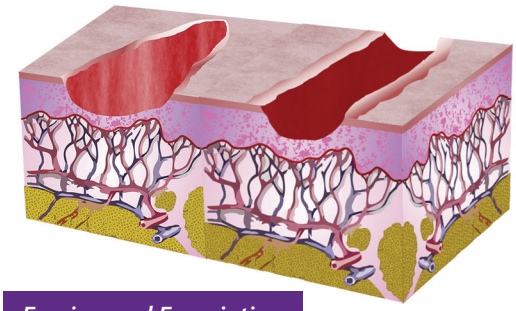
Nodule and Cyst



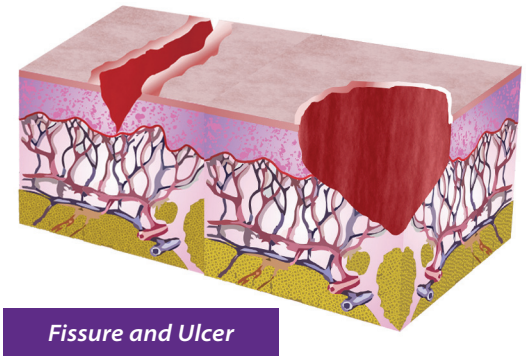
Vesicle and Bulla



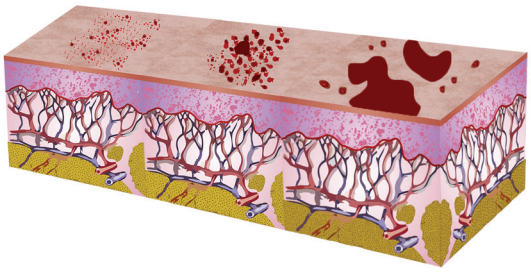
Scale and Crust



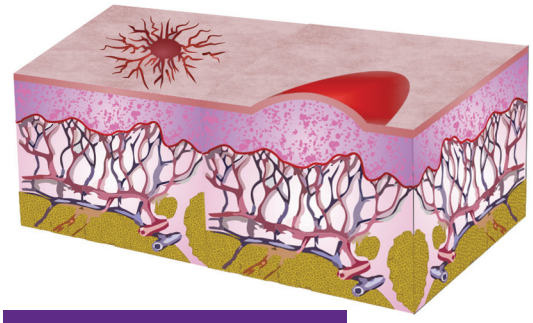
Erosion and Excoriation



Fissure and Ulcer



Petechiae, Purpura and Ecchymosis



Spider angioma and Wheal

- **Secondary Lesions**
  - Alteration of primary lesion by evolution over time or exogenous factors (eg, trauma, scratching or infection).
    - **Pustule:** Small, circumscribed, pus-filled papule. Usually white or yellow on physical exam (eg, acne vulgaris).
    - **Abscess:** Walled-off purulent material, usually within the dermis. Fluctuant on physical exam (eg, furuncle).
    - **Scale:** Superficial dead epidermal cells appearing as whitish or gray friable material adherent to a lesion (eg, pityriasis rosea).
    - **Crust:** Yellow-to-brown dried exudate atop lesion ("scab"). May occur secondary to superimposed bacterial infection (eg, impetigo).
    - **Lichenification:** Thickening and roughening of the skin with accentuated white skin markings. Usually occurs secondary to chronic rubbing or scratching (eg, lichen simplex chronicus).
    - **Scar:** Fibrous tissue that has replaced damaged skin (eg, burns).
    - **Keloid:** Abnormal scar that continues beyond the boundaries of the original skin injury. May occur after minor trauma (eg, piercing).
    - **Erosion:** Shallow, focal loss of skin surface involving the epidermis only (eg, intertrigo).
    - **Excoriation:** Superficial linear erosion secondary to scratching. Commonly seen in pruritic disorders (eg, atopic dermatitis).
    - **Fissure:** Thin, linear skin cleft; may involve the epidermis and dermis (eg, tinea pedis).
    - **Ulcer:** Deep loss of skin surface that may involve the epidermis, dermis and subcutaneous tissue (eg, stasis ulcer).

- **Miscellaneous Lesions**
  - **Hemorrhagic lesions:** Red-to-purpuric lesions caused by blood extravasation into the skin, *nonblanchable* and *nonpalpable*. Commonly seen in **platelet, coagulation** and **vascular disorders** (eg, disseminated intravascular coagulation).
    - **Petechiae** (< 0.5 cm in diameter)
    - **Purpura** (0.5 to 1 cm in diameter)
    - **Ecchymosis** (> 1 cm in diameter)
  - **Telangiectasia:** Prominent fine and irregular dilated superficial blood vessels; *blanchable* (eg, hereditary hemorrhagic telangiectasia).
  - **Spider angioma:** Small, red, vascular macule with radiating spider-like superficial vessels; *blanchable*. Commonly seen in patients with hyperestrogenism (eg, cirrhosis).
  - **Wheal (hive):** Superficial dermal swelling leading to a transient, edematous papule or plaque (eg, urticaria).

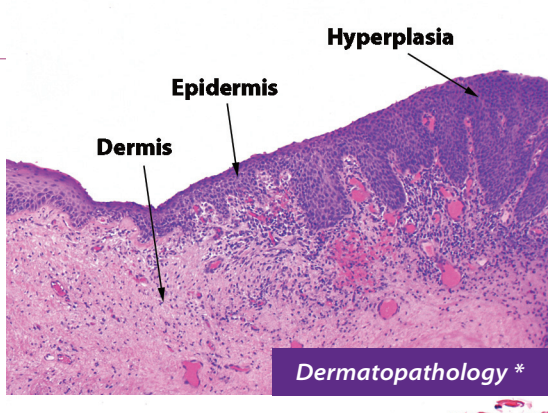
9. COMMON TERMS IN DERMATOPATHOLOGY

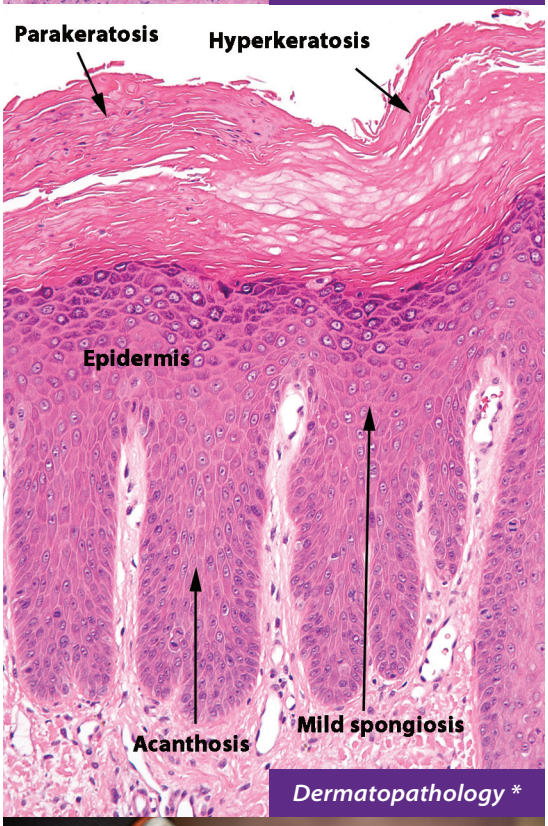
- Histopathological study of skin disorders is often necessary when a diagnosis is uncertain or to support a clinical diagnosis. The microscopic view of skin lesions may also correlate with clinical findings.
  - **Hyperplasia:** Increase in the total number of keratinocytes within the epidermis (eg, squamous cell carcinoma).
  - **Hyperkeratosis:** Thickening of the stratum corneum *without retention* of keratinocytes nuclei. Clinically, the skin may show scaling (eg, ichthyosis vulgaris).
  - **Parakeratosis:** Thickening of the stratum corneum *with retention* of keratinocytes nuclei. Clinically, the skin may show scaling (eg, psoriasis).
  - **Acanthosis:** Increase in thickness of the epidermis. Clinically, the skin may be thickened (eg, seborrheic keratosis).
  - **Epidermal atrophy:** Decreased thickness of the epidermal layer. Clinically, the skin may be thinned, fragile and dyspigmented (eg, lichen sclerosus).
  - **Papillomatosis:** Finger-like projection of dermal papillae above the surrounding epidermal surface. Clinically, the skin may be elevated and verrucous (eg, warts).
  - **Spongiosis:** Edema between keratinocytes. The epidermis has a "net-like" appearance, often accompanied by dilation of dermal vessels and lymphatics. Clinically, the skin may be edematous and elevated, often with vesicles (eg, eczema).
  - **Acantholysis:** Separation of keratinocytes due to loss of intercellular attachments (desmosomes). Clinically, the skin may be fragile and detaching (eg, pemphigus vulgaris).
  - **Palisading:** Organization of cells in a linear or picket fence-like pattern at the periphery of a lesion (eg, basal cell carcinoma).

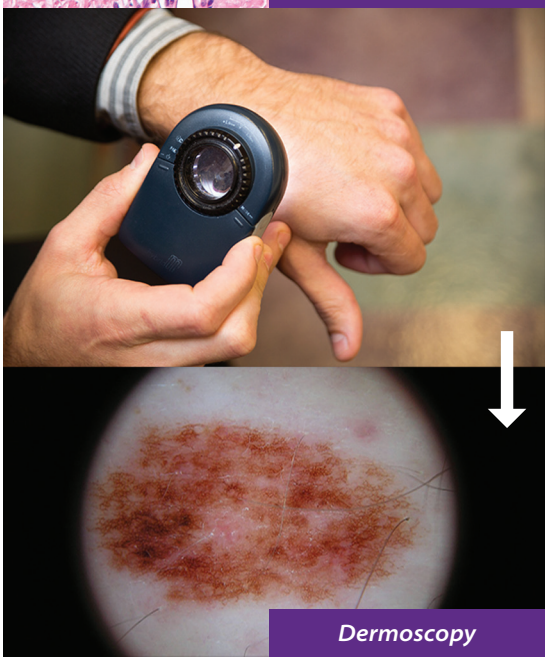
10. DIAGNOSTIC PROCEDURES IN DERMATOLOGY

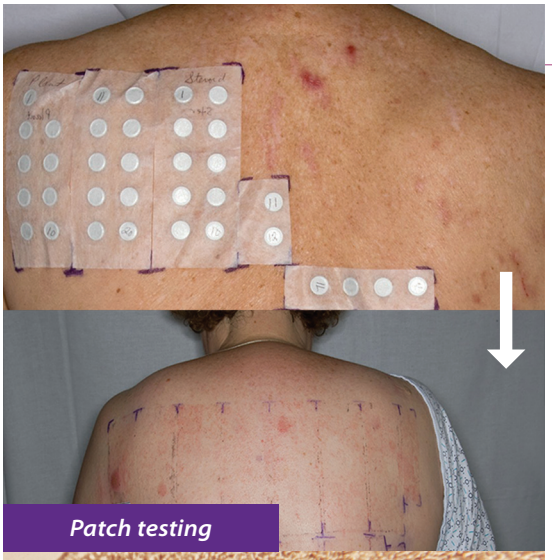
- **Dermoscopy (dermatoscopy):** Noninvasive external examination of the skin using a handheld skin-surface microscope **(dermatoscope),** similar to a magnifying glass. Dermoscopy permits the physician to look into the *epidermis* and *superficial dermis* to see skin details not visible to the naked eye. Common uses for dermoscopy include:
  - **Pigmented lesions** (aids in differentiating benign from malignant)
  - **Scabies** and **lice infestation**
  - **Splinter injuries**
  - **Psoriasis, warts** and **molluscum contagiosum**
  - **Nail capillaries**

- **Patch testing:** Skin test used to identify offending allergens in chronic eczematous disorders **(eg, allergic contact dermatitis).** Most commonly the skin of the upper back is covered with a bandage that contains small disks of commonly encountered allergens. The bandage is left for **48 hours** and subsequently removed to inspect the skin for irritation and allergy. The skin is reevaluated at **96 hours** and often the following week. A **positive result** is *erythema, papules and/or vesicles* on the skin that was in contact with the specific allergen. A similar test called **photopatch testing** is used for **photoallergic reactions.**

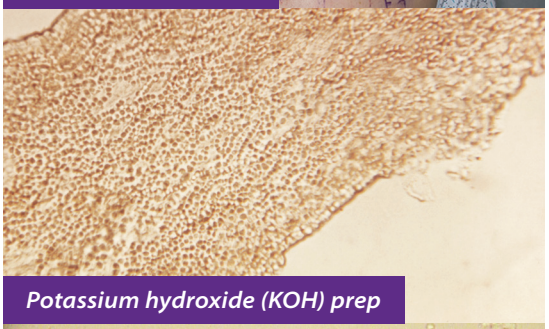




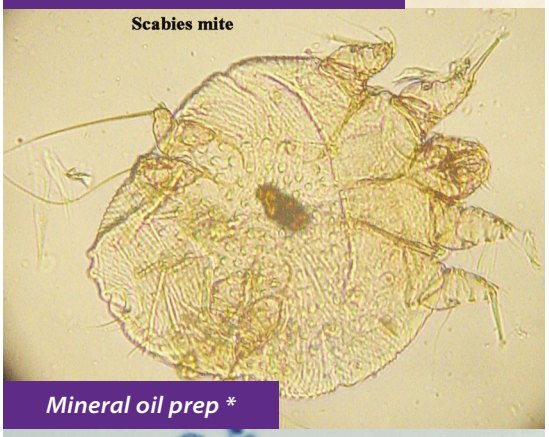




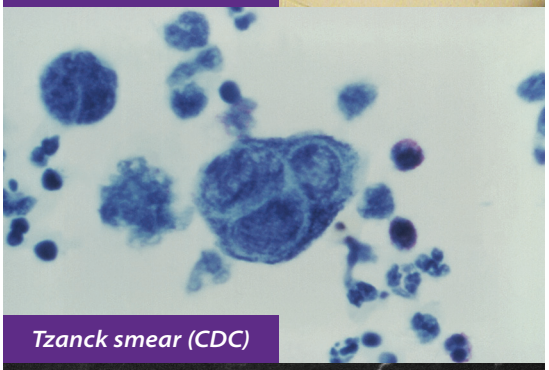
Patch testing



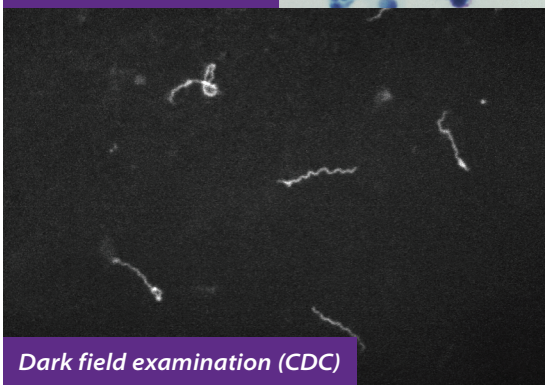
Potassium hydroxide (KOH) prep



Mineral oil prep *



Tzanck smear (CDC)



Dark field examination (CDC)

- **Diascopy:** Mainly used to distinguish between **inflammatory processes** and **hemorrhagic lesions.** A glass slide is pressed against erythematous lesions to see if it **blanches** (whitens). If the lesion **blanches,** it is an inflammatory process (vasodilation or increased blood flow). If the lesion **does not blanch,** it is a hemorrhagic lesion (extravasated blood).

- **Skin, hair or nail scraping:** Specimen obtained via scraping with a metal blade or glass slide. The sample can be used for any of the following procedures:
  - **Potassium hydroxide preparation (KOH prep):** Potassium hydroxide (KOH) solution is applied to the collected sample to dissolve keratin (eg, skin) allowing microscopic visualization of remaining fungus or yeast. Mainly used for diagnosing **superficial fungal infections** (eg, tinea versicolor, candidiasis and dermatophytosis).
  - **Mineral oil preparation:** Skin scrapings are obtained using an oil-dipped scalpel and placed on a glass slide with mineral oil. Microscopic examination of the sample allows detection of **scabies mites, eggs and/or fecal matter.**
  - **Tzanck smear:** Nuclear stains (Giemsa, Wright's or Hansel) are applied to scrapings obtained from the base of an ulcer or vesicle allowing microscopic detection of *multinucleated giant cells* or *Tzanck cells*. Mainly used for rapid detection of **herpes simplex, varicella** and **zoster** infections, although it cannot differentiate among them.
  - **Dark field examination:** Scrapings are usually obtained from the base and edge of an ulcer suspicious for **syphilis** and visualized under dark field microscopy for spirochetes.

- **Wood's lamp examination:** Noninvasive examination of *skin, hair* or *urine* under a black light emitted by the Wood's lamp. Used to enhance variations is skin pigmentation and examine **fluorescent color patterns** not visible to the naked eye. Common uses include:
  - **Erythrasma** (*coral red* fluorescence)
  - **Vitiligo** and **tuberous sclerosis** "ash-leaf spots" (*blue-white* fluorescence)
  - **Porphyria cutanea tarda urine** (*red-pink* fluorescence)
  - **Tinea capitis** (differentiate among dermatophytes)
    - *Microsporum canis* or *M. audouinii* (*blue-green* fluorescence)
    - *Trichophyton* sp. (no fluorescence)

- **Skin biopsy:** Procedure in which a sample of skin is removed for histopathological studies. Generally done to **confirm or refute a clinical diagnosis** (eg, suspicious malignant lesions) or as a **treatment modality.** Samples are routinely stained with hematoxylin and eosin (H&E) and analyzed under light microscopy. Additionally, samples can be used for **cultures, direct immunofluorescence studies** and **electron microscopy. Special stains** are available to aid in identification of specific cell types, tissue types and infectious organisms. Different types of biopsies are used for different skin disorders. Common examples include:
  - **Shave biopsy:** A scalpel or blade is used to remove a thin layer of superficial skin. Usually, no stitches are required for wound closure and the skin heals in 1 to 2 weeks. Mainly used for skin diseases that affect only the *epidermis* and *superficial dermis* or as a treatment modality to remove small cutaneous lesions (eg, seborrheic or actinic keratoses, acrochordons, verrucae and superficial BCCs and SCCs). Shave biopsies are generally *not* useful to visualize processes deep in the dermis or subcutaneous tissue.

- **Punch biopsy:** A cylindrical, cookie cutter-like tool is used to quickly and conveniently obtain a round, *full-thickness* skin sample with minimal tissue damage. Punch biopsies range in size from 2 to 8 mm in diameter and usually require 1 to 2 stitches for wound closure. Mainly used for pathologies involving the *epidermis* and *dermis* (eg, eczema, psoriasis, drug eruption, vasculitis and autoimmune or blistering disorders).
- **Incisional biopsy:** A scalpel is used to remove a *full thickness* piece of skin lesion. Usually requires sutures for wound closure. Mainly used when larger samples are needed or when the suspected pathology involves deeper tissues, such as *subcutaneous fat* or *fascia* (eg, erythema nodosum).
- **Excisional biopsy:** A scalpel is used to remove the *entire lesion* including margins, most commonly using an elliptical excision. Sutures or more significant skin closure techniques (eg, skin grafting) are needed. Mainly used for dermal, subcutaneous and melanocytic neoplasms or as a treatment modality (eg, melanoma).

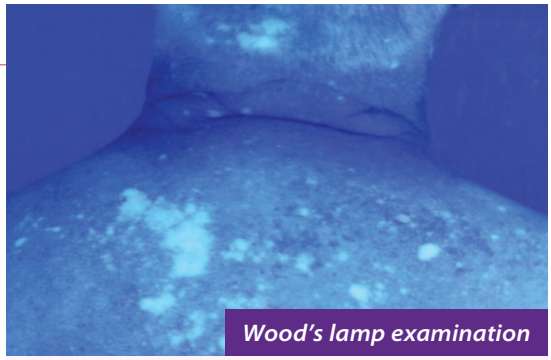
- **Direct immunofluorescence (DIF) studies:** A known antibody is linked to a fluorescent agent that targets a specific antigen. When the antibody binds the target antigen, it **fluoresces** and can be seen under microscopy. The *pattern* and *location* of the fluorescence are used to diagnose specific skin diseases including **blistering disorders** (eg, bullous pemphigoid) and **autoimmune skin diseases** (eg, lupus erythematosus).

11. COMMON TREATMENTS IN DERMATOLOGY

- **Topical steroids:** Topical preparation that functions as **anti-inflammatory** and **antipruritic** agent by inhibiting mitosis and DNA synthesis. **Side effects** include skin atrophy, striae and hypopigmentation. Preparations vary by potency:
  - **Low potency:** Hydrocortisone and desonide.
  - **Intermediate potency:** Triamcinolone and fluocinolone.
  - **High potency:** Betamethasone and fluocinonide.
  - **Ultra high potency:** Clobetasol and halobetasol.

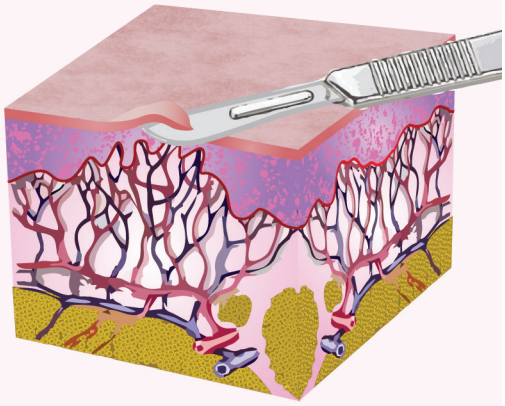
- **Bleaching agents:** Used to **lighten skin** in different hyperpigmentation disorders. **Side effects** include hyper- or hypopigmentation. The main agents used for this purpose are:
  - **Hydroquinone**
  - **Topical retinoids** (vitamin A derivatives)
  - **Topical steroids**

- **Phototherapy:** Therapeutic exposure of affected skin to specific wavelengths of **UV-A or UV-B light.** Phototherapy works by decelerating keratinocyte proliferation and suppressing immune response. A common type of phototherapy is **PUVA,** which is the combination of a skin sensitizer (**P**soralen) plus UV-A light **(UVA).** The patient ingests the skin sensitizer followed by exposure of affected area to UV-A lamps. Major **side effects** of phototherapy include: burning, itching, hyperpigmentation, eye damage, skin aging and cancer. Common uses for phototherapy are:
  - **Atopic dermatitis**
  - **Cutaneous lymphoma**
  - **Psoriasis**
  - **Vitiligo**

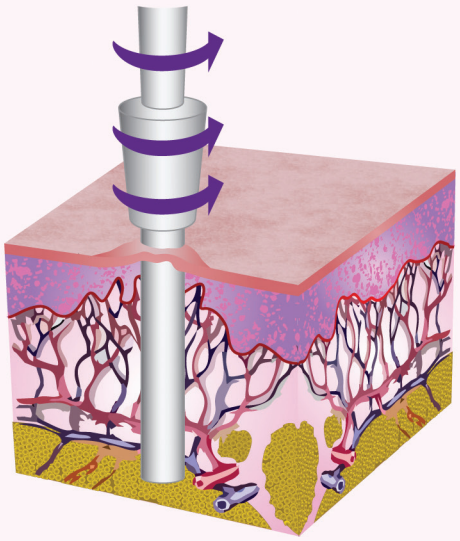


Wood's lamp examination

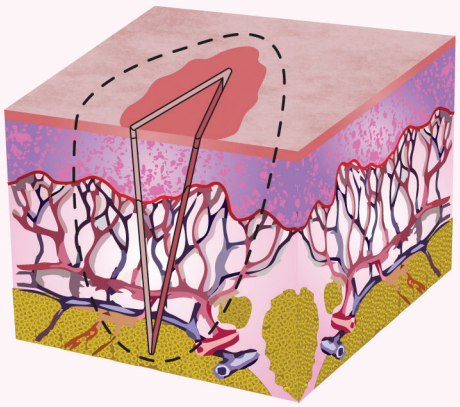
Shave Biopsy



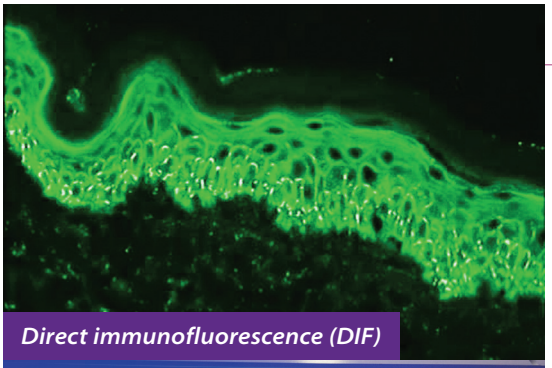
Punch Biopsy



Incisional & Excisional Biopsy



Skin biopsies



Direct immunofluorescence (DIF)

Phototherapy

Cryotherapy

- **Mohs micrographic microsurgery (MMM):** Specialized surgical technique used for the **removal of skin cancers** (eg, melanomas, SCCs and BCCs). Thin layers of cancer-containing skin are progressively removed and examined under the microscope until only cancer-free tissue remains. Used for **aggressive and recurrent cancers** and when **maximum cosmetic results** are needed (eg, facial skin cancers).

- **Cryotherapy:** Destruction of skin lesions using **liquid nitrogen.** This is an office-based procedure that is quick, convenient and safe. Common **side effects** include: pain, hypopigmentation and scar formation. This treatment modality is mainly used for:
  - **Actinic keratoses**
  - **Seborrheic keratoses**
  - **Warts**

- **Miscellaneous:** Certain antimicrobials are used over prolonged periods of time in low doses to take advantage of the **immunomodulatory** and **anti-inflammatory** properties. The most common agents used for this purpose are:
  - **Dapsone** (used for pyoderma gangrenosum and dermatitis herpetiformis)
  - **Hydroxychloroquine** (used for rheumatoid arthritis and cutaneous lupus erythematosus)
  - **Minocycline and doxycycline** (used for bullous pemphigoid)

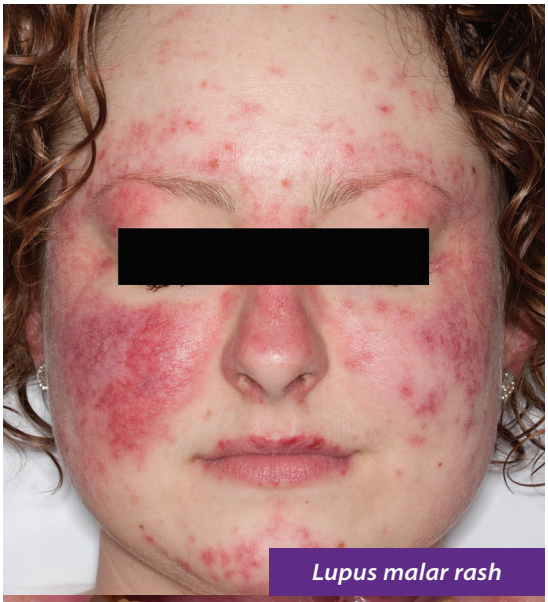
Chapter 2

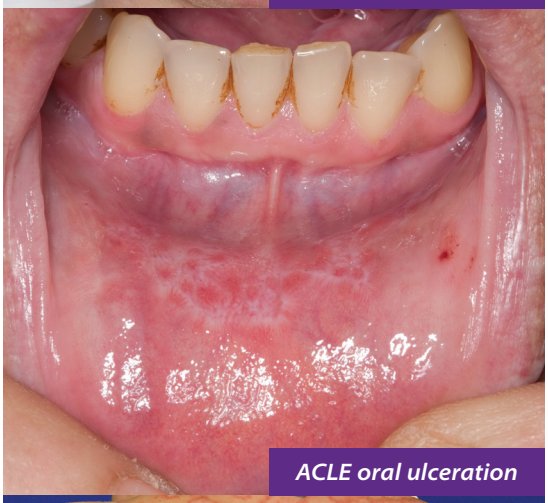
AUTOIMMUNE SKIN DISORDERS

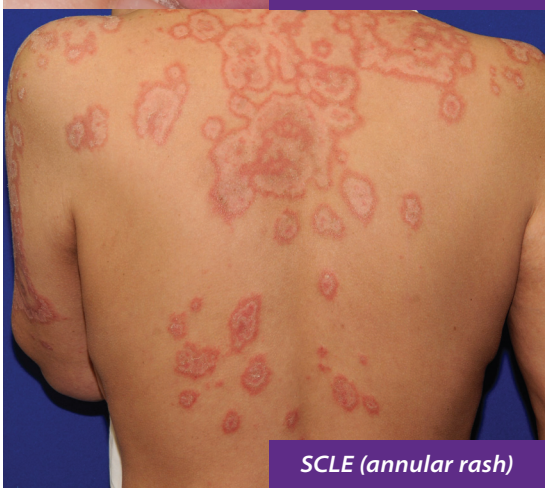
1. LUPUS ERYTHEMATOSUS (LE)

- **General:** Complex, multifactorial autoimmune disorder characterized by a chronic relapsing and remitting course and **prominent skin involvement.** Broadly divided into *systemic lupus erythematosus* (SLE) and *cutaneous lupus erythematosus* (CLE). SLE is the most common and severe type of LE affecting multiple organ-systems. CLE primarily affect the skin although many patients also present with systemic manifestations and go on to develop SLE. SLE is a female predominant disease and more prevalent in **African American females.** Production of **autoantibodies** and **circulating immune complexes** are thought to play an important role in the pathogenesis. The important antibodies to consider in SLE are:
  - **Anti-nuclear antibody (ANA):** The most sensitive but least specific. May be positive in healthy individuals (eg, elderly) and in many other systemic diseases.
  - **Anti-double-stranded DNA antibody (Anti-dsDNA):** Most useful, very sensitive and specific. Correlates with *disease activity, exacerbations, prognosis* and *renal involvement*.
  - **Anti-Smith antibody (Anti-Sm):** Less sensitive but most specific (if positive, high chance of having lupus).
  - **Anti-phospholipid antibody (aPL):** Associated with **anti-phospholipid syndrome** (APS). APS is characterized by multiple **thrombus formation** and **spontaneous abortions.**
  - **Anti-SSA (Anti-Ro) and anti-SSB (Anti-La):** Neither specific nor sensitive for lupus. When positive, it is associated with **neonatal heart block.** Anti-SSA and anti-SSB may also be positive in **Sjögren syndrome,** rheumatoid arthritis (RA), systemic sclerosis and polymyositis.

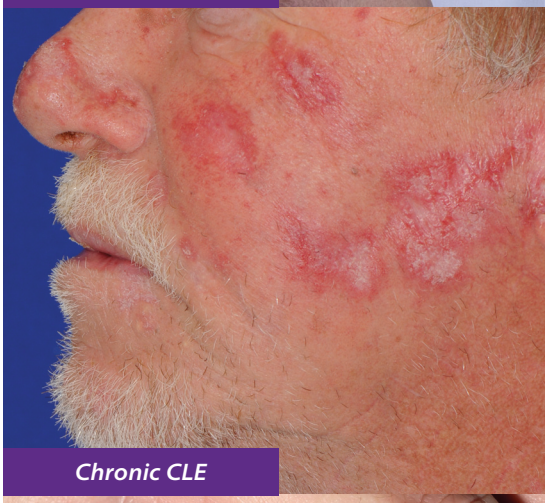
- **Clinical:** Cutaneous lupus erythematosus (CLE) is further subdivided into *acute, subacute* and *chronic CLE*.
  - **Acute Cutaneous Lupus Erythematosus (ACLE):** This type of cutaneous lupus is characterized by the classic **facial malar or "butterfly" rash** *and* a photosensitive, erythematous maculopapular rash predominantly on sun-exposed areas. **Oral** and **nasal mucosal ulcerations** are common. Most patients with ACLE will have SLE and also present with systemic symptoms and internal organ involvement, such as:
    - **Blood:** Leukopenia, anemia and thrombocytopenia.
    - **Brain:** Seizures and psychosis.
    - **Heart:** Pericarditis, myocarditis and arrhythmias.
    - **Kidney:** Renal failure and nephritis.
    - **Lung:** Pleural effusion and pleuritis.
    - **Musculoskeletal:** Arthritis and arthralgias.
    - **Constitutional symptoms:** Fever, fatigue, lymphadenopathy and weight loss.








SCLE (psoriasis-like rash)


Chronic CLE


Chronic CLE alopecia

- **Subacute Cutaneous Lupus Erythematosus (SCLE):** This type of cutaneous lupus typically presents with erythematous **annular lesions** with raised borders and central clearing *or* **psoriasis-like** scaly papules and plaques. Sun-exposed areas such as the upper extremities, chest and face are mainly affected. About half of patients with SCLE have SLE and also present with systemic manifestations.
- **Chronic Cutaneous Lupus Erythematosus (CCLE):** Most commonly presents with **erythematous, inflamed** and **round (discoid)** scaly plaques with **central atrophy** and **white patches.** Lesions are located *above the neck* 80% of the time and may heal with scarring. Scalp involvement may lead to **permanent alopecia.** Patients with CCLE less commonly have SLE or systemic symptoms.

- **Diagnosis**
  - **Best initial test:** Clinical + CBC (anemia, thrombocytopenia and leukopenia) + urinalysis, BUN and Cr + autoantibody assays to detect *anti-nuclear antibody, anti-dsDNA* and *anti-Sm*. If patient has renal involvement, perform a renal biopsy *before* initiating treatment (biopsy guides treatment).
  - **Most accurate test:** Skin biopsy showing epidermal atrophy and inflammation at the DEJ and perivascularly. **Direct immunofluorescence (DIF)** studies revealing a granular pattern of IgG, IgM, IgA and C3 along the DEJ.

- **Treatment**
  - **First line:** Avoid and protect from sun + topical steroids and hydroxychloroquine.
  - **Second line:** Systemic therapy with steroids, methotrexate, cyclophosphamide or azathioprine for severe disease.

- **USMLE Pearls: Drug-Induced Lupus:** A subtype of lupus erythematosus induced by drugs. The main culprits are: **hydralazine, isoniazid, procainamide,** quinidine, diltiazem, minocycline and proton pump inhibitors (PPIs). May arise months to years after drug exposure. Presents similar to SLE but **without CNS or kidney involvement.** *Diagnosis* based on clinical features and presence of **anti-histone antibody.** *Treat* by discontinuing offending drug.

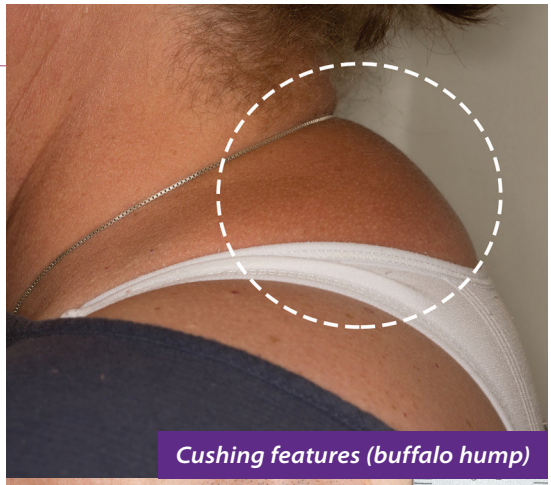
- **USMLE Pearls:** Patients with autoimmune disorders are commonly under **chronic systemic corticosteroid therapy.** Abruptly discontinuing or insufficient supply of steroids in these patients may lead to an **Addisonian crisis** secondary to hypothalamic-pituitary-adrenal (HPA) axis imbalance. They present with **hypotension, confusion, weakness, muscle and abdominal pain** and **electrolytes imbalance** (high K^+ and low Na^+). These episodes are usually provoked by stressful situations such as a surgery or systemic infections. Chronic steroid therapy may also lead to **important side effects,** including:
  - **Infections**
  - **Osteoporosis** or **avascular necrosis of bones** (eg, hip, wrist).
  - **Cushing features, high blood glucose** and **weight gain.**
  - Fatigue, headaches and myalgias.
  - **Depression,** insomnia, **psychosis** and delirium.
  - Leukocytosis with high neutrophil count.

2. SYSTEMIC SCLEROSIS (SCLERODERMA)

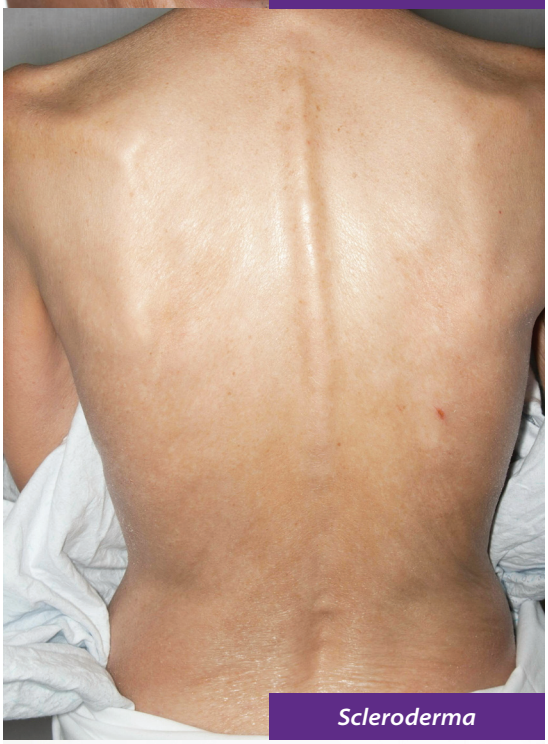
- **General:** Complex, multifactorial autoimmune systemic disease of unknown etiology characterized by **abnormal collagen deposition** in different organs. Overproduction of *transforming growth factor beta* (TGF-β) is thought to play an important role in the pathogenesis. It is a female predominant disease with an average age of onset between age 30 to 50. Major organs affected are:
  - **Lungs:** Interstitial lung disease (fibrosis) and pulmonary hypertension (lung disease is the most common cause of death).
  - **Kidney:** Renal failure and hypertension (renal crisis).
  - **Vascular:** Raynaud, ischemia (ulcers) and telangiectasias.
  - **Heart:** Pericarditis, restrictive cardiomyopathy and arrhythmias.
  - **Musculoskeletal:** Myalgias, weakness and arthralgia.
  - **GI tract: Dysphagia** (esophageal dysmotility), **chronic GERD** (immobile esophageal sphincter), **diarrhea, bloating** and **vitamin B12 deficiency** (small intestine bacterial overgrowth secondary to GI dysmotility).

- **Clinical:** Subdivided into *diffuse* and *limited systemic sclerosis.*
  - **Diffuse Systemic Sclerosis:** Worst prognosis; progressive disease that may affect any of the organs listed above. Commonly starts with **Raynaud phenomenon,** a vasospasm reaction to cold that causes fingers to turn *white-blue-red*. The skin becomes **firm, shiny and thickened** resulting in marked **skin tightness;** when these cutaneous manifestations affect the fingers or toes, it is known as **sclerodactyly.** These skin changes can result in **limited mobility, flexion contractures** and **loss of facial expression. Digital ulcers** commonly develop secondary to poor vascular circulation. The skin may have a mixture of hyper- and hypopigmentation and permanent scarring may occur in late stages.
  - **Limited Systemic Sclerosis (CREST syndrome):** Rarely involves internal organs, it is characterized by:
    - **C**alcinosis
    - **R**aynaud phenomenon
    - **E**sophageal dysfunction
    - **S**clerodactyly
    - **T**elangiectasias

- **Diagnosis**
  - **Best initial test:** Clinical + autoantibody assays to detect *anti-nuclear antibody, anti-topoisomerase I (anti-Scl-70)* and *anti-centromere* (CREST syndrome). Depending on initial presentation, consider any of the following tests:
    - **Lung:** High-resolution chest CT scan and pulmonary function tests (PFTs).
    - **Kidney:** Renal function tests (BUN and Cr).
    - **Heart:** Echocardiography and ECG.
    - **GI tract:** Esophageal manometry and gastric emptying studies.
  - **Most accurate test:** Skin biopsy showing epidermal atrophy and intense collagen deposition in dermis with sclerosis and loss of fat around adnexal structures.

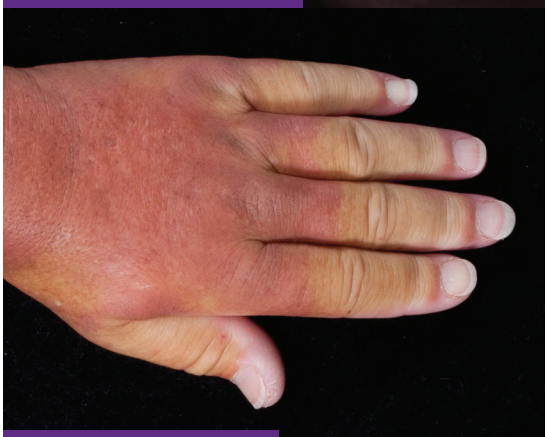

Cushing features (buffalo hump)

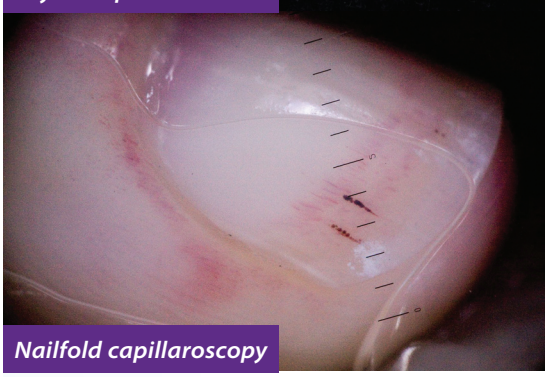

Scleroderma

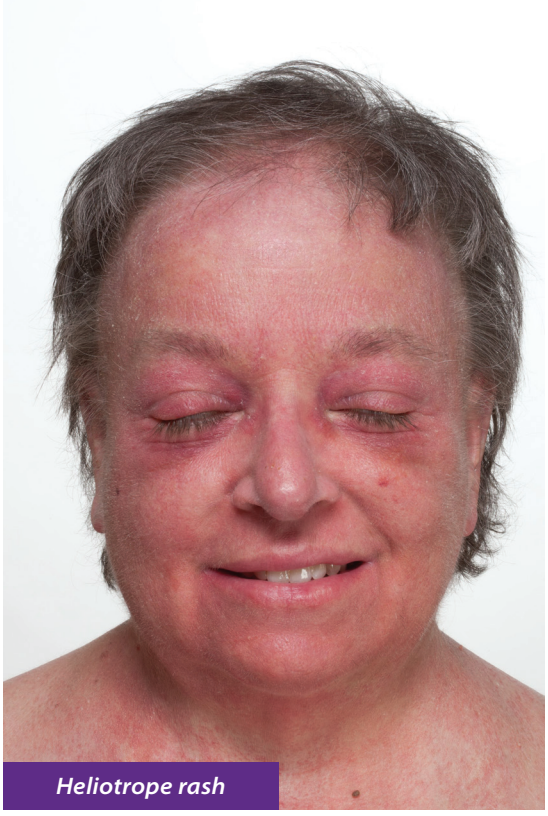

Scleroderma


Sclerodactyly


Scleroderma digital ulcers


Raynaud phenomenom


Nailfold capillaroscopy


Heliotrope rash

- **Treatment**
  - **First line:**
    - **Raynaud phenomenon:** Calcium channel blockers (eg, nifedipine).
    - **Pulmonary hypertension:** Prostacyclin analogues (eg, epoprostenol) or endothelin antagonists (eg, bosentan).
    - **Renal crisis:** ACE inhibitors (eg, captopril).
    - **Interstitial lung disease (ILD):** Cyclophosphamide or mycophenolate mofetil.
    - **GI tract:** *PPIs* for GERD, *metoclopramide* for GI dysmotility and *antibiotics* for small intestine bacterial overgrowth.
  - **Second line:** Systemic therapy with steroids, methotrexate or D-penicillamine for severe disease.

- **USMLE Pearls: Raynaud Phenomenon:** Divided into *primary* and *secondary Raynaud phenomenon*. **Primary Raynaud** (Raynaud disease) occurs idiopathically without an associated underlying medical condition. **Secondary Raynaud,** commonly referred to as Raynaud phenomenon, is associated with an underlying systemic disease such as *scleroderma* or *SLE*. To distinguish between the two, perform a **nailfold capillaroscopy.** This test is done by placing a drop of oil on the fingernail and observing it closely with a dermatoscope. An **abnormal nail arterial pattern** is a **positive test** and means that the patient has secondary Raynaud.

3. DERMATOMYOSITIS

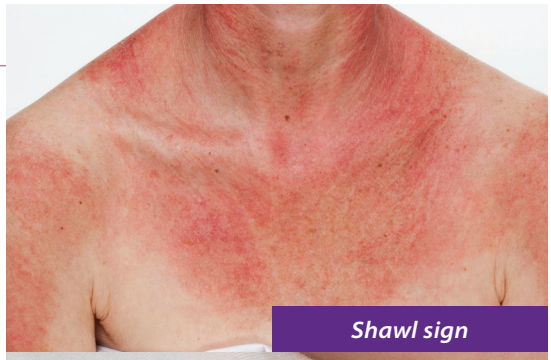
- **General:** Complex, multisystemic autoimmune **inflammatory myopathy** of unknown etiology characterized by prominent **cutaneous involvement.** It is thought that autoantibodies and other unknown factors activate the complement cascade in muscle capillaries and arterioles leading to muscle microinfarction. **Polymyositis** is another inflammatory myopathy with similar clinical presentation but *without* cutaneous involvement. The main organs affected in dermatomyositis are:
  - **GI tract:** Dysphagia and GERD.
  - **Heart:** Dilated cardiomyopathy, arrhythmias and heart block.
  - **Lung:** Interstitial lung disease (ILD).
  - **Constitutional symptoms:** Fatigue, weakness and weight loss.
  - **Musculoskeletal:** Symmetric proximal muscle involvement leading to inability to climb stairs, brush hair, rise from sitting position or reach objects above shoulder level.

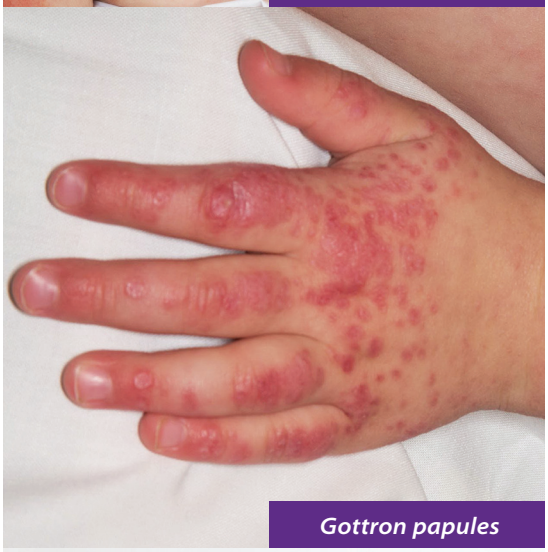
- **Clinical:** Cutaneous manifestations vary. They may be the initial and only sign of dermatomyositis.
  - **Heliotrope rash:** Symmetric and edematous purplish-red periorbital rash.
  - **Shawl sign:** Erythematous and pruritic rash with telangiectasias predominantly affecting the upper chest, upper back, shoulders and extensor surface of arms in a **"cape-like"** distribution.
  - **Gottron papules:** Red-to-purple, flat-topped papules on the interphalangeal joints (knuckles). **Gottron sign** is a violaceous discoloration on the knees, elbows or feet.
  - **Mechanic's hands:** Roughened, thickened and cracked palmar and lateral aspects of hands.
  - **Ragged nail cuticles.**

- **Diagnosis**
  - **Best initial test:** Clinical + labs (creatinine kinase, aldolase, ESR and CRP) + autoantibody assays to detect *anti-Jo-1 (anti-histidyl t-RNA synthetase)* and *anti-Mi-2* (very specific). Pulmonary function tests (PFTs) to identify underlying lung disease. Electromyography (EMG) or MRI are useful to investigate specific muscle damage and guide biopsy site.
  - **Most accurate test:** Muscle biopsy showing a perifascicular and perivascular lymphocytic infiltrate and muscle fiber degeneration.

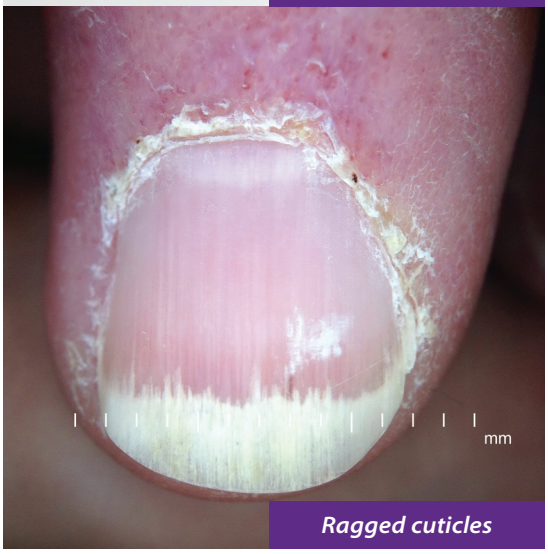
- **Treatment**
  - **First line:** Systemic steroids.
  - **Second line:** Methotrexate, mycophenolate mofetil or IVIG.

- **USMLE Pearls:** Approximately **20 to 40**% of patients diagnosed with dermatomyositis have an underlying **malignancy** (eg, lung, ovarian, breast). Treating the cancer may result in symptomatic resolution of dermatomyositis. **Screen for malignancies** at the time of diagnosis and yearly during the first 3 years with:
  - **Urinalysis** and **FOBT or colonoscopy**
  - **Serum PSA** and **CA-125**
  - **Mammogram** and **pelvic ultrasound**
  - **CT scan of chest, abdomen and pelvis**


Shawl sign


Gottron papules


Mechanic's hands



Ragged cuticles

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Chapter 3

BENIGN SKIN DISORDERS

1. KELOID

- **General:** Benign dense **collagenous overgrowth** that usually develops at the site of a healing skin injury. The uncontrolled collagen deposition results in vascular fibrous tissue **extending beyond the borders** of the original cutaneous injury (as opposed to hypertrophic scar; see below). High levels of *transforming growth factor beta* (TGF-β) are thought to contribute to the formation process. Keloids are prevalent in **African Americans.**

- **Clinical:** Characterized by a flesh-colored or hyperpigmented, **smooth, firm and rubbery** nodule or plaque with well-defined borders. Keloids commonly develop on the **chest and ears** but can appear almost anywhere. The size of keloids varies greatly; they can grow rapidly in days or develop gradually over months. The shape generally depends on the **initial skin injury pattern,** but commonly they are circular to oblong. Keloids are usually asymptomatic but may become irritated and pruritic.

- **Diagnosis**
  - **Best initial test:** Clinical.
  - **Most accurate test:** Skin biopsy showing granulation tissue and dense dermal collagen arranged in a **whorled or disorganized** pattern.

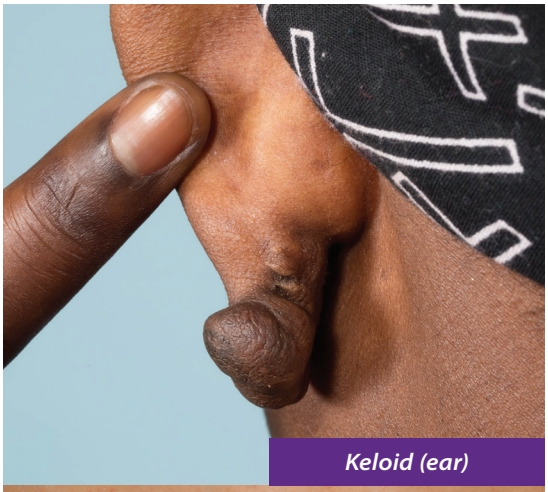
- **Treatment**
  - **First line:** Intralesional steroids + avoid trauma (eg, earrings, cuts, etc).
  - **Second line:** Surgical excision (high rate of recurrence), radiotherapy, compression devices, cryotherapy, laser or occlusive silicone dressings.

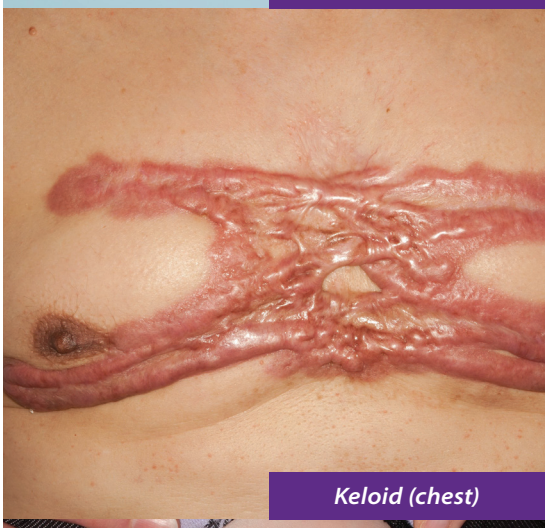
- **USMLE Pearls: Hypertrophic Scar:** This is also a benign dense **collagenous deposition** that occurs after healing of a cutaneous injury. It may be confused with a keloid. However, hypertrophic scars:
  - **Do not extend beyond** the margins of the original injury.
  - May **spontaneously regress** after months.
  - Have a more **organized (parallel) pattern** of dermal collagen deposition.

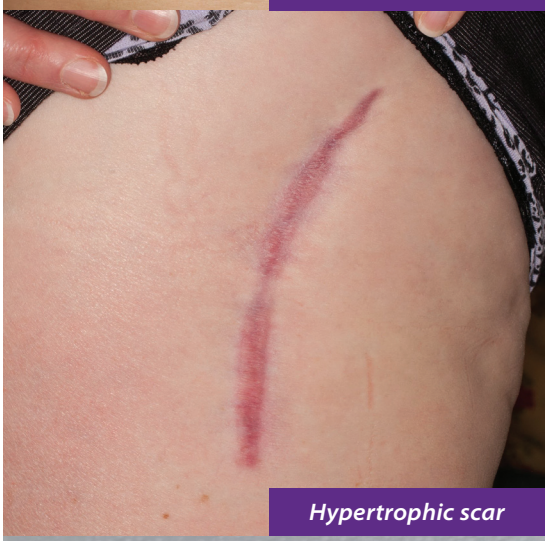
2. DERMATOFIBROMA

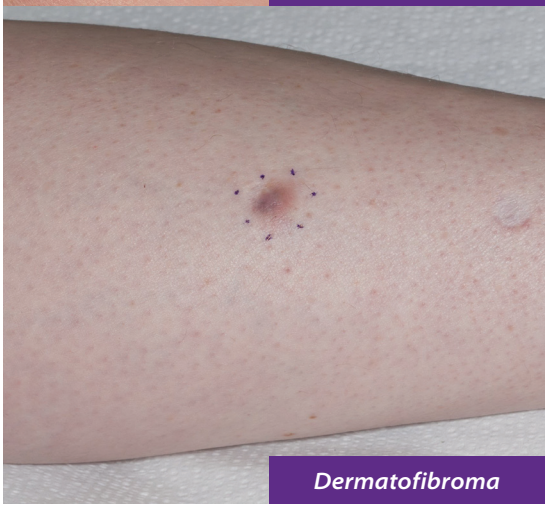
- **General:** Also known as **fibrous histiocytoma,** a common, benign dermal papule that occurs idiopathically or **secondary to trauma** such as a shaving or splinter injury, insect bite or ruptured cyst.

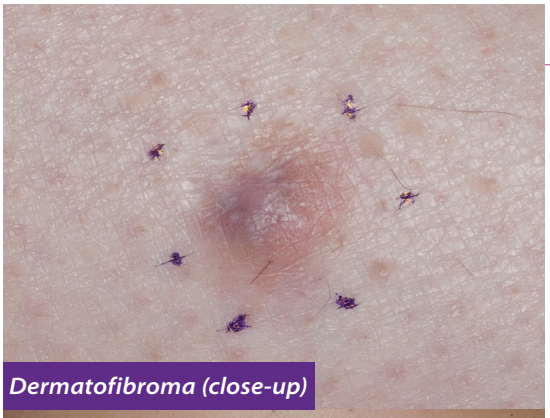
- **Clinical:** Characterized by a single (or multiple), well-defined, firm and nontender papule or nodule. Lesions are usually smaller than 1 cm in diameter and vary in color from **tan to brown.** The most common location is **lower extremities** but can occur anywhere. Dermatofibromas are usually asymptomatic, however, they may become irritated and pruritic. The classic feature is the "**dimple sign.**" The nodule *dimples in the center* when pinched.


Keloid (ear)


Keloid (chest)


Hypertrophic scar

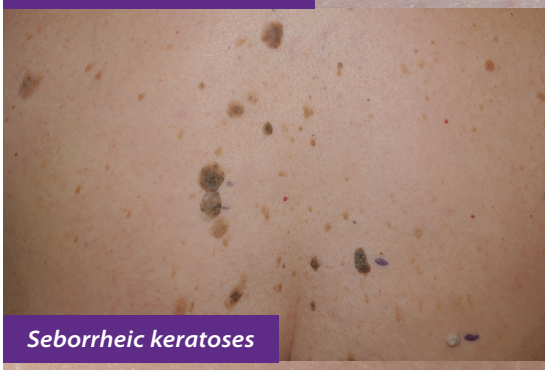

Dermatofibroma


Dermatofibroma (close-up)

- **Diagnosis**
  - **Best initial test:** Clinical.
  - **Most accurate test:** Skin biopsy showing fibrohistiocytic cell proliferation in the dermis with entrapment of collagen at the periphery.

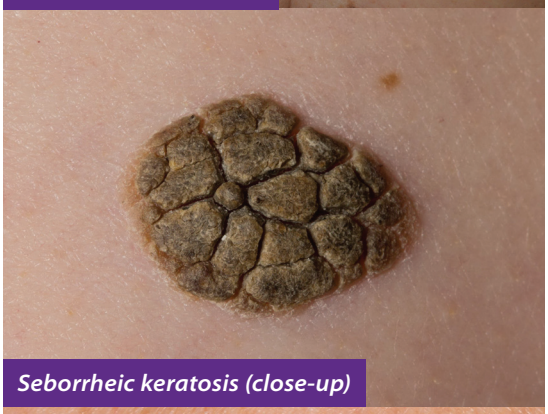
- **Treatment**
  - **First line:** Reassurance.
  - **Second line:** Surgical excision for symptomatic lesions or cosmetics.

3. SEBORRHEIC KERATOSIS


Seborrheic keratoses

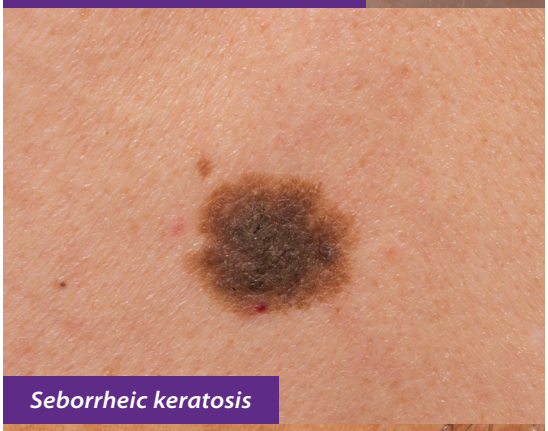
- **General:** Also known as **senile or brown warts,** a benign pigmented tumor **derived from epidermal cells.** Seborrheic keratoses are the most common tumor in people **older than 50 years.** Lesions gradually increase in number with aging.

- **Clinical:** Characterized by an asymptomatic, **waxy, "stuck-on"** appearing papule with a **rough** and **irregular "greasy"** surface. Seborrheic keratoses color varies from **tan to brown** or even **black** and some have irregular borders. With the exception of palms and soles, seborrheic keratosis can occur anywhere, though the most common locations are the **extremities** and **trunk.** Patients may have from one to several dozen lesions and may rarely complain of pruritus.
  - **Leser-Trélat sign:** *Rapid* and *sudden* increase in number of pruritic seborrheic keratoses associated with underlying **malignancy** in the **stomach,** colon, lung or breast.


Seborrheic keratosis (close-up)

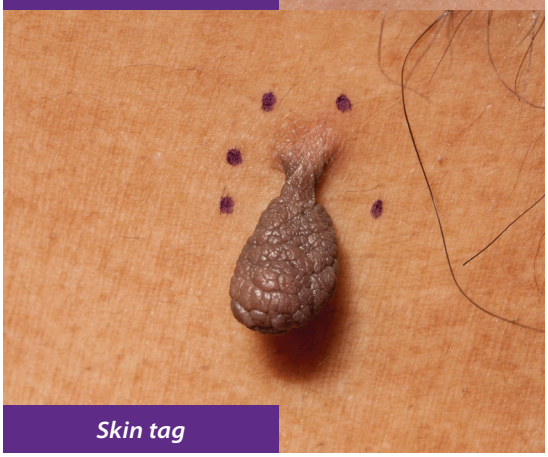
- **Diagnosis**
  - **Best initial test:** Clinical.
  - **Most accurate test:** Skin biopsy showing a papillomatous epidermis with thick basal layer and formation of keratin-filled **"horn cysts."**

- **Treatment**
  - **First line:** Reassurance.
  - **Second line:** Cryotherapy, curettage, laser or surgical excision for symptomatic lesions or cosmetics.


Seborrheic keratosis

- **USMLE Pearls:** Unevenly pigmented, **black seborrheic keratoses** with **irregular borders** can be clinically confused with **malignant melanoma.** If in doubt, perform an excisional biopsy with 1 to 3 mm margins to confirm the diagnosis.

4. ACROCHORDON


Skin tag

- **General:** Also known as **skin tag** or **fibroepithelial polyp.** Benign skin growth with no malignant potential; common in elderly patients. Acrochordons are associated with **insulin resistance:**
  - **Diabetes mellitus** (DM) and **metabolic syndrome**
  - **Polycystic ovarian syndrome** (PCOS)
  - **Pregnancy** (due to human placental lactogen)

- **Clinical:** Characterized by a **pedunculated,** tan-to-brown **soft tag** of skin attached to the body by a stalk. Mainly located in **areas of friction** such as the axillae, groin, neck and eyelids. Skin tags may be single or

multiple and range in size from 1 to 5 mm in diameter. They are usually asymptomatic but can become irritated and bleed with manipulation.

- **Diagnosis**
  - **Best initial test:** Clinical.
  - **Most accurate test:** Skin biopsy showing fibrovascular cores covered by normal squamous epithelium.

- **Treatment**
  - **First line:** Reassurance.
  - **Second line:** Snip excision or cryotherapy for symptomatic lesions or cosmetics.

5. LIPOMA

- **General:** Most common benign soft tissue tumor. Lipomas are encapsulated, slow-growing subcutaneous tumors **composed of mature white (fat) adipocytes** with normal overlying epithelium. Often referred to as a **"golf ball"** inside the skin.

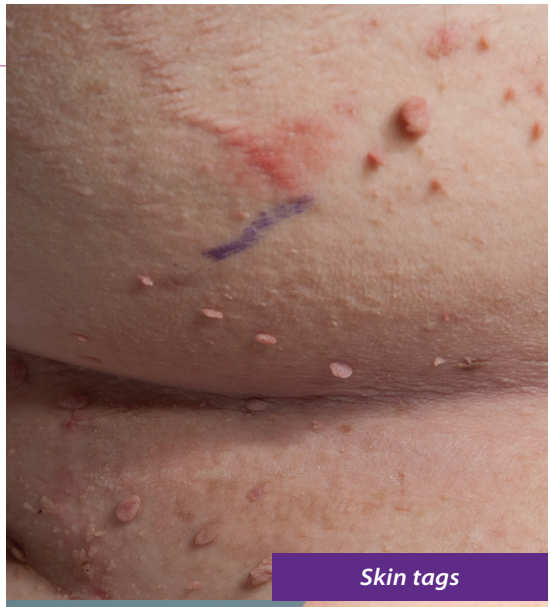
- **Clinical:** Characterized by a soft-to-rubbery, **freely mobile,** deep nodule or mass most commonly located in the trunk, back, neck or proximal extremities. The nodule slips out of the examiner's fingers when pinching it **("slippage sign").** Mostly asymptomatic but can rarely grow big and compress internal organs such as:
  - **Trachea or bronchi** (respiratory symptoms)
  - **Pharynx, esophagus or colon** (signs of GI obstruction)
  - **Muscles or nerves** (pain and neuropathies)

- **Diagnosis**
  - **Best initial test:** Clinical. Consider imaging studies such as U/S, CT scan or MRI for deep and rapidly enlarging lesions to exclude malignancy (eg, liposarcoma).
  - **Most accurate test:** Skin biopsy showing aggregated mature white adipose tissue without atypia in subcutis.

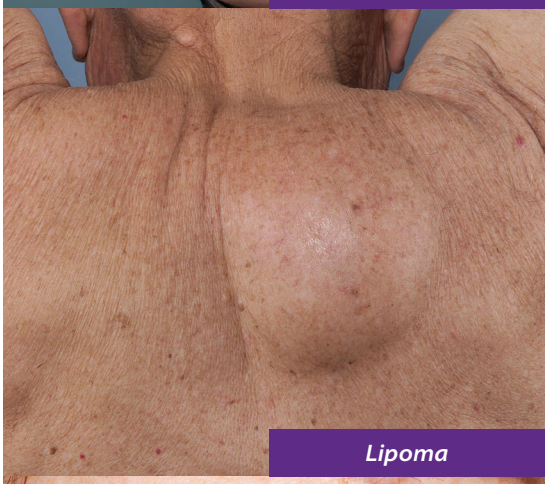
- **Treatment**
  - **First line:** Observation.
  - **Second line:** Surgical excision for cosmetics, symptomatic lesions or lipomas > 5 cm in diameter.

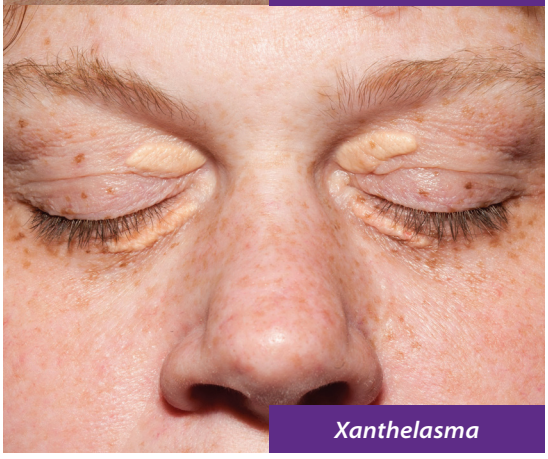
6. XANTHOMA

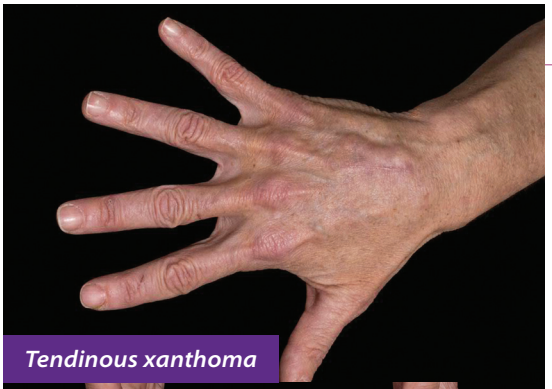
- **General:** Common skin condition characterized by accumulations of **cholesterol or triglycerides** inside skin macrophages (foam cells). Usually caused by underlying lipid metabolism disorders. Xanthomas are associated with:
  - **Primary biliary cirrhosis** and **sclerosing cholangitis**
  - **Hypothyroidism** (deficient clearing of lipids)
  - **Diabetes mellitus** (increased synthesis of lipids)
  - **Hereditary hypertriglyceridemia**
  - **Nephrotic syndrome** (increased synthesis and decreased clearance of lipids)


Skin tags

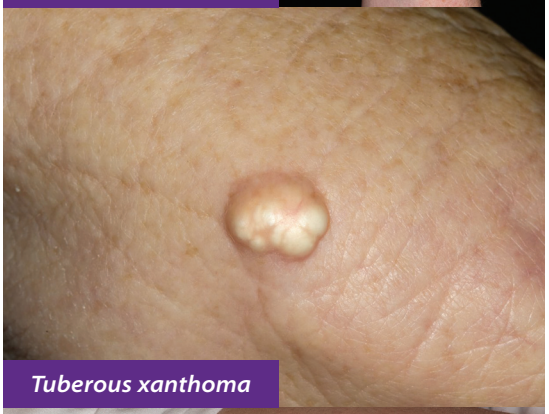

Lipoma

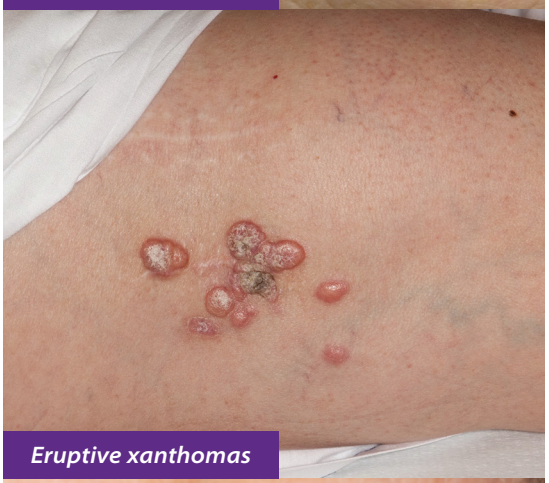

Lipoma

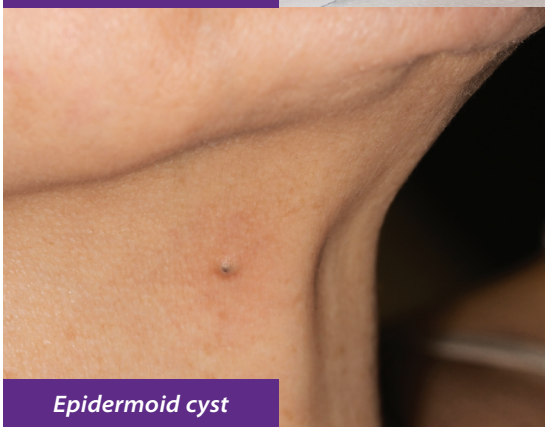

Xanthelasma


Tendinous xanthoma


Tendinous xanthoma


Tuberous xanthoma


Eruptive xanthomas


Epidermoid cyst

- **Clinical:** There are several types of xanthomas. They vary clinically depending on the location and morphology.
  - **Xanthelasma:** Soft, tan-to-yellow, painless papule or plaque on the eyelids.
  - **Tendinous xanthoma:** Smooth, flesh-colored, enlarging subcutaneous nodules in tendons or ligaments (eg, hands, feet, Achilles tendon).
  - **Tuberous xanthoma:** Firm, reddish-to-yellow nodules on extensor surfaces of extremities (eg, knees, elbows) and buttocks.
  - **Eruptive xanthomas:** Pruritic and tender reddish-to-yellow papules ranging in size from 1 to 8 mm in diameter. Develop suddenly and can appear almost anywhere. Associated with very high triglyceride levels **(> 1000 mg/dL).**

- **Diagnosis**
  - **Best initial test:** Clinical + order total cholesterol and triglycerides levels to assess cardiac risk and monitor disease.
  - **Most accurate test:** Skin biopsy showing lipid-filled, foamy macrophages in dermis.

- **Treatment**
  - **First line:** Optimize diabetic control + treat hyperlipidemia with diet, statins and/or fenofibrate.
  - **Second line:** Laser, electrocautery or surgical excision for cosmetics or symptomatic lesions.

- **USMLE Pearls:** Look for a patient with **epigastric pain** and high levels of **amylase and lipase** and one of the manifestations described above (eg, eruptive xanthomas). The patient may have pancreatitis secondary to **severe hypertriglyceridemia** (> 1000 mg/dL). Remember the main causes of **pancreatitis:**
  - **Iatrogenic** (eg, ERCP, cholangiography)
  - **Alcoholism**
  - **Gallstones** in common bile duct (block the pancreatic duct)
  - **Hypercalcemia** (activate the pancreatic enzymes)
  - **Hypertriglyceridemia** (> 1000 mg/dL)
  - **Drugs** (eg, NSAIDS, furosemide, thiazides, didanosine)
  - **Duodenal ulcer** (gastric acid erodes the pancreas and activate pancreatic enzymes)

7. EPIDERMAL INCLUSION CYST (EPIDERMOID CYST)

- **General:** Benign keratin-filled cyst derived from **epidermal cells of the hair follicle.** Epidermoid cysts are the *most common* cutaneous cyst; they may develop secondary to penetrating skin trauma such as a cut, needle or splinter injury.

- **Clinical:** Characterized by a flesh-colored-to-white, smooth, firm and movable **dome-shaped papule.** The classic feature is that the cyst has a **central punctum,** although not always present. Usually located in the face, neck, base of ears or trunk, but can occur anywhere. Some cysts regress to later recur in the same site. Spontaneous inflammation and rupture may occur, releasing a **malodorous, yellowish** and **cheesy keratin.**

- **Diagnosis**
  - **Best initial test:** Clinical.
  - **Most accurate test:** Skin biopsy showing a cystic structure with *loose and thin* laminated keratin inside. The cyst is lined by flattened epidermal cells *with* a granular layer.

- **Treatment**
  - **First line:** Observation.
  - **Second line:** Complete surgical excision for symptomatic lesions or cosmetics (cyst may recur). Consider intralesional steroids + antibiotics for acutely inflamed cysts.

- **USMLE Pearls: Pilar Cyst:** Also known as **trichilemmal cyst,** another common cutaneous cyst that may be clinically confused with epidermoid cyst. However, pilar cysts:
  - **Lack the central punctum.**
  - Are most commonly located in the **scalp (90%) or scrotum.**
  - Contain a **dense and thick keratin,** often with calcifications.
  - The cellular lining of the cyst **lacks a granular layer.**

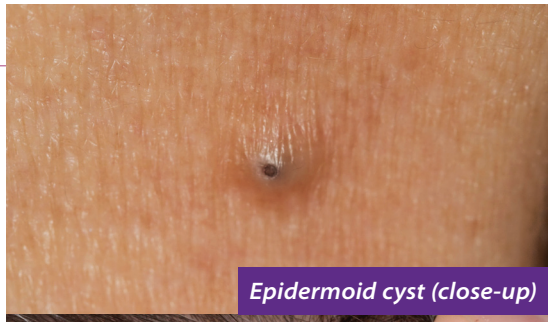
8. DERMOID CYST

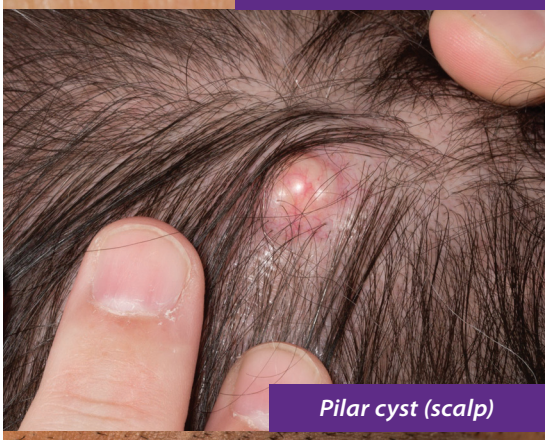
- **General:** Benign **hamartomatous tumor** caused by sequestration of ectodermal tissue along embryonal lines of closure. Dermoid cysts are tumors composed of poorly-to-fully differentiated **ectodermal tissue** such as keratinocytes, fat, hair follicles and sebaceous glands. They usually appear in the skin at **birth** or during early **childhood.**

- **Clinical:** Characterized by a single, nontender, **dough-like subcutaneous nodule** that typically varies in size from 1 to 6 cm in diameter. Most commonly located on the **head and neck area** (eg, forehead, **lateral eyebrow,** scalp, nasal root, jaw) but can occur almost anywhere. Dermoid cysts may have an associated sinus tract connected to underlying tissue **(brain, spine or nerves)** and need to be handled carefully. If left untreated, dermoid cysts may continue to grow and lead to **soft tissue and skeletal deformities, local infection, meningitis** or **brain abscesses.**

- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + excisional biopsy showing a subcutaneous tumor composed of epidermal cells, hair follicles, fat globules and glands. If the lesion has a **sinus tract** or is **midline,** order MRI or CT scan to look for tumor extension before performing excision.

- **Treatment**
  - **First line:** Complete surgical excision.


Epidermoid cyst (close-up)


Pilar cyst (scalp)


Pilar cyst (scrotum)


Dermoid cyst


Dermoid cyst

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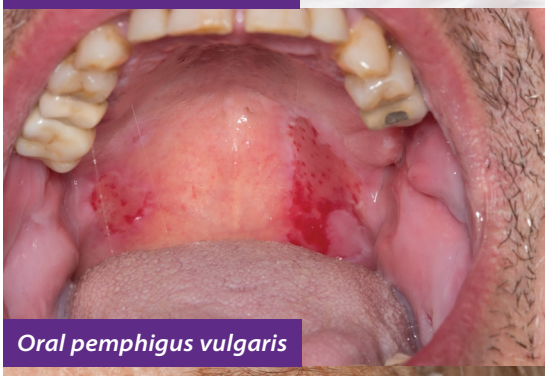
Chapter 4

BLISTERING SKIN DISORDERS

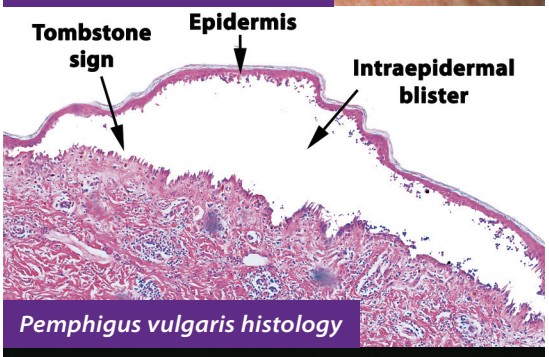
Table 4.1. Blistering Disorders Summary

Blistering Disease	Blistering Characteristics	Antibodies or Defect	Histological Features	Disease Associations and Characteristics
Pemphigus Vulgaris (PV)	• **Flaccid and broken** • **Diffuse distribution** • **Painful** • **Not pruritic**	**Anti-desmosomal IgG** (DSG1 and DSG3)	**H&E:** *Intraepidermal* blisters with a mixed inflammatory infiltrate **Tombstone sign** **DIF:** Intraepidermal IgG in a "chicken wire" or "net-like" pattern	• Middle-aged patients • Positive Nikolsky sign • Severe mucosal involvement • High mortality
Bullous Pemphigoid (BP)	• **Firm and tense** • **Diffuse distribution** • **Painless** • **Pruritic**	**Anti-hemidesmosomal** IgG (BP180 and BP230)	**H&E:** *Subepidermal* blisters with an eosinophilic infiltrate **DIF:** Linear C3 > IgG deposits at the DEJ	• Elderly patients • Urticarial plaques • Low mortality • Neurodegenerative disorders
Dermatitis Herpetiformis (DH)	• **Firm and tense** • **Grouped** • **Extensor surfaces** • **Extremely pruritic**	**IgA autoantibodies** Anti-reticulin Anti-gliadin Anti-endomysial Anti-transglutaminase	**H&E:** *Subepidermal* blisters and neutrophilic clusters forming microabscesses in papillary dermis **DIF:** Granular IgA deposits in dermal papillae	• Gluten intolerance (celiac disease) • Fat-soluble vitamin deficiencies (ADEK) • Chronic diarrhea
Porphyria Cutanea Tarda (PCT)	• **Firm and tense** • **Dorsal hands** • **Painless** • **Sun-induced**	**Deficiency of uroporphyrinogen decarboxylase** (UROD)	**H&E:** *Subepidermal* blisters with no inflammatory infiltrate (pauci-immune) **DIF:** C3 > IgG deposits at DEJ and around dermal capillaries	• Hyperpigmented skin • Hypertrichosis • Hepatitis C, hemochromatosis • Alcohol, estrogens and drugs • Red-pink fluorescent urine
Epidermolysis Bullosa Simplex (EBS)	• **Flaccid and broken** • **Hands, feet and extensor surfaces** • **Trauma-induced**	**Mutation in keratin 5 or 14**	**H&E:** *Intraepidermal* blisters with degenerated basal cells **DIF:** No significant findings (no antibodies)	• May be present at birth • Young patients (infants)
Epidermolysis Bullosa Acquisita (EBA)	• **Firm and tense** • **Hands, feet and extensor surfaces** • **Trauma-induced**	**Anti-collagen VII IgG**	**H&E:** *Subepidermal* blisters with a mixed inflammatory infiltrate **DIF:** Linear IgG > C3 deposits at the DEJ	• Scarring and milia • Elderly patients

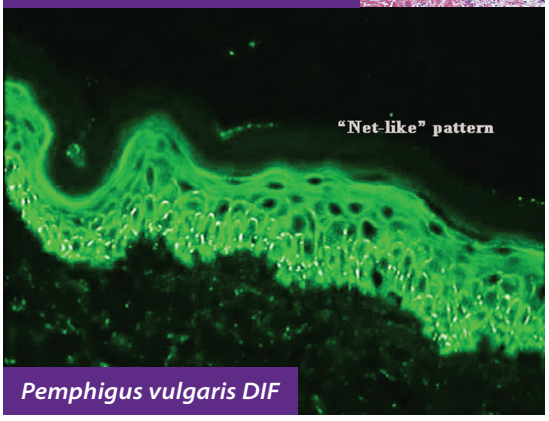

Pemphigus vulgaris (PV)


Oral pemphigus vulgaris


Ocular pemphigus vulgaris



Pemphigus vulgaris histology



Pemphigus vulgaris DIF

Intraepidermal Blistering Disorders

1. PEMPHIGUS VULGARIS (PV)

- **General:** Rare, life-threatening mucocutaneous blistering disorder characterized by circulating **IgG autoantibodies** against keratinocytes **desmosomal proteins,** *desmoglein 1 and 3* (type II hypersensitivity). It can be *autoimmune* or *drug-induced,* with the most common culprit drugs being **penicillamine** and **ACE inhibitors.** PV is more severe than bullous pemphigoid (BP) and usually affects **middle-aged patients** between 30 and 50 years of age. Mortality associated with **secondary infections** and **pulmonary embolism.**

- **Clinical:** Characterized by **flaccid, clear vesicles and bullae** and **erosions** on the skin and mucous membranes (eg, oral cavity). On physical exam, the majority of the vesicles will be **broken** and present as **erythematous, painful, crusted erosions.** Classically, the outer epidermis separates from the basal layer with minimal pressure **(positive Nikolsky sign).** Pharynx and GI tract involvement may lead to severe **respiratory and feeding problems,** respectively. Lesions usually heal without scarring but may leave a hyperpigmented area. PV lesions are usually **painful** but **not pruritic,** as opposed to BP.

- **Diagnosis**
  - **Best initial test:** Clinical + serological studies (ELISA) to detect circulating IgG autoantibodies against epidermal desmosomes *(anti-DSG1 and anti-DSG3).*
  - **Most accurate test:** Skin biopsy showing suprabasal acantholysis with intraepidermal blisters. A single layer of basal cells lines the floor of the blister producing a *"tombstone"* pattern. **Direct immunofluorescence (DIF):** IgG and C3 between epidermal cells fluoresce to produce a *"chicken wire"* or *"net-like"* pattern.

- **Treatment**
  - **First line:** Replace fluid and electrolytes + systemic steroids (eg, prednisone).
  - **Second line:** Azathioprine, cyclophosphamide, mycophenolate mofetil, rituximab and/or IVIG.

- **USMLE Pearls: Pemphigus Foliaceus (PF):** Milder form of pemphigus vulgaris (PV) with autoantibodies to **desmoglein 1 (DSG1)** in upper epidermis (granular layer). PF rarely has mucosal involvement **(no oral ulcers)** and often **regresses spontaneously.** Histologic findings are similar to PV but more superficial in the epidermis. Scales may resemble corn-flake cereal.

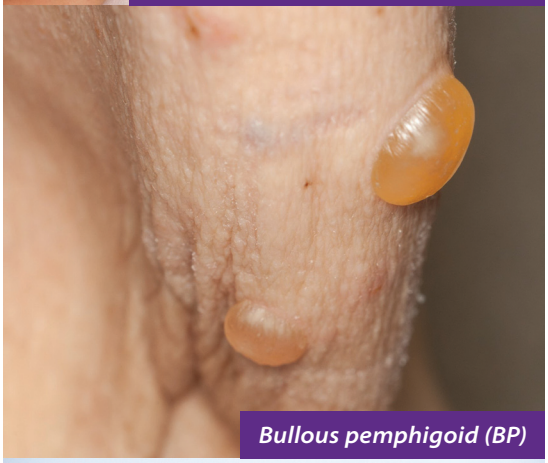
- **USMLE Pearls: Paraneoplastic Pemphigus (PNP):** Rare paraneoplastic blistering disorder that may develop in patients with underlying neoplasm. Most commonly associated with **non-Hodgkin lymphoma,** but may be seen with **chronic lymphocytic leukemia** (CLL), **Castleman disease** and **thymoma.** Presents with variable skin lesions that may resemble *pemphigus vulgaris, lichen planus, erythema multiforme* or *bullous pemphigoid*. Hemorrhagic stomatitis and bronchiolitis obliterans are commonly associated.

- **USMLE Pearls: Epidermolysis Bullosa Simplex (EBS):** Genetic mechanobullous disease caused by mutations in **keratin 5 or keratin 14** (intermediate filaments). These mutations result in disruption of epidermal keratinocyte attachments and **trauma-induced blisters.** EBS may present as early as **birth** with blisters and erosions predominantly on areas prone to **frictional trauma (eg, hands and feet).** *Treat* by minimizing trauma and providing skin care.

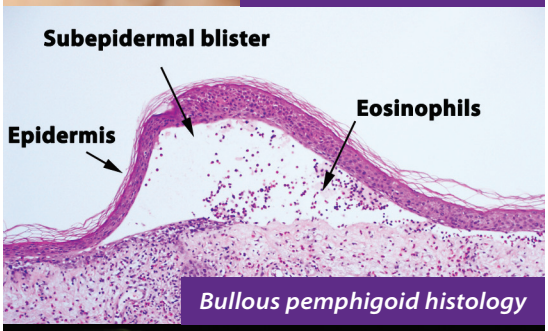

Epidermolysis bullosa simplex (EBS)

Subepidermal Blistering Disorders

2. BULLOUS PEMPHIGOID (BP)


Bullous pemphigoid (BP)

- **General:** Fairly rare, chronic autoimmune blistering disorder characterized by circulating **IgG autoantibodies** against basement membrane **hemidesmosomal proteins,** *BP180 and BP230.* Activation of the complement cascade by IgG autoantibodies results in basement membrane **C3 deposition** as well. Bullous pemphigoid is **milder** than pemphigus vulgaris and can spontaneously subside after months without treatment. Factors that may trigger BP are:
  - **Furosemide**
  - **UV-light** and **radiation**
  - **Neurodegenerative disease** (eg, cerebrovascular disease, dementia, Parkinson disease).



Bullous pemphigoid histology

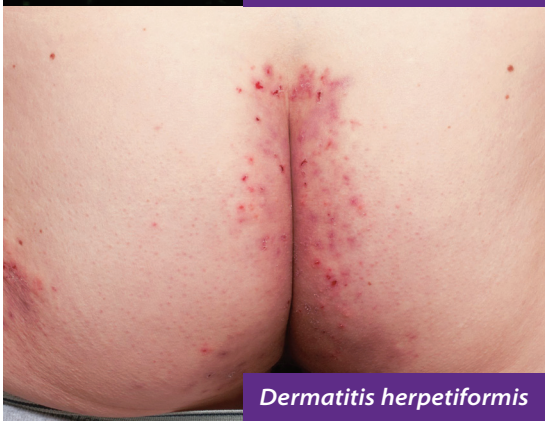
- **Clinical:** Usually occurs in **elderly** patients between 60 and 80 years of age. Characterized by **intact, tense, clear or hemorrhagic** vesicles and bullae on the skin, often accompanied by **urticaria-like plaques** and **pruritus.** BP generally **lack oral lesions** and has **negative Nikolsky sign,** as opposed to pemphigus vulgaris.


Bullous pemphigoid DIF

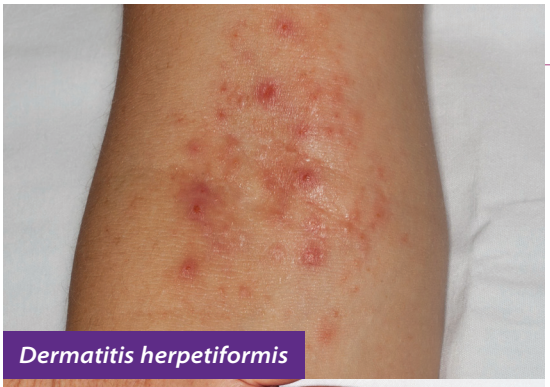
- **Diagnosis**
  - **Best initial test:** Clinical + serological studies to detect circulating IgG autoantibodies against hemidesmosomes *(BP180 and BP230).*
  - **Most accurate test:** Skin biopsy showing subepidermal blisters, often with an eosinophilic infiltrate. **DIF:** Linear pattern of C3 and IgG deposition at the DEJ.

- **Treatment**
  - **First line:** Potent topical steroids or oral steroids.
  - **Second line:** Azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide or nicotinamide combined with tetracycline, doxycycline, minocycline or erythromycin.

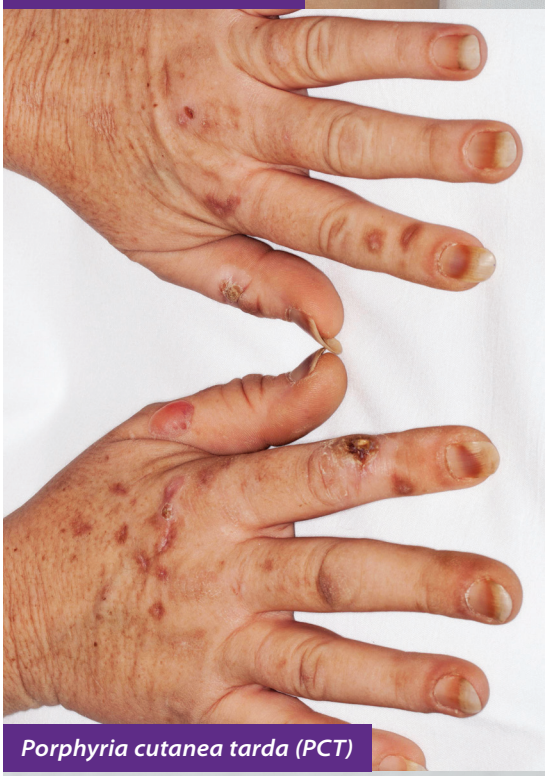
3. DERMATITIS HERPETIFORMIS (DH)


Dermatitis herpetiformis

- **General:** Chronic autoimmune blistering disorder characterized by circulating **IgA autoantibodies** against *epidermal transglutaminase* (e-TG) at the tips of **dermal papillae** (between DEJ and dermis). Associated with **celiac disease** (90%) and **HLA-DQ2/DQ8.**



Dermatitis herpetiformis



Porphyria cutanea tarda (PCT)

PCT urine

PCT urine Wood's lamp

- **Clinical:** Characterized by **extremely pruritic, clustered** or **"herpetiform"** erythematous papules and vesicles symmetrically distributed on **extensor surfaces** (eg, elbows, knees, back and buttocks). Broken vesicles and **excoriations** are commonly seen secondary to intense scratching. DH is generally a manifestation of gluten intolerance; patients will also complain of **loose fatty stools after eating gluten-containing foods.** Chronic malabsorption may lead to fat-soluble vitamin deficiencies such as:
  - **Vitamin A deficiency:** Night blindness and dry skin.
  - **Vitamin D deficiency:** Osteomalacia and hypocalcemic tetany.
  - **Vitamin E deficiency:** Neurological dysfunction and hemolysis.
  - **Vitamin K deficiency:** Hemorrhagic lesions and prolonged PT and PTT.

- **Diagnosis**
  - **Best initial test:** Clinical + serological studies to detect IgA autoantibodies *(anti-endomysial, anti-gliadin, anti-reticulin and anti-tissue transglutaminase antibodies).*
  - **Most accurate test:** Skin biopsy showing subepidermal vesicles with dense clusters of neutrophils forming microabscesses in papillary dermis. **DIF:** *Granular pattern* of IgA deposits in dermal papillae.

- **Treatment**
  - **First line:** Dapsone + gluten-free diet (no wheat, rye and barley).
  - **Second line:** Sulfapyridine or topical steroids.

- **USMLE Pearls: Linear IgA Bullous Dermatosis:** Also known as **chronic bullous disease of childhood** when it occurs in children. Another subepidermal blistering disease caused by IgA autoantibodies deposition. Important triggering agent is **vancomycin.** Characterized by small, tense blisters **grouped in an annular fashion** creating a **"string of beads"** pattern. **DIF** studies will show a *linear pattern* of IgA deposition at the DEJ.

4. PORPHYRIA CUTANEA TARDA (PCT)

- **General:** *Autosomal dominant* genetic or acquired blistering disorder caused by deficiency of **uroporphyrinogen decarboxylase (UROD) enzyme** in the heme synthesis pathway. Porphyrin metabolites deposit in the skin and cause the clinical manifestations. PCT is associated with **hepatitis C virus** and **hemochromatosis** and is exacerbated by:
  - **Sunlight**
  - **Alcohol and estrogens** (eg, OCPs)
  - **Drugs** that induce the *cytochrome P450* metabolic pathway (eg, phenobarbital, phenytoin, carbamazepine, rifampin, St. John's wort).

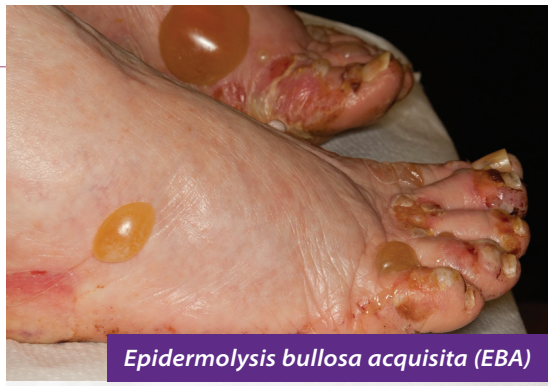
- **Clinical:** Characterized by **hypertrichosis** and **photosensitive, fragile skin** that develop **painless** blisters when exposed to sunlight and after trauma. Most commonly affect the **dorsal hands** and **arms.** Lesions may heal with **hyperpigmentation** and superficial atrophic scarring.

- **Diagnosis**
  - **Best initial test:** Clinical + 24-hour urine studies showing increased urinary uroporphyrins and coproporphyrins. Urine is red wine color on voiding and *reddish-pink fluorescent* when viewed under Wood's lamp.

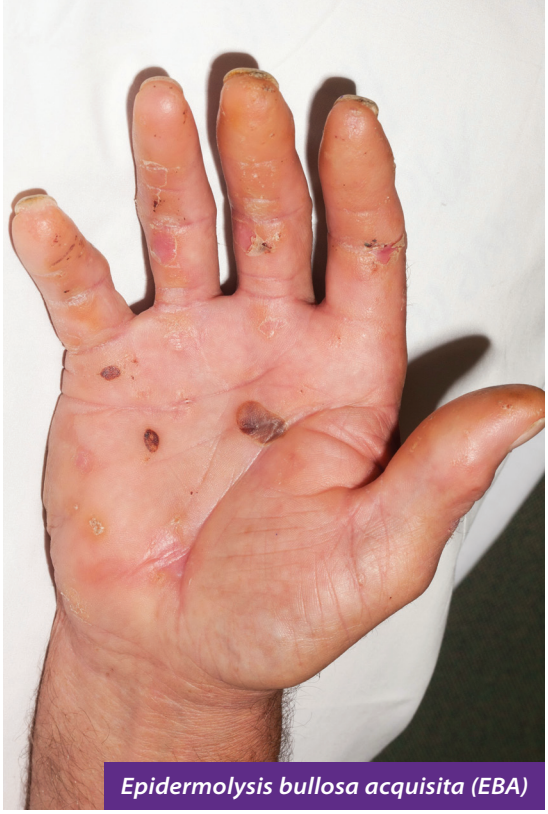
- **Most accurate test:** Skin biopsy showing subepidermal blisters with absent or minimal dermal inflammation (pauci-immune). **DIF:** IgG, C3 and fibrinogen deposition around dermal capillaries and at the DEJ.

- **Treatment**
  - **First line:** Photoprotection + discontinuation and avoidance of other exacerbating agents (discussed above). Consider phlebotomy or deferoxamine to decrease iron levels.
  - **Second line:** Hydroxychloroquine.

- **USMLE Pearls: Epidermolysis Bullosa Acquisita (EBA):** Rare, acquired autoimmune subepidermal blistering disorder characterized by **IgG autoantibodies** against **collagen type VII.** Blisters usually develop in areas prone to trauma **(hands, feet and extensor surfaces)** and may heal with severe scarring. *Epidermolysis bullosa simplex (EBS)* and *epidermolysis bullosa acquisita (EBA)* are mechanobullous disorders that can mimic any blistering disease (eg, PCT, BP, PV). Key features that *distinguish* EBA from EBS are:
  - **EBA** occurs in **older patients.**
  - Presents with **tense and firm blisters.**
  - Has circulating **IgG autoantibodies against collagen type VII** (EBS has no autoantibodies).
  - **DIF** will show **linear IgG deposition at the DEJ.**



Epidermolysis bullosa acquisita (EBA)



Epidermolysis bullosa acquisita (EBA)

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Chapter 5

CUTANEOUS MANIFESTATIONS OF INTERNAL DISEASES

1. ERYTHEMA NODOSUM (EN)

- **General:** Most common cause of adipose (fat) tissue inflammation **(panniculitis).** It is a granulomatous cell-mediated hypersensitivity reaction that occurs in the subcutaneous fat. EN is associated with:
  - **Streptococcal infection:** Most common cause of EN; most commonly occurs in children.
  - **Sarcoidosis (Löfgren syndrome):** Triad of EN, bilateral hilar lymphadenopathy and arthralgias.
  - **Inflammatory bowel disease** (ulcerative colitis and Crohn disease)
  - **Pregnancy** and **oral contraceptive (OCP)** use
  - ***M. tuberculosis* (TB),** coccidioidomycosis and histoplasmosis
  - Reactive arthritis, Behçet disease and ankylosing spondylitis

- **Clinical:** Characterized by **raised, erythematous, painful nodules** and plaques. Most commonly located in the **anterior and lateral shin.** Typically subsides spontaneously in 3 to 6 weeks and often leaves a **hyperpigmented area.** EN may be accompanied by arthralgias, fever, body aches, episcleritis, conjunctivitis and fatigue.

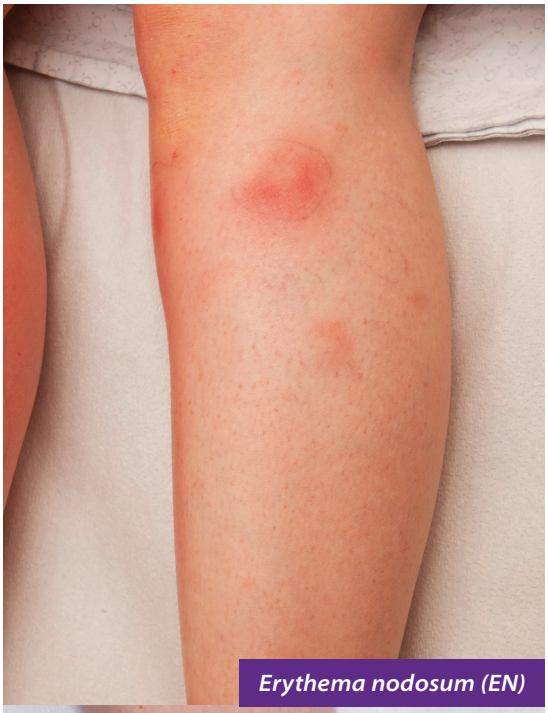
- **Diagnosis**
  - **Best initial test:** Clinical. Investigate underlying triggers based on H&P. Consider ASO titers or colonoscopy if suspect streptococcal infection or inflammatory bowel disease (IBD), respectively.
  - **Most accurate test:** Skin biopsy showing granulomatous inflammation of subcutaneous fat (septal panniculitis).

- **Treatment**
  - **First line:** Identify and treat underlying cause + NSAIDs (indomethacin or aspirin).
  - **Second line:** Potassium iodide. Consider oral steroids for severe disease.

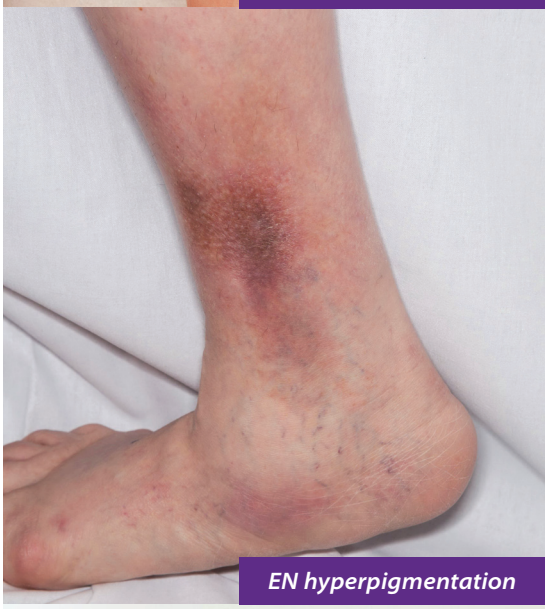
- **USMLE Pearls:** Be familiar with the association of erythema nodosum (EN) with **sarcoidosis** and **inflammatory bowel disease** (IBD). *Histologically,* erythema nodosum shows only panniculitis; it is **not useful** to confirm the diagnosis of sarcoidosis or IBD.

2. PYODERMA GANGRENOSUM (PG)

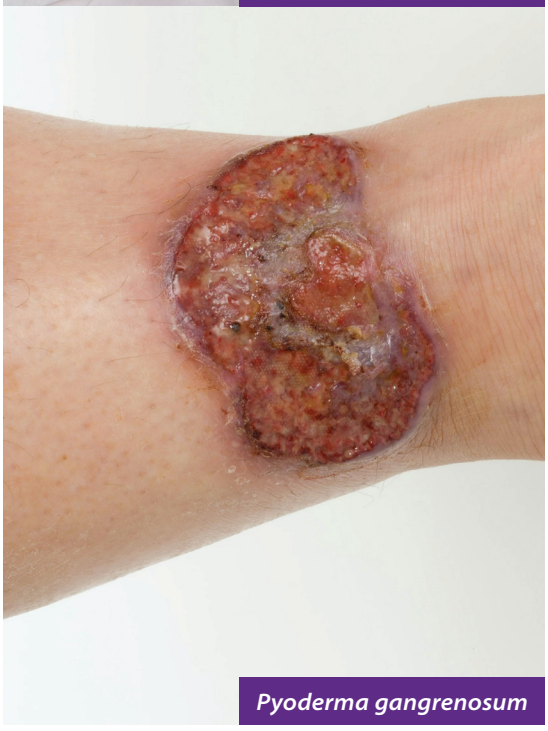
- **General:** Ulcerative dermatosis of unknown etiology characterized by dysregulation of the immune system with **abnormal neutrophil function.** Skin lesions may be initiated by trauma (pathergy). Associated with:
  - **Inflammatory bowel disease** (IBD)
  - **Myeloproliferative disorders:** Leukemias (eg, AML and CML), lymphomas, multiple myeloma and monoclonal gammopathies (primarily IgA).
  - **Vasculitis:** Granulomatosis with polyangiitis (Wegener)
  - **Rheumatoid arthritis (RA)** and **seronegative arthritis**



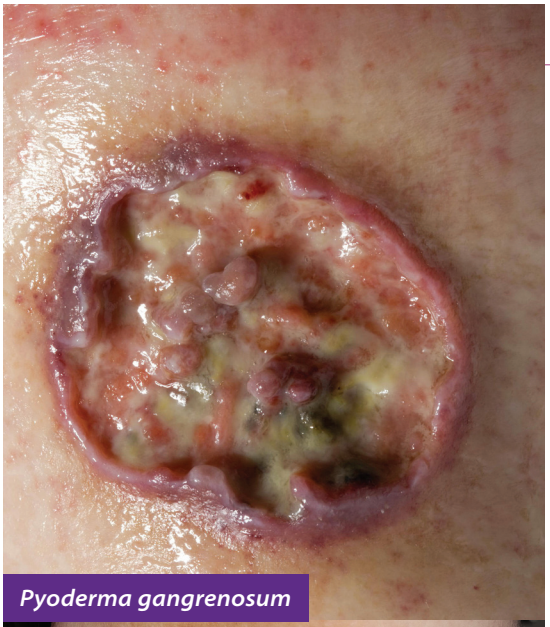
Erythema nodosum (EN)



EN hyperpigmentation



Pyoderma gangrenosum

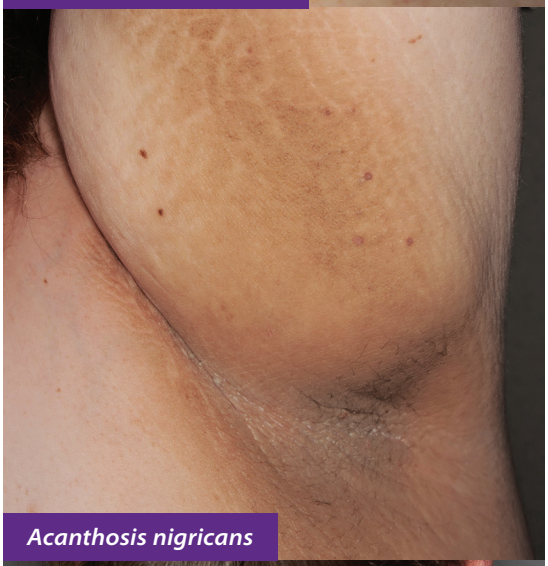


Pyoderma gangrenosum

- **Clinical:** Begins as a small red pustule/papule that evolves into a single (or multiple) **enlarging ulcer.** Classically, the ulcer has a **purulent necrotic base** with **thick violaceous, undermined borders** and **surrounding erythema.** Deep ulcers heal with scarring in a criss-cross (cribriform) pattern. Lesions are usually located in the lower extremities but can occur anywhere (eg, genitals). PG can mimic a brown recluse spider bite or a sexually transmitted infection (STI).

- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + skin biopsy showing prominent *neutrophilic infiltration* with epidermal necrosis. PG is a diagnosis of exclusion. Order wound stain and cultures to rule out infectious processes.

- **Treatment**
  - **First line:** Treat underlying disorder + wound care + topical steroids or calcineurin inhibitors.
  - **Second line:** Dapsone, minocycline or intralesional steroids. Consider systemic therapy with corticosteroids, anti-TNF-α inhibitors, cyclosporine, mycophenolate mofetil or IVIG for severe disease.



Acanthosis nigricans

3. ACANTHOSIS NIGRICANS (AN)

- **General:** Skin disorder characterized by **darkening** and **thickening** of the **skin.** Acanthosis nigricans may be caused by: Insulin resistance → hyperinsulinemia → high IGF-1 levels → induction of epidermal and dermal proliferation. AN is associated with:
  - **Diabetes mellitus, obesity** and **metabolic syndrome**
  - **Malignancy** (most commonly gastric)
  - **Pregnancy** (human placental lactogen)
  - **Acromegaly** and **Cushing syndrome**
  - **Polycystic ovarian syndrome** (PCOS)
  - **Insulin receptor deficiency**
  - **Trisomy 21** (Down syndrome)

Acanthosis nigricans

- **Clinical:** Characterized by **thickened, brown-to-black velvety** and **verrucous** skin. Commonly located on **intertriginous areas** such as axilla, groin, back of neck and under breasts. *Rapid* and *sudden* appearance of pruritic acanthosis nigricans may be associated with **malignancy,** especially **gastric,** lung, ovarian or breast.

- **Diagnosis**
  - **Best initial test:** Clinical. Consider investigating underlying glucose intolerance and malignancy.
  - **Most accurate test:** Skin biopsy showing epidermal hyperkeratosis and papillomatosis with increased basal layer pigmentation.

Acanthosis nigricans

- **Treatment**
  - **First line:** May regress by treating the underlying condition (eg, cancer excision, optimal diabetes control, weight loss).
  - **Second line:** Topical tretinoin, dermabrasion and/or laser for cosmetics.

4. SARCOIDOSIS

- **General:** Sarcoidosis is a multisystemic, chronic, granulomatous inflammatory disorder of unknown etiology. It involves the lung parenchyma and hilar lymph nodes over 90% of the time. It is more prevalent in **African Americans, Scandinavians** and **Puerto Ricans.** The main organs affected in sarcoidosis are:
  - **Lungs:** *Bilateral hilar adenopathy,* interstitial fibrosis, pulmonary hypertension and restrictive lung disease.
  - **Eyes:** Bilateral granulomatous uveitis.
  - **Brain:** *Cranial nerve palsies,* diabetes insipidus and central hypogonadism.
  - **Heart:** Heart block, arrhythmias and restrictive cardiomyopathy.
  - **Liver and spleen:** Hepatosplenomegaly and pancytopenia (hypersplenism).
  - **Systemic:** Fever, *weight loss,* night sweats, malaise, *arthralgias, lymphadenopathy* and enlarged salivary and lacrimal glands.

- **Clinical:** The **skin** is commonly involved in sarcoidosis. It usually presents with nonspecific red-brown-to-purple macules, papules or nodules involving the **face** and **extensor surfaces.** The most characteristic cutaneous manifestation is **lupus pernio;** this lesion is unrelated to lupus erythematosus. It is characterized by **reddish-to-dark-purple papules, plaques or nodules** commonly located on the **nose, lips, cheeks and ears,** but can occur anywhere. Severe lupus pernio may cause permanent cosmetic disfigurement.

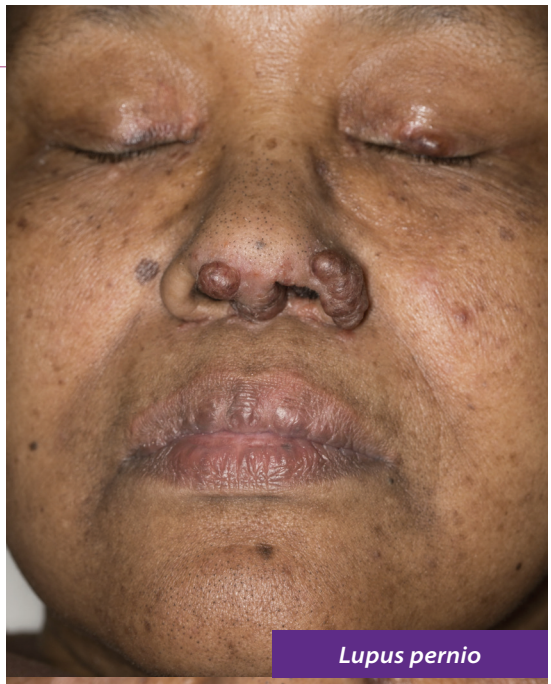
- **Diagnosis**
  - **Best initial test:** Clinical + chest x-ray *(bilateral hilar LAD)* + lab investigation showing hypercalcemia, high ACE levels and elevated CD4:CD8 T-cell ratio. Consider ophthalmologic evaluation.
  - **Most accurate test:** Skin biopsy showing noncaseating granulomas and giant cells with *Schaumann and asteroid bodies.*

- **Treatment**
  - **First line:** Topical or intralesional steroids for limited skin disease. Oral steroids for generalized disease.
  - **Second line:** Methotrexate, thalidomide, antimalarials (eg, hydroxychloroquine), anti-TNF-α inhibitors or phototherapy.

5. ACQUIRED PERFORATING DERMATOSIS (APD)

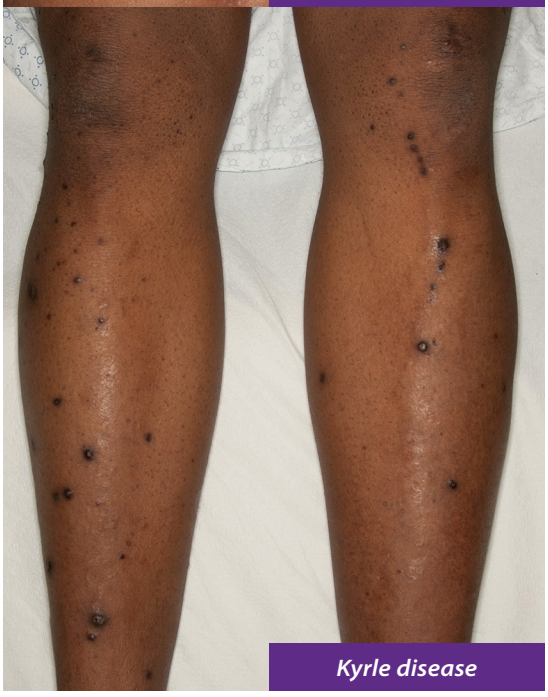
- **General:** Also known as **Kyrle disease,** APD is a skin disorder of unknown etiology characterized by dermal collagen and keratin perforating through the epidermis. APD most commonly affect **African American** patients with underlying **chronic kidney disease** who require dialysis and **diabetic patients** with nephropathy.

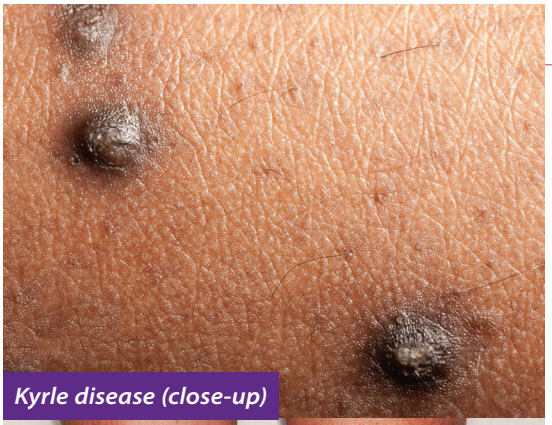
- **Clinical:** The characteristic lesions are **red-to-brown enlarging scaly papules** or **nodules** with **central keratin plugs.** Lesions may be tender and very pruritic. Most commonly affect the **legs** but can occur anywhere (eg, arms, head, neck).

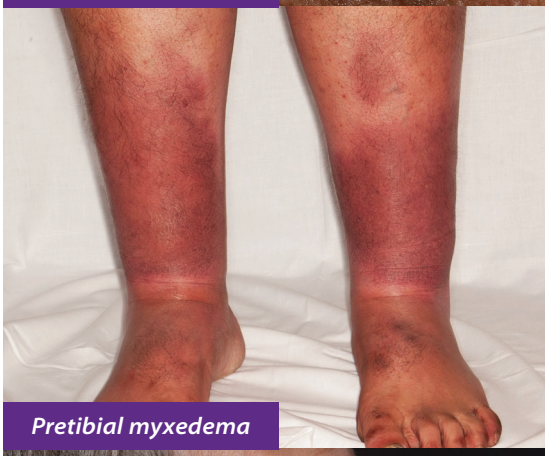

Lupus pernio

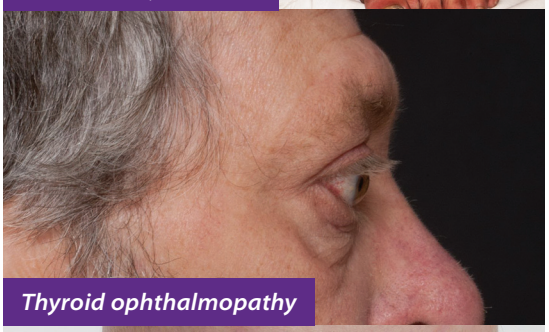

Lupus pernio (close-up)

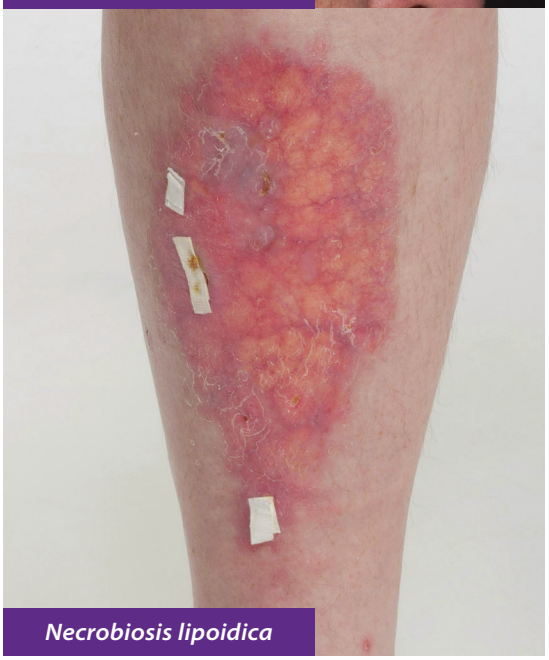

Lupus pernio


Kyrle disease


Kyrle disease (close-up)


Pretibial myxedema


Thyroid ophthalmopathy


Necrobiosis lipoidica

- **Diagnosis**
  - **Best initial test:** Clinical + investigate underlying diabetes and kidney disease.
  - **Most accurate test:** Skin biopsy showing hyperkeratotic plugs and transepidermal elimination of degenerated connective tissue.

- **Treatment**
  - **First line:** Treat underlying condition + topical steroids or antihistamines for pruritus.
  - **Second line:** Phototherapy or retinoids.

6. PRETIBIAL MYXEDEMA

- **General:** Also known as **localized myxedema** or **thyroid dermopathy,** a localized dermatosis characterized by dermal **deposition of glycosaminoglycans,** particularly hyaluronic acid. Commonly seen in **Grave disease** but can occur in any thyroid disorder.

- **Clinical:** Characterized by asymptomatic, **nonpitting, edematous purple-to-brown asymmetrical plaques** and/or nodules. Most commonly affect the anterior or lateral aspects of **bilateral shins** but can occur anywhere. Prominent hair follicles often resemble the appearance of an orange peel **("peau d'orange").**

- **Diagnosis**
  - **Best initial test:** Clinical + order TSH to detect any underlying thyroid abnormality.
  - **Most accurate test:** Skin biopsy showing mucin deposition in reticular dermis.

- **Treatment**
  - **First line:** Topical steroids + compression stockings.
  - **Second line:** Oral steroids or pentoxifylline for severe disease.

- **USMLE Pearls: Necrobiosis lipoidica:** Another dermatosis that presents on the **shins;** do not confuse with pretibial myxedema. More commonly occurs in patients with underlying **diabetes mellitus.** It presents with asymptomatic, **enlarging, red-brown patches** that evolve into **yellow-orange atrophic plaques.** Lesions may have **telangiectatic vessels** and **ulceration.** Most commonly located on the pretibial area. *Diagnosis* is clinical. Histology shows a granulomatous reaction surrounding central degenerated collagen. Difficult to treat; may respond to topical steroids.

7. GRAFT VERSUS HOST DISEASE (GVHD)

- **General:** Characterized by **dermatitis, enteritis and hepatitis** following the transplantation of *lymphoid-rich organs, allogenic stem cells* or *unirradiated blood products.* Immunocompetent cells in graft mount an immune response against host antigens. Reactivation of HHV-6 and co-infection with EBV are thought to contribute to GVHD. **Acute GVHD** occurs less than 100 days after transplant, while **chronic GVHD** occurs after 100 days. Main organs affected are:
  - **Liver:** Jaundice and pruritus with abnormal liver function tests (elevated AST, ALT, ALP and bilirubin).

- **GI tract:** Diarrhea, intestinal bleeding, abdominal pain, ileus and GI obstruction.
- **Skin** (described below)

- **Clinical:** Characterized by an **erythematous maculopapular rash** that usually begins on the face, palms and soles. **Perifollicular** macules and papules may coalesce to form a widespread rash that involves the whole body **(erythroderma).** In severe cases, there may be subepidermal bullae and desquamation of the skin resembling SJS/TEN.

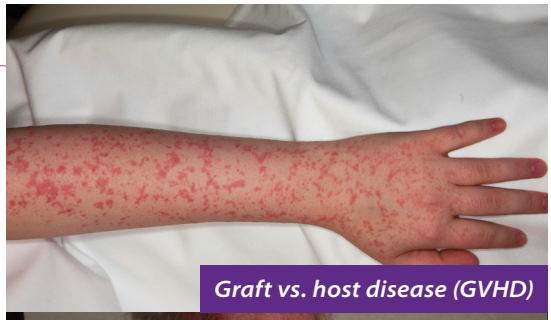
- **Diagnosis**
  - **Best initial test:** Clinical + order fecal occult blood test (FOBT) and liver function tests (LFTs) to detect GI tract and hepatic damage, respectively.
  - **Most accurate test:** Skin biopsy showing a perivascular and dermal lymphocytic inflammation, necrosis of keratinocytes and degenerated basal cells.

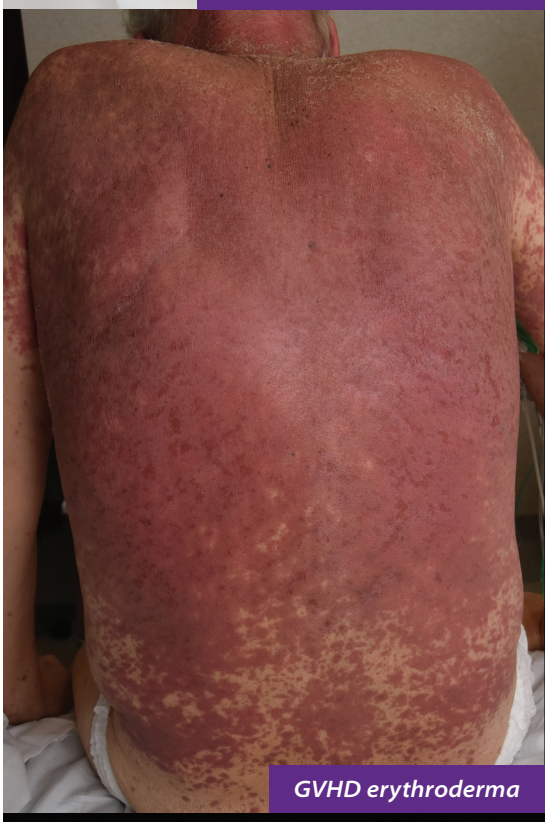
- **Treatment**
  - **First line:** Topical steroids or calcineurin inhibitors for limited skin disease. For extensive skin involvement, oral steroids are typically added to the patient's immunosuppressive regimen.
  - **Second line:** Mycophenolate mofetil or anti-TNF-α inhibitors.

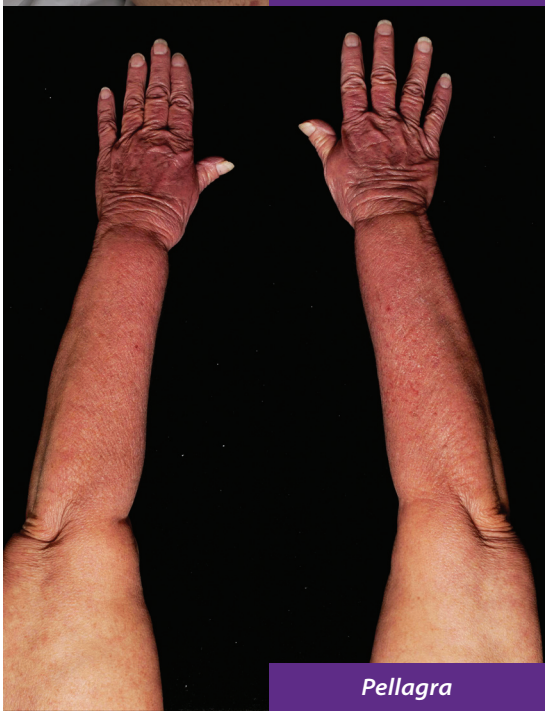
8. PELLAGRA

- **General:** Systemic disease caused by severe **deficiency of vitamin B3,** also known as **niacin** or **nicotinic acid.** Niacin is essential for *glycolysis, energy production, immunomodulation* and *protein/fatty acid metabolism*. Niacin is endogenously synthesized from **tryptophan** and needs **vitamin B6** (pyridoxine) as a cofactor. Classically presents with the **4 Ds: D**iarrhea, **D**ermatitis, **D**ementia and **D**eath. The major causes of pellagra are:
  - **Corn-based** and **restrictive diets,** malnutrition and parenteral nutrition.
  - **Chronic malabsorption** and **alcoholism.**
  - **Carcinoid syndrome** (overproduction of serotonin depletes tryptophan).
  - **Hartnup syndrome** (inborn error of tryptophan metabolism).
  - **Isoniazid therapy** (depletes vitamin B6 and biochemically competes with niacin).

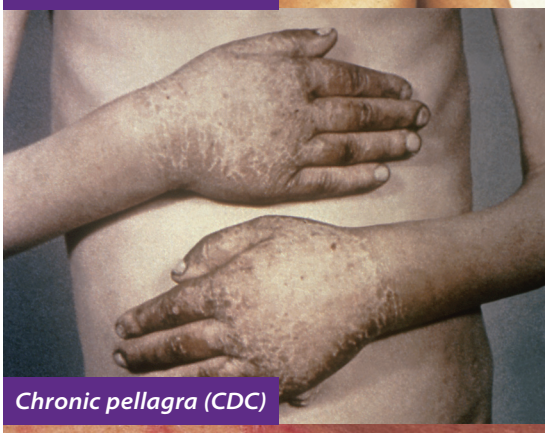
- **Clinical:** The manifestations of pellagra can be divided into *cutaneous, neurological* and *gastrointestinal*.
  - **Skin:** Begins with a well-defined, pruritic and scaly **erythematous photodistributed rash.** May form vesicles and bullae that rupture to leave denuded, brown-to-black **hyperpigmented skin.** As the disease progresses, the skin becomes more **dry, thickened** and **progressively harder.** Most commonly affect the face, neck, dorsa of hands and feet and areas of friction (eg, intertriginous). The characteristic lesion is a **broad raised band around the neck** known as *"Casal's necklace."*
  - **Brain:** Demyelination of the CNS results in irritability, tremors, ataxia, depression, psychosis, delusions and dementia.
  - **GI tract:** Vomiting, watery diarrhea, gastritis, cachexia and glossitis with loss of tongue papillae.

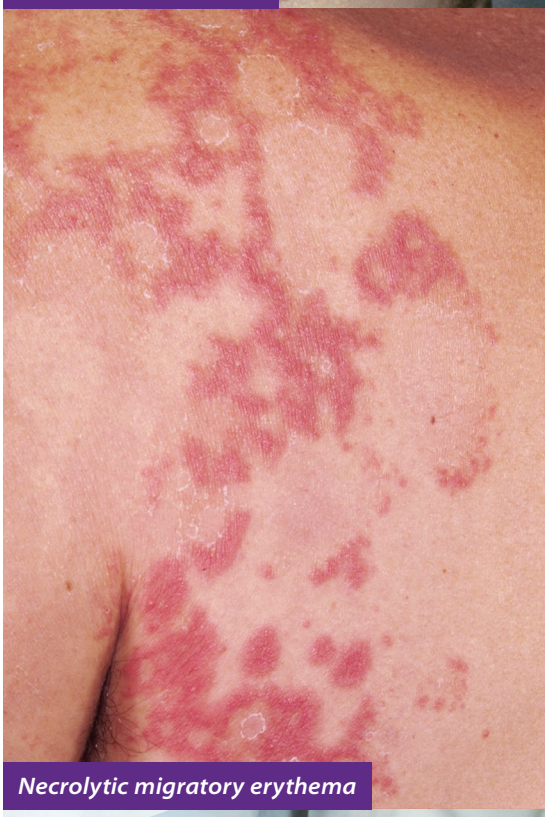

Graft vs. host disease (GVHD)

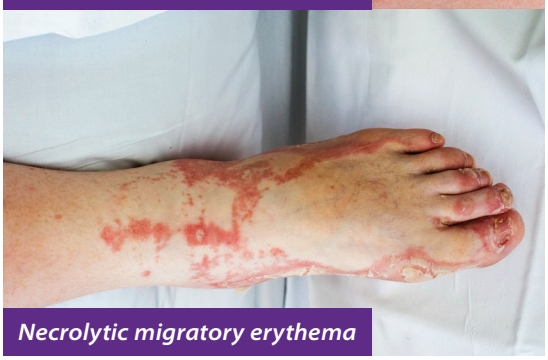

GVHD erythroderma


Pellagra


Casal's necklace (CDC)


Chronic pellagra (CDC)


Necrolytic migratory erythema


Necrolytic migratory erythema

- **Diagnosis**
  - **Best initial test:** Clinical + niacin, tryptophan and nicotinamide-adenine dinucleotide (NAD) levels. Therapeutic response to nicotinamide confirms the diagnosis.
  - **Most accurate test:** Urinary liquid chromatography for niacin metabolites.

- **Treatment**
  - **First line:** IV or oral niacin or nicotinamide + multivitamins and sun protection.

- **USMLE Pearls: Necrolytic migratory erythema (NME):** Rare skin eruption that may be confused with pellagra skin manifestations. Most commonly occurs in patients with **high levels of glucagon,** such as those with underlying glucagon secreting-tumor of the pancreas **(glucagonoma).** These endocrine tumors manifest with **diabetes, diarrhea, weight loss** and the appearance of NME. Necrolytic migratory erythema is characterized by **pruritic, painful** and **erythematous annular patches with blisters.** In few days, the blisters may erode and crust to leave **dry, hyperpigmented areas.** Most commonly affect the lower abdomen, perineum, groin, buttocks, distal extremities and perioral and acral areas. High glucagon levels and CT scan imaging establish the diagnosis. Somatostatin scan may detect occult metastasis. *Treat* with octreotide and tumor resection.

Chapter 6

DISORDERS OF THE FOLLICULAR PILOSEBACEOUS UNIT

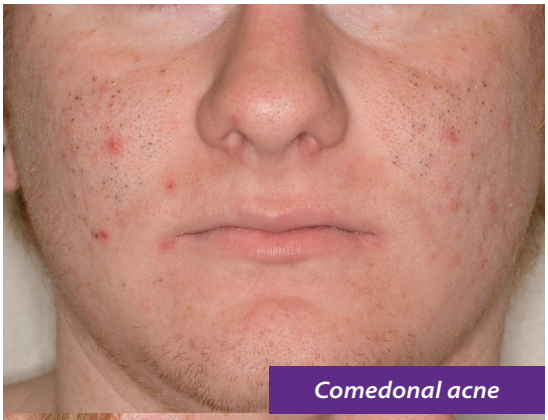
1. ACNE VULGARIS

- **General:** Multifactorial disorder of the pilosebaceous unit that leads to a variety of *acne* lesions. The most common skin disorder seen by dermatologists. Affects predominantly **adolescents,** although anyone can be affected. Associated with underlying hyperandrogenism such as **polycystic ovarian syndrome** (PCOS), **congenital adrenal hyperplasia** (CAH), **XYY karyotype, Cushing syndrome** and **exogenous androgen consumption.** The multifactorial process of acne lesion formation is summarized below:
  - **First step:** Corneocytes **accumulate and block** the upper portion of the hair follicle, leading to *open* and *closed comedones* **(noninflammatory acne).**
  - **Second step:** Closely packed keratinocytes and sebum increase intrafollicular pressure and lead to **comedo rupture** with extrusion of immunogenic material into the dermis and epidermis. This process is accelerated by:
    - **Testosterone and dihydrotestosterone (DHT):** Bind to androgen receptors in hair follicles and **increase sebum production.**
    - ***Propionibacterium acnes*:** Gram-positive rod-shaped bacterium that produces **inflammatory cytokines** and **destructive enzymes.**
  - **Third step:** The inflammatory response to the immunogenic material results in **inflammatory acne.** The clinical lesions depend on the *type of inflammatory cells* in the reaction:
    - If *neutrophils* predominate, the clinical result is usually pustules.
    - If *lymphocytes* predominate, the clinical result is usually papules, nodules and/or cysts.

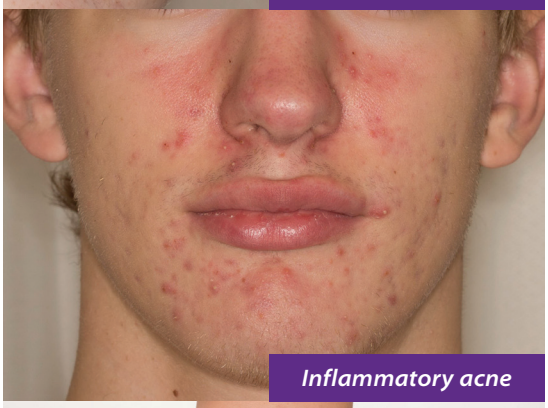
- **Clinical:** Commonly affect areas rich in sebaceous glands, such as the face and upper trunk. Clinical presentation is divided into:
  - **Noninflammatory acne:** Also known as *comedonal acne,* it is composed of *closed* and *open comedones*. **Closed comedones (whiteheads)** are small, skin-colored, dome-shaped papules *without* a follicular opening. **Open comedones (blackheads)** are small, skin-colored, dome-shaped papules *with* a central black-colored follicular opening. Comedones have minimal or no inflammation surrounding the lesions.
  - **Inflammatory acne:** Mainly composed of **papules, pustules, nodules and cysts.** Dome-shaped **papules** are surrounded by erythema and inflammation. **Pustules** are pus-filled and clinically present as erythematous, whitish-yellow small papules. **Nodules and cysts** are bigger and are usually tender, indurated and markedly inflamed. Nodules and cysts can merge to form plaques and draining sinuses **(nodulocystic acne).**

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical.

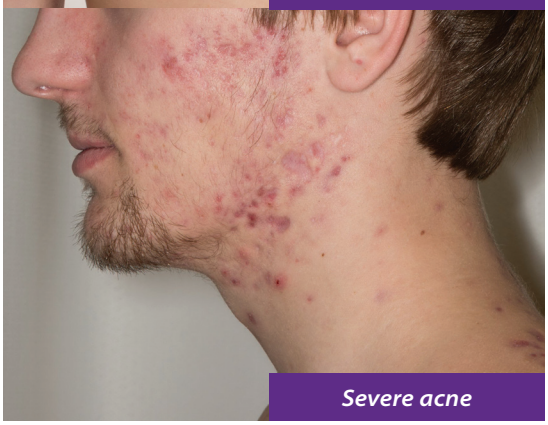
- **Treatment:** In patients with oily skin, use **water-based cleansers** (avoid oil-based). The treatment of acne depends on the **type of acne** and severity.
  - **Noninflammatory acne**
    - **Mild (5 to 30 lesions):** Start with *benzoyl peroxide* and/or *topical retinoids* (eg, tretinoin, tazarotene, adapalene) plus *organic acids* such as salicylic, azelaic or glycolic acid.

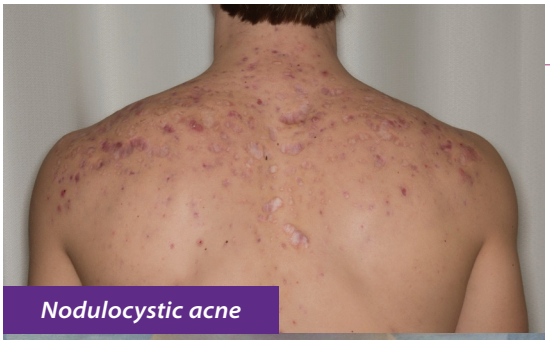

Comedonal acne

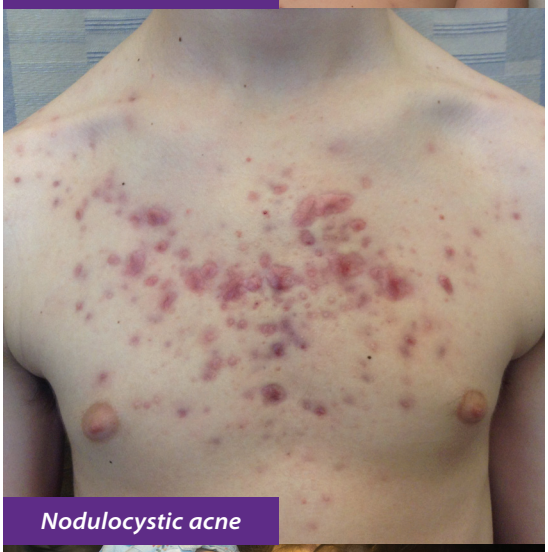

Mild acne


Inflammatory acne

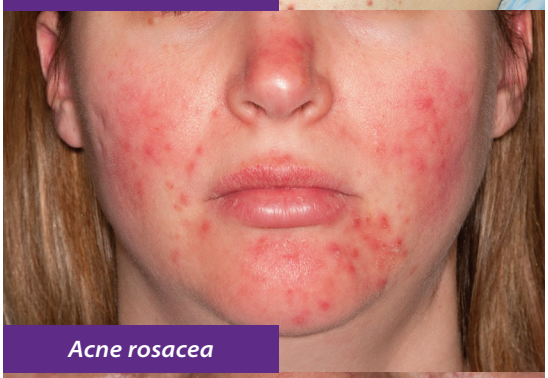

Moderate acne

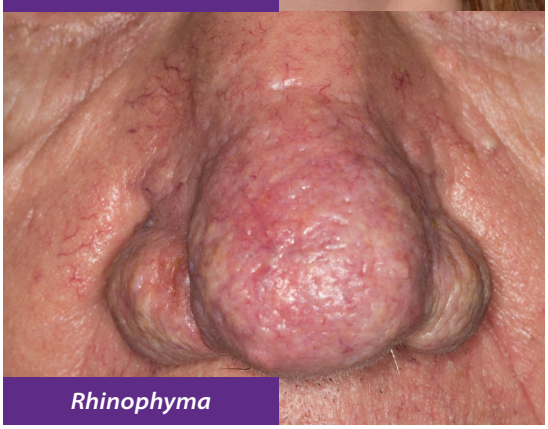

Severe acne


Nodulocystic acne


Nodulocystic acne


Steroid-induced acne


Acne rosacea


Rhinophyma

- **Inflammatory or diffuse acne**
  - **Moderate acne (30 to 125 lesions):** Use previous regimen plus additional *topical antibiotics* such as clindamycin or erythromycin.
  - **Severe acne (nodulocystic or > 125 lesions):** Change from topical to *systemic antibiotics* such as oral minocycline, doxycycline or erythromycin. If not responsive, consider *oral retinoids* such as isotretinoin. In patients with severe nodulocystic acne, use isotretinoin from the start.

- **USMLE Pearls: Oral contraceptives (OCPs)** increase hormone-binding globulins production, hence decreasing free testosterone levels. **Spironolactone** decreases sebum production as an androgen receptor antagonist in the hair follicle. Both treatments are effective in treating acne in selected **patients with hyperandrogenism.** When using OCPs, monitor for important side effects such as **hyperpigmentation, liver adenomas** and **clot formation** (eg, DVT, pulmonary embolism). When using spironolactone, monitor for **gynecomastia** and **hyperkalemia.**

- **USMLE Pearls: Isotretinoin** decreases follicular plugging and inflammation by *decreasing follicular keratinization, sebum production* and *bacterial count*. Oral retinoids are extremely **teratogenic;** two forms of contraception and two negative pregnancy tests are required before starting therapy. Common side effects include **hepatotoxicity, myopathy** and **hyperlipidemia;** must monitor LFTs, lipid panel and creatine phosphokinase (**CPK**) levels. **Doxycycline** and **tetracycline** cause phototoxicity and are teratogenic. Avoid combining isotretinoin and tetracycline, as both increase risk of **pseudotumor cerebri.**

- **USMLE Pearls: Steroid-induced acne:** Sudden outcropping of **monomorphic, pustular,** acneiform eruption predominantly on the **trunk** and **arms.** Occurs on patients receiving **systemic corticosteroids** in high doses or for a prolonged period of time (eg, autoimmune diseases, organ transplantation). *Treat* by discontinuing steroids; if steroids are absolutely needed, use retinoids.

2. ACNE ROSACEA

- **General:** Chronic inflammatory disorder of the pilosebaceous units of *facial skin*. There may be a causal association with the mite ***Demodex folliculorum*.** Rosacea is exacerbated by:
  - **Topical steroids**
  - **Oil-based creams**
  - **Hot drinks** and **climate** (sun)
  - **Spicy foods, caffeine** and **alcohol** (eg, red wine)
  - **Stress, exercise** and **emotions**
  - **Hormonal fluctuations** (eg, ovulation, menstruation and menopause)

- **Clinical:** Usually seen in female patients with light skin and eyes. Characterized by **acneiform papules and pustules** with **flushing** and **telangiectasia** over the cheeks, nose and chin. Rosacea is associated with:
  - **Rhinophyma** (hyperplasia and hypertrophy of sebaceous gland in the nose)
  - **Conjunctivitis**
  - **Blepharitis** (inflammation of the eyelids)

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical.

- **Treatment**
  - **First line:** Use sunscreen and avoid triggers + topical metronidazole, clindamycin or ivermectin.
  - **Second line:** Oral doxycycline, minocycline or metronidazole for severe disease. Consider laser or topical vasoconstrictors (eg, brimonidine) for telangiectasias.

3. HIDRADENITIS SUPPURATIVA

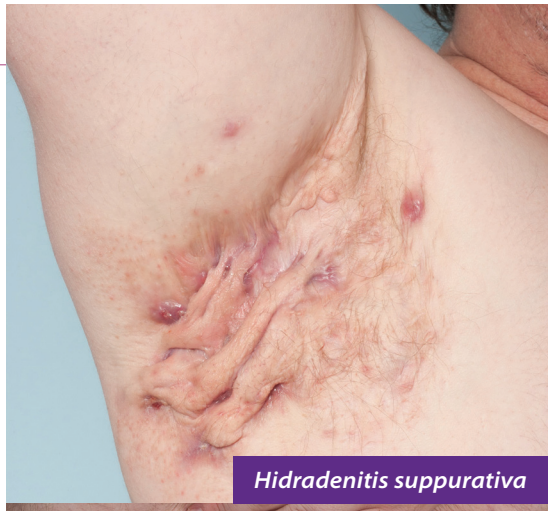
- **General:** Also known as **acne inversa,** a chronic relapsing inflammatory condition caused by **occlusion of the terminal follicular epithelium.** Plugging of the follicle results in follicular duct rupture with extrusion of foreign material into the dermis. Subsequent inflammatory reaction results in granulomas and epithelial strands that form **draining sinuses.** Secondary bacterial infections are very common and often lead to **abscess formation.** Hidradenitis suppurativa is exacerbated by:
  - **Smoking**
  - **Obesity**
  - **High glycemic diets** (high IGF-1→ increased keratinocyte proliferation → increased follicular plugging)
  - **Mechanical stress** and **skin obstruction** (eg, tight clothing)
  - **Heat** and **humidity**

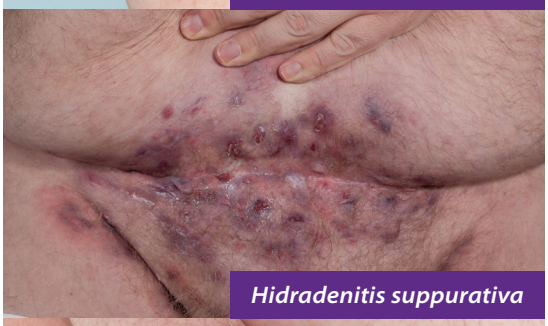
- **Clinical:** Characterized by single or multiple, **inflamed** and **painful nodules** and **abscesses with purulent draining sinuses.** If focal, lesions are commonly located in areas prone to follicular obstruction such as **axillae, anogenital** and **inguinal regions, inframammary** and **underbelly folds.** Severe, generalized and recurrent disease may affect the whole body and lead to **permanent disfiguring scarring.**

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical. Stain and culture active lesions to identify and treat secondary infections.

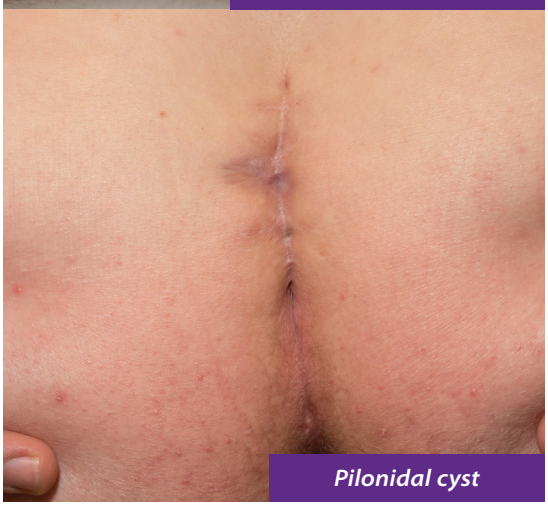
- **Treatment**
  - **First line:** Lifestyle modifications (eg, decrease weight, avoid trauma, low glycemic diet, smoking cessation, wearing loose clothing). Secondary bacterial infections are usually treated with *clindamycin and rifampin* combination. *Incision and drainage* (I&D) for unresponsive abscesses and nodules.
  - **Second line:** Isotretinoin or anti-TNF-α inhibitors (eg, adalimumab, infliximab, etanercept) for recalcitrant or severe disease.

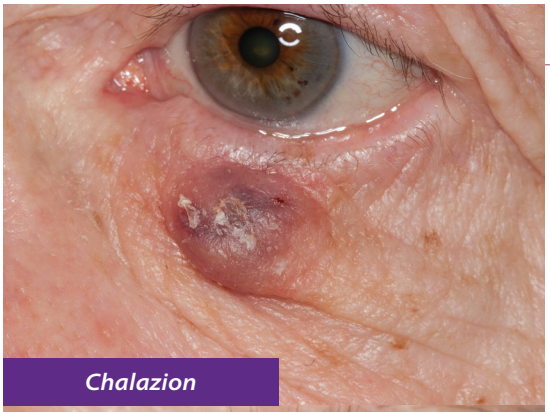
- **USMLE Pearls: Pilonidal Cyst:** An inflammatory reaction thought to occur from **penetration of hair** into the subcutaneous tissue. Secondary bacterial infection with ***S. aureus*** and **anaerobes** lead to abscess formation. Lesions are most commonly located on the **sacrococcygeal area** around the gluteal cleft. Major risk factor is **prolonged sitting** (eg, truck drivers, secretaries, programmers). Physical exam may reveal a **fluctuant area with erythema** and a **sinus tract.** *Diagnosis* is clinical and *treatment* is incision and drainage (I & D); antibiotics alone will not work.


Hidradenitis suppurativa


Hidradenitis suppurativa

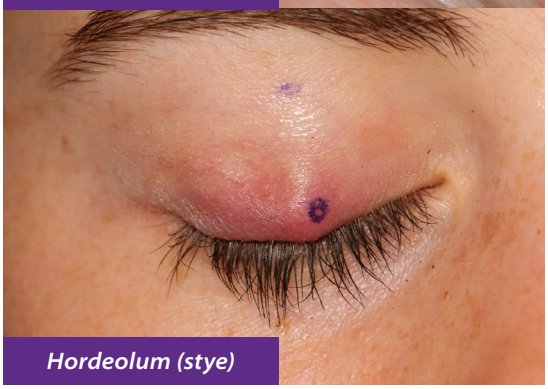

Hidradenitis suppurativa


Pilonidal cyst



Chalazion

Chalazion



Hordeolum (stye)

4. CHALAZION

- **General:** Most common inflammatory lesion of the *eyelid*. Starts with obstruction of the **Zeis or meibomian sebaceous glands.** The result is retention of lipid breakdown products, inciting a **granulomatous and sterile** inflammatory reaction limited to the eyelid.

- **Clinical:** Most commonly presents with a **painless, nonfluctuant,** papule in the **eyelid** with or without inflammation. Chalazia usually measure 2 to 8 mm in diameter and may cause impaired vision and eye discomfort. May occasionally become infected and painful. Nodules can spontaneously regress and later recur in the same location. Chronic and recurrent lesions are often **confused with eyelid malignancy** (eg, basal cell or sebaceous carcinoma).

- **Diagnosis**
  - **Best initial test:** Clinical. If recurrent or unresponsive to therapy, perform a biopsy to rule out malignancy.
  - **Most accurate test:** Skin biopsy showing a chronic granulomatous reaction with lipid-filled giant cells.

- **Treatment**
  - **First line:** *Warm compresses + lid hygiene + lid massage* (melt lipids, remove debris and facilitate drainage, respectively).
  - **Second line:** Topical or intralesional steroids for inflamed lesions. Consider incision and curettage for unresponsive lesions.

- **USMLE Pearls: Hordeolum (Stye):** Important differential diagnosis for chalazion. A hordeolum is characterized by **acute focal inflammation with or without infection** of the sebaceous glands of Zeis or apocrine glands of Moll. Eyelid gland obstruction results in stasis of secretions and frequent secondary bacterial infection with ***S. aureus.*** A hordeolum is a **local abscess** and will present with **pain, erythema, tenderness** and a **swollen red lump** on the eyelid. *Diagnosis* is clinical; however, a biopsy shows neutrophils and necrotic material. *Treatment* is eyelid massage, warm compresses and topical or oral antibiotics against *S. aureus*.

Chapter 7

DISORDERS OF THE HAIR

Phases of hair growth

- **Anagen phase:** *Growth phase,* lasts for years; around **90 to 95%** of all hairs are normally in anagen phase.
- **Catagen phase:** *Transitional phase,* cessation of hair growth, lasts for weeks; very few hairs are in this phase at any given time.
- **Telogen phase:** *Resting phase* before hair shedding, lasts approximately 3 months; around **5 to 10%** of all hairs are normally in telogen phase. **Telogen hairs** have a characteristic rounded **"club-shaped"** bulb at the proximal end identified under magnification. It is normal to lose 50 to 100 telogen hairs per day.

Table 7.1. Hair Disorders Summary

Hair Disorder	Hair Loss Pattern	Associations	Unique Characteristic	Treatment
Alopecia Areata	• Round-oval circular patch, usually single • Involves scalp, less often face and body	• Autoimmune diseases (thyroid) • Atopic disorders • Psychiatric disorders	**"Exclamation point" hairs** and **pitted nails** Relapsing and remitting course	Intralesional steroids
Trichotillomania	• Geometrical (no specific pattern) • Dominant hand side • Involves scalp, face and body	• Repetitive behavior • Psychiatric disorders • Trichophagia (hairballs)	**Friar Tuck sign:** Broken hair of varying length surrounded by unaffected hair	Psychiatric evaluation Behavioral therapy
Telogen Effluvium	• Diffuse • Mainly limited to scalp	• Physiologic stress • Metabolic abnormalities • Medications • Systemic diseases	Positive **"hair pull"** test	Remove underlying stressor
Androgenetic Alopecia	• Receding hair line, frontal and vertex (male) • Crown (female) • Limited to scalp	• Male predominance • Hereditary (family history) • Hyperandrogenism	**Vellus (thin) hair**	Minoxidil and/or finasteride

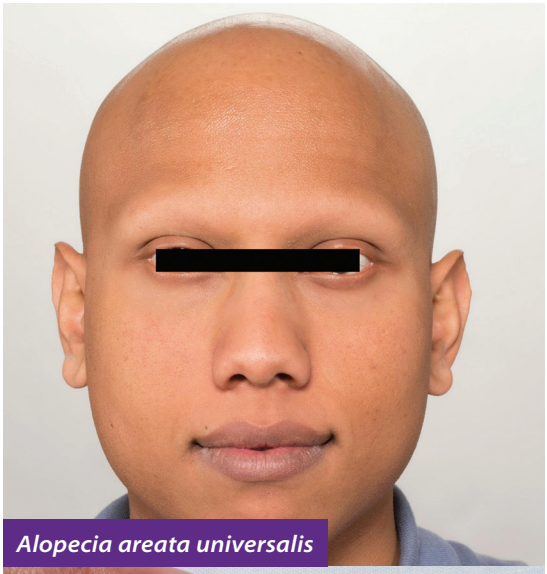
1. ALOPECIA AREATA

- **General:** Nonscarring autoimmune hair loss of unknown etiology that affects any hair-bearing area of the body (often identified on the scalp). It affects patients of all ages and there may be a positive family history. Alopecia areata is associated with:
  - **Atopic disorders:** Atopic dermatitis, asthma and allergic rhinitis.
  - **Autoimmune diseases:** Vitiligo, **autoimmune thyroid disease,** type 1 diabetes, inflammatory bowel disease (IBD), pernicious anemia and rheumatoid arthritis (RA).
  - **Psychiatric disorders:** Depression, major stressors, paranoid disorders and anxiety.

- **Clinical:** Characterized by **single** (or multiple), **round-to-oval alopecic patch** on the scalp (most common) or any other hair-bearing area (eg, beard). Generally follows a **relapsing and remitting** unpredictable course. Mostly asymptomatic, although a few patients complain of burning and pruritus in alopecic patches. Uncommonly leads to total scalp hair

Alopecia areata

Alopecia areata


Alopecia areata universalis


Nail pitting


Trichotillomania


Friar Tuck sign

loss **(alopecia areata totalis)** or total body and scalp hair loss **(alopecia areata universalis).** The characteristic finding is hairs with a tapered end, known as **"exclamation point" hairs.** Fingernails can be affected and usually present with **nail pitting.**

- **Diagnosis**
  - **Best initial test:** Clinical. Trichoscopy may reveal the presence of yellow dots on alopecic patches.
  - **Most accurate test:** Skin biopsy showing a lymphocytic infiltration around hair follicles.

- **Treatment**
  - **First line:** Usually self-limited; for hastened resolution, use topical or intralesional steroids +/- topical minoxidil.
  - **Second line:** Oral steroids.

2. TRICHOTILLOMANIA

- **General:** Hair-pulling disorder that commonly affects **children** and **adolescents.** Classified as a type of **obsessive-compulsive disorder** in which the patient feels a repeated urge to pull the hair. This behavior causes significant distress with impairment in social and occupational functioning. Trichotillomania is associated with:
  - **Repetitive behavior:** Nail and cheek biting and skin pricking.
  - **Trichophagia:** Ingesting hair leads to GI trichobezoars **(hairballs).** This may present with GI tract obstruction and bleeding, nausea or vomiting, hematemesis and anemia.
  - **Psychiatric disorders:** Anxiety, ADHD, body dysmorphic disorder and mood and tic disorders.

- **Clinical:** Most commonly affects the scalp but can occur in any hair-bearing area of the body. Hair loss often **favors the dominant hand side** and alopecic patches are usually geometrical in shape (no specific pattern). The **"Friar Tuck" sign** is the presence of **broken hairs of varying length** in the alopecic patches surrounded by unaffected hair. Other important findings are **empty hair follicles, regrowing hairs** and **corkscrew-shaped hair shafts.**

- **Diagnosis**
  - **Best initial test:** Clinical. Parents often report child's hair-pulling behavior.
  - **Most accurate test:** Skin biopsy showing anagen hairs and empty or distorted hair follicles without significant inflammation.

- **Treatment**
  - **First line:** Psychiatric evaluation (behavioral therapy).
  - **Second line:** Selective serotonin reuptake inhibitors (SSRIs) such as clomipramine.

3. TELOGEN EFFLUVIUM

- **General:** Nonscarring, **diffuse hair loss** occurring when a large amount of hair is induced to enter the **telogen phase** and is subsequently shed. Typically seen several months *after* an inciting event. Telogen effluvium affects people of all ages and is commonly triggered by:

- **Physiologic stress:** Febrile illness, major injuries, surgeries, infections, hospitalizations, pregnancy, childbirth and immunizations.
- **Metabolic abnormalities:** Crash diets, anorexia and iron deficiency.
- **Systemic diseases:** Cancer, autoimmune diseases, hypothyroidism and renal or liver disease.
- **Medications:** β-blockers, retinoids, propylthiouracil (PTU), heparin, anticonvulsants and discontinuation of oral contraceptives (OCPs).

- **Clinical:** Characterized by a **diffuse pattern of scalp hair loss** that may be perceived as hair thinning. The hair loss can occur suddenly over days or continuously over months. No patches have total hair loss; affected areas usually have short new hairs growing out. Inflammation is *absent* and other parts of the body are rarely affected. **Preceding trauma or stressor** can almost always be identified.

- **Diagnosis**
  - **Best initial test:** Clinical. Identify underlying stressor. In active disease, the **"hair pull" test** will yield a positive result (> 20% of total hairs pulled out are in telogen phase).
  - **Most accurate test:** Skin biopsy showing **> 25%** of hairs in telogen phase.

- **Treatment**
  - **First line:** Reassurance, correct underlying cause if found.
  - **Second line:** Topical minoxidil.

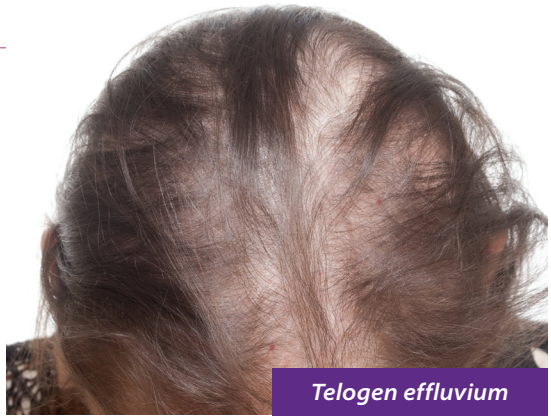
4. ANDROGENETIC ALOPECIA

- **General:** Male or female pattern genetic hair disorder; the *most common* type of hair loss in **adults.** Conversion of **testosterone** into **dihydrotestosterone** (DHT) **by 5-alpha-reductase** induces terminal thick hair to become **thin, miniaturized vellus hair,** which eventually falls off. The anagen phase is shortened and more hairs are in the telogen phase at one time.

- **Clinical:** Generally presents in adults over 30 years old. In *males,* the characteristic pattern is a **gradual receding hairline** with pronounced hair loss in the **frontal** and **vertex scalp.** In *females,* the hair loss is mainly in the **crown** (topmost part of head); females rarely present with total hair loss.

- **Diagnosis**
  - **Best initial test:** Clinical. There is usually a family history. In females, consider ruling out hyperandrogenism.
  - **Most accurate test:** Skin biopsy showing the majority of the hair follicles miniaturized (vellus) and disappearance of follicular units.

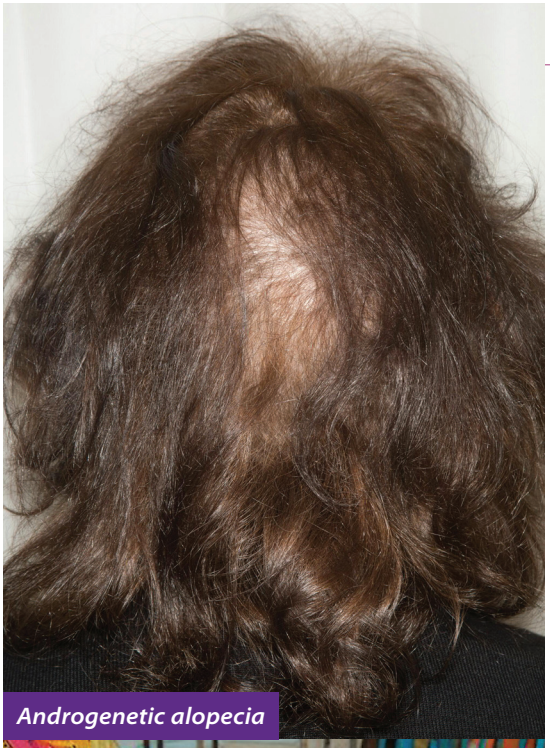
- **Treatment**
  - **First line:** Minoxidil and/or finasteride (5-alpha-reductase inhibitor).
  - **Second line:** Spironolactone or oral contraceptive pills (OCPs) can be tried in selected female patients.


Telogen effluvium


Telogen effluvium


Androgenetic alopecia


Androgenetic alopecia



Androgenetic alopecia

*Menkes kinky hair syndrome**

- **USMLE Pearls:** Important associations related to hair disorders:
  - **Hypothyroidism:** Presents with coarse hair and loss of the lateral third of the eyebrows.
  - **Anorexia nervosa:** Presents with lanugo body hair.
  - **Leprosy:** Presents with loss of eyebrows and eyelashes.
  - **Hirsutism:** Male pattern hair growth in a female; it may be a sign of androgen excess. Hirsutism is associated with:
    - **Polycystic ovarian syndrome** (PCOS)
    - **Congenital adrenal hyperplasia** (CAH)
    - **Cushing syndrome**
    - **Androgen-secreting tumors** (eg, ovarian cancer)
    - **Drugs** (eg, anabolic steroids, cyclosporine, minoxidil, danazol, phenytoin)
  - **Menkes kinky hair syndrome:** *X-linked recessive* neurodegenerative disorder due to ***ATP7A*** gene mutation. The result is impaired copper transport and poorly distributed copper levels around body tissues. *Lysyl oxidase insufficiency* (copper-dependent) results in abnormally pigmented **(white or gray), sparse** and **brittle kinky hair.**

Chapter 8

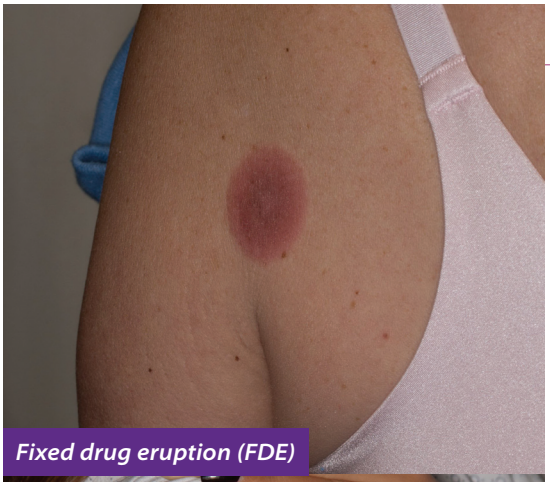
DRUG REACTIONS

Drug reactions vary in severity and presentation. Some of the drug reactions presented in this chapter are thought to be a *cell-mediated hypersensitivity* to an offending antigen. This explains why the **initial reaction may take weeks** to develop but on antigen re-exposure, the reaction tends to be faster and more severe. The most important therapeutic intervention is discontinuation of the offending drug. **Common medications** that frequently elicit drug reactions are:

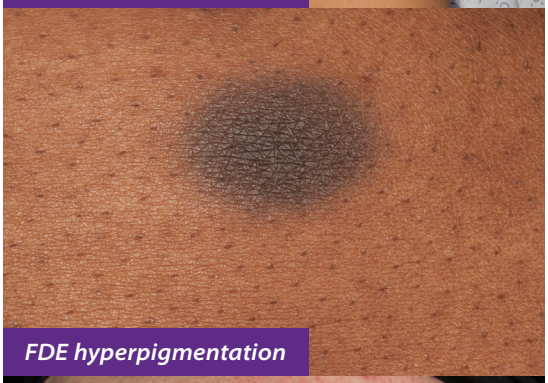
- **Antibiotics** (eg, penicillins, cephalosporins, tetracyclines)
- **Sulfonamides** (eg, thiazides, furosemide, sulfonylureas)
- **Antiepileptic drugs** (eg, phenytoin, lamotrigine, carbamazepine, barbiturates)
- **Allopurinol** and **nonsteroidal antiinflammatory drugs** (NSAIDs)

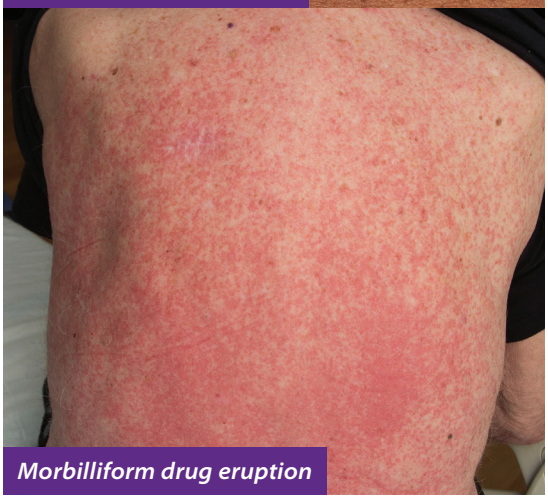
Table 8.1. Drug Reactions Summary

Drug Reaction	Skin Necrosis	Mucous Membrane Involvement	Vesicle/Bulla Formation	Nikolsky Sign	Eruption Characteristics	Course/ Outcome
Fixed Drug Eruption (FDE)	Rare	None	Rare	Negative	Circumscribed eruption occurring on **same anatomical location** after drug exposure; leaves **hyperpigmented macule or patch.**	No permanent sequelae
Morbilliform Drug Eruption	None	None	None	Negative	**Dot-like-to-macular erythematous rash** that usually starts on the trunk and symmetrically spreads to extremities **(resembles measles exanthem)**.	No permanent sequelae
Erythema Multiforme (EM)	**Upper epidermis**	None	**Likely** (usually vesicles)	Negative	**Target-like eruption** usually occurring after **HSV** or ***M. pneumoniae*** infection; starts on palms and soles or extremities and spreads to trunk.	No permanent sequelae
SJS/TEN	**Full thickness epidermis**	**Severe** (Oral, ocular and genital)	**Likely** (vesicles/ bullae)	**Positive**	Erythematous macular eruption with or without **necrosis** and **sheets of skin detachment;** usually starts on the trunk and spreads to extremities. **Severe systemic symptoms**.	**High morbidity** (blindness, skin grafts, feeding tubes, intubation) and **high mortality**
Warfarin-Induced Skin Necrosis	**Full thickness epidermis**	None	**Likely** (Hemorrhagic vesicles/bullae)	Negative	Begins 2 to 5 days **after warfarin initiation**. Severe pain and sharply demarcated erythema, followed by the rapid development of **purplish skin discoloration** and **extensive skin necrosis**.	**High morbidity**
DRESS	None	**Mild-to-severe** (oral and genital swelling)	Rare	Negative	**Morbilliform eruption** most often occurring on the face, upper trunk and extremities. **Facial edema** is characteristic.	**Severe organ involvement** may occur (**hepatitis**, myocarditis, nephritis, thyroiditis and pneumonitis)


Fixed drug eruption (FDE)


Fixed drug eruption (FDE)


FDE hyperpigmentation


Morbilliform drug eruption

1. FIXED DRUG ERUPTION (FDE)

- **General:** Common drug reaction characterized by an eruption appearing in the **same anatomic (fixed) location** after exposure to culprit drug. The initial eruption may take weeks to appear and usually presents as a **single, solitary lesion.** On drug re-exposure, the eruption may develop within hours; older lesions become more prominent and **new lesions** tend to appear. **Sulfonamides** are the most commonly implicated drugs. Occasionally, there is a family history of **atopic disorders** (eg, allergic rhinitis, asthma, eczema).

- **Clinical:** Characterized by a single (or multiple), **well-defined** and **circumscribed** erythematous macule or patch ranging from 0.5 to 6 cm in diameter. **Pruritus, burning,** edema and blisters may accompany the lesion(s). Classically, fixed drug eruptions fade away in days to weeks, leaving a **purplish-to-brown hyperpigmented area.** Common sites involved are the **lips, anogenital area (glans penis),** limbs, hands and feet, but can occur anywhere.

- **Diagnosis**
  - **Best initial test:** Clinical. Challenging suspicious culprit drug may elicit diagnosis.
  - **Most accurate test:** Skin biopsy showing necrosis of keratinocytes and degeneration of basal cells with mixed dermal inflammation +/- pigment incontinence.

- **Treatment**
  - **First line:** Avoid and discontinue offending drug + topical steroids and antihistamines.
  - **Second line:** Oral steroids.

2. MORBILLIFORM DRUG ERUPTION

- **General:** Commonly known as a **maculopapular or exanthematous drug eruption; "morbilliform"** means the eruption resembles that of measles. This type of eruption represents **95%** of all drug-mediated skin reactions. The most common culprits are **anticonvulsants** and **antibiotics** (eg, beta-lactams). A morbilliform eruption in an adult is usually a drug reaction but in a **pediatric patient** is usually an **infectious exanthem.** Viral or bacterial exanthems must be distinguished from drug reactions by *serologic testing* and by taking a careful history of the *rash onset, sick contacts, drug allergies* and *new medications*.

- **Clinical:** Usually begins 7 to 14 days after drug exposure. The eruption is characterized by **widespread, pink-to-red dot-like** macules and papules, often with **pruritus** and **fever.** The eruption tends to initially appear on the trunk and then spread to the limbs in a **symmetrical pattern.** Morbilliform eruptions are *milder* than EM and SJS/TEN *without* vesicle/bulla formation or mucous membrane involvement.

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical. Complete blood count (CBC) may show leukocytosis and eosinophilia. Skin biopsy showing mild superficial dermal and perivascular inflammation with eosinophils supports the diagnosis.

- **Treatment**
  - **First line:** Avoid and discontinue offending drug +/- topical steroids and antihistamines.
  - **Second line:** Oral steroids.

- **USMLE Pearls:** Patients with **infectious mononucleosis** (EBV or CMV) erroneously treated with **beta-lactam antibiotics (eg, ampicillin)** will develop a **pruritic, maculopapular eruption > 90%** of the time. It occurs 5 to 10 days *after* drug exposure and mainly affects the extensor surfaces. This is an idiosyncratic **hypersensitivity reaction to the drug** and *not* a real drug allergy. Beta-lactam antibiotics can be safely used in these patients after infection resolution.

3. ERYTHEMA MULTIFORME (EM)

- **General:** Drug reaction that is **triggered by infection** 90% of the time. The most common culprits are **herpes simplex virus** (HSV) and ***M. pneumoniae.*** Erythema multiforme (EM) is generally **self-limited,** but may be **recurrent.**

- **Clinical:** Characterized by **"targetoid"** or **"iris-like"** erythematous papules that usually begin on the **palms and soles** or **extremities** and centripetally spread to the trunk. Vesicles may develop in the center of the target lesion. Lesions **do not** involve mucosal surfaces. EM may be accompanied by pruritus and a mild fever.

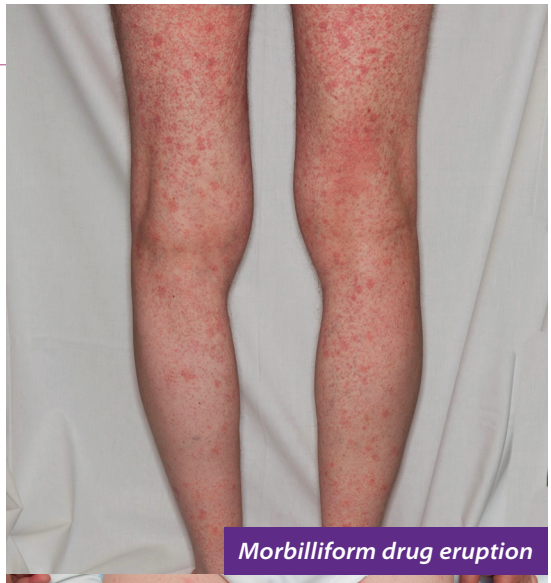
- **Diagnosis**
  - **Best initial test:** Clinical. CBC may show leukocytosis with eosinophilia.
  - **Most accurate test:** Skin biopsy showing degeneration of basal cells with superficial dermal lymphocytic inflammation +/- subepidermal blisters and *upper epidermal necrosis*.

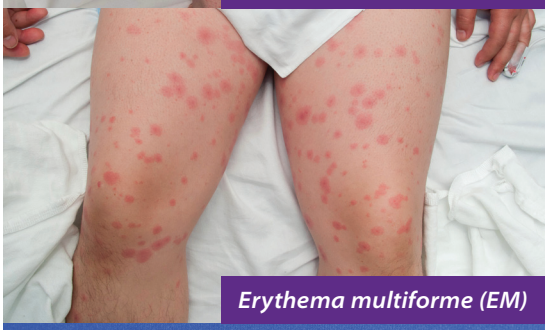
- **Treatment**
  - **First line:** Topical steroids and antihistamines.
  - **Second line:** Prophylaxis with antivirals (eg, acyclovir) or immunosuppression (eg, azathioprine) for recurrent disease.

- **USMLE Pearls:** The main *differences* to distinguish **erythema multiforme** (EM) from SJS/TEN are:
  - EM **does not** have sheets of skin detachment.
  - **Does not** involve mucous membranes.
  - **Rarely** develop bullae or significant systemic symptoms.
  - Eruption begins acrally on **palms and soles.**
  - **Recovery is usually spontaneous** without permanent sequelae.
  - **Younger patients** (median 24 years old) vs. SJS/TEN (median 45 years old).

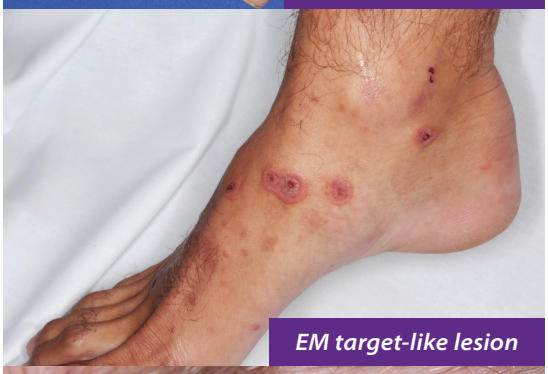
4. STEVENS-JOHNSON SYNDROME (SJS)/ TOXIC EPIDERMAL NECROLYSIS (TEN)

- **General:** Life-threatening **systemic syndrome** that occurs as a reaction to an adverse antigen. The most common identified culprits are **drugs.** However, **GVHD, malignancies, vaccinations, infections**


Morbilliform drug eruption

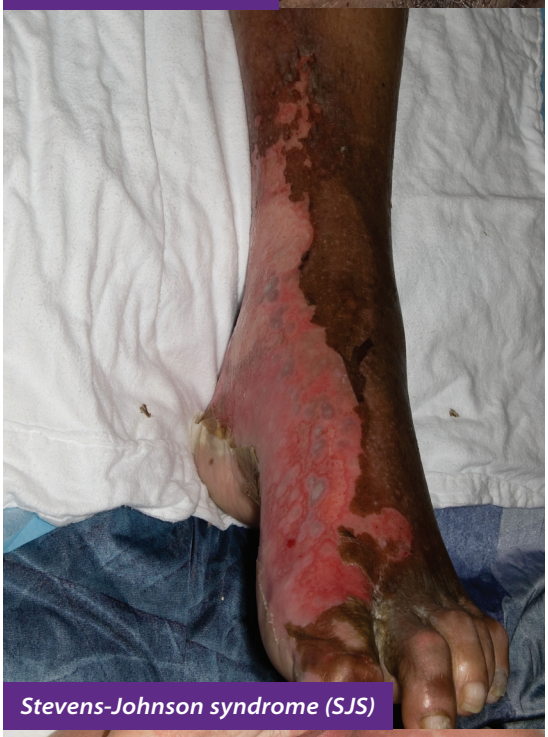

Erythema multiforme (EM)

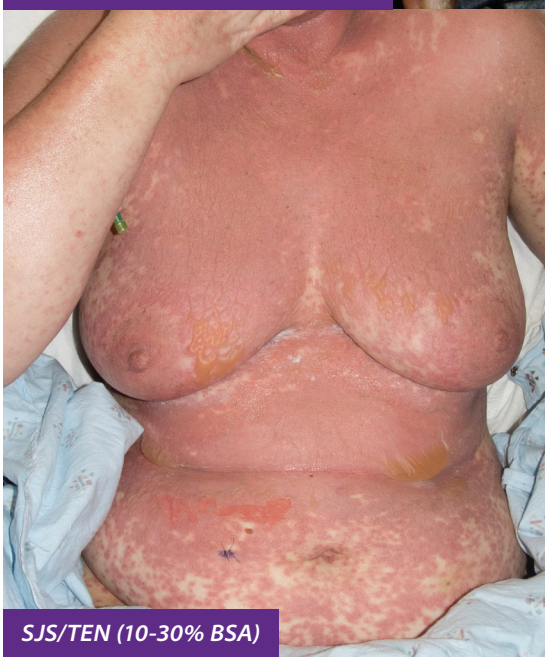

EM target-like lesion


EM target-like lesion


SJS mucositis


SJS mucositis


Stevens-Johnson syndrome (SJS)


SJS/TEN (10-30% BSA)

(eg, *M. pneumoniae*) and **systemic illnesses** can lead to SJS/TEN and morbilliform eruptions. SJS/TEN leads to keratinocyte death and bullae formation by **two different mechanisms:** T-cells release **granzyme B and perforin** directly into keratinocytes *or* release of **Fas ligand** to form the **Fas/Fas-ligand complex** (apoptosis). SJS and TEN are considered a spectrum of the same disease:

- **SJS:** Skin detachment of **< 10%** body surface area (BSA).
- **SJS/TEN overlap:** Skin detachment of **10 to 30%** BSA.
- **TEN:** Skin detachment of **> 30%** BSA.

- **Clinical:** Begins with a flu-like illness and systemic symptoms, followed by a skin eruption days after drug exposure. The eruption is characterized by dusky, **erythematous macules** with or without **skin necrosis** and **extensive bullous skin detachment.** It usually **begins on the trunk** and then spreads to the extremities involving the palms and soles. When bullae rupture, they leave extensive areas of **denuded skin** and **erythematous erosions** with a **hemorrhagic crust.** Classically, manual traction of the skin leads to skin detachment **(positive Nikolsky sign).** Mucous membrane involvement can result in:
  - **Eyes:** Corneal ulcerations, conjunctivitis and blindness.
  - **GI tract:** Inability to eat, diarrhea, GI bleeding and obstruction.
  - **Respiratory tract:** Difficulty breathing and respiratory failure.
  - **Genitourinary tract:** Dysuria, genitourinary bleeding and obstruction and renal failure.

- **Diagnosis**
  - **Best initial test:** Clinical.
  - **Most accurate test:** Skin biopsy showing degeneration of basal cells with minimal dermal and perivascular lymphocytic inflammation + subepidermal blisters and *full-thickness epidermal necrosis*.

- **Treatment**
  - **First line:** Avoid and discontinue offending drug + fluid and electrolytes + analgesics. Patients should be admitted to the *burn unit* for continued monitoring and management (mitigating temperature loss and preventing secondary infections).
  - **Second line:** Intravenous immunoglobulins (IVIG) or plasmapheresis (not proven to improve mortality).

5. WARFARIN-INDUCED SKIN NECROSIS

- **General:** Warfarin works by inhibiting **antithrombotic factors** (protein C and S) and **procoagulant factors** (II, VII, IX and X). The early inhibition of protein C leads to a **transient hyperthrombotic state** in which the patient is vulnerable to **sudden thrombus formation.** During this period, a thrombus big enough may lead to severe ischemia with resultant skin necrosis. Patients with **hereditary protein C deficiency** are prone to developing warfarin-induced skin necrosis.

- **Clinical:** Look for a patient that started warfarin 2 to 5 days prior *without* heparin bridge therapy. The reaction usually begins with **severe pain** on a specific anatomic location and **sharply demarcated erythema,** followed by the rapid development of **purplish skin discoloration** and **extensive skin necrosis.** Common locations include areas of skin with high levels of fat, such as the **breasts, buttocks, thighs** and **abdomen.**

- **Diagnosis**
  - **Best initial test:** Clinical.
  - **Most accurate test:** Skin biopsy showing an occlusive, non-inflammatory thrombosis of dermal vessels with epidermal necrosis.

- **Treatment**
  - **First line:** Discontinue warfarin and administer vitamin K +/- protein C concentrate. Use heparin if anticoagulation is required.
  - **Second line:** Skin grafting for severe necrosis.

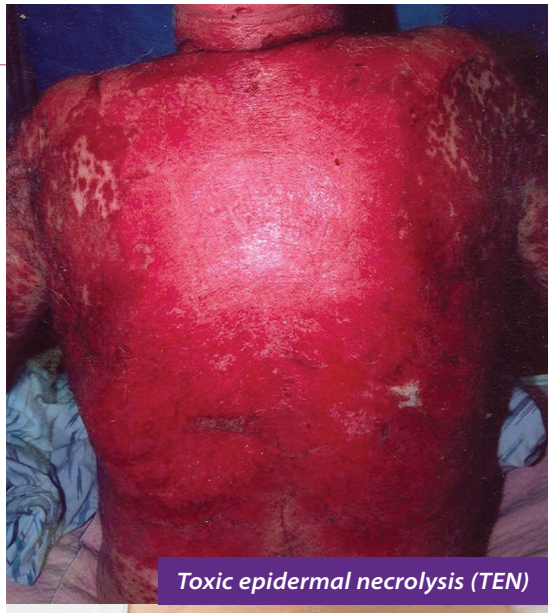
6. DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

- **General:** Fairly rare and potentially life-threatening **drug-induced hypersensitivity syndrome** often involving **extracutaneous organs** (eg, liver, kidney, heart, lungs). The most commonly implicated drugs are **allopurinol** and **anticonvulsants** (eg, phenobarbital, carbamazepine, phenytoin). **Atypical lymphocytes** and marked **peripheral eosinophilia** are often seen. DRESS may be associated with **HHV-6** and **HHV-7.**

- **Clinical:** Symptoms characteristically occur **2 to 6 weeks after** drug exposure. Usually begins with malaise, **high fever, lymphadenopathy** and a **morbilliform eruption,** progressing to a generalized erythematous rash with **follicular accentuation. Symmetric facial edema** is a hallmark of the disease. Other less common skin manifestations are pustules, vesicles, bullae and exfoliation. Severe cases present with **oral and genital swelling** and **internal organ involvement,** most commonly **hepatitis.** Other presentations include **acute interstitial nephritis, pneumonitis,** myocarditis, encephalitis and thyroiditis.

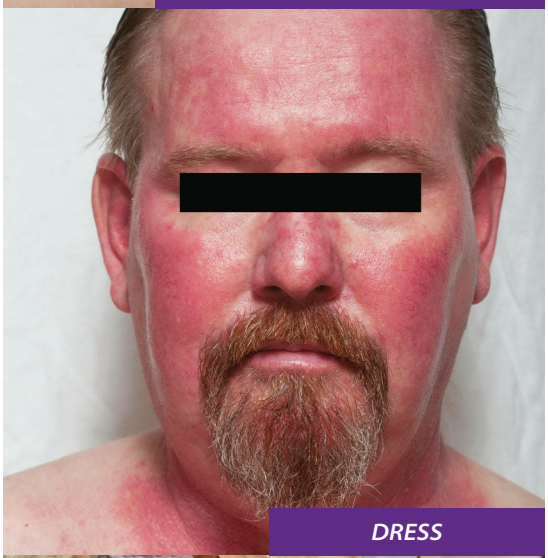
- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + CBC with peripheral smear to detect *peripheral eosinophilia* and *atypical lymphocytes*. Additional tests may be required to investigate internal organ involvement (LFTs, chest x-ray or CT scan, Cr and BUN, echocardiography and TFTs).

- **Treatment**
  - **First line:** Avoid and discontinue offending drug. Topical steroids and antihistamines for mild cases with limited skin involvement. Systemic corticosteroids for extensive skin and/or internal organ involvement.



Toxic epidermal necrolysis (TEN)

Warfarin-induced skin necrosis



DRESS

DRESS

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Chapter 9

ECZEMA (DERMATITIS)

Eczema is also called *dermatitis;* both terms are often used interchangeably. Eczema refers to a common group of skin disorders characterized by **skin inflammation** with associated **pruritus.** *Histopathologically,* eczema is characterized by **epidermal intercellular edema** (spongiosis) with **dermal inflammation** (dermatitis). If there is sufficient edema, vesicles or bullae will develop. This **"spongiotic dermatitis"** tissue reaction pattern is **not specific** to eczema and can be seen in other skin disorders. **Skin biopsies** are generally used to support the clinical diagnosis and exclude other pathologies. **Swab cultures, KOH prep** and **HSV PCR** are important additional tests used to rule out secondary bacterial, fungal and viral infections. **Treatment** is usually with moisturizers and steroids. *Clinically* and *histologically,* eczema can be divided as follows:

- **Acute eczema:** *Clinically* presents with **weeping (oozing), erythematous, swollen and pruritic** papules and plaques with or without **vesiculation.** *Histologically,* there is moderate to severe intercellular edema, often with intraepidermal vesicles and prominent dermal inflammation **(acute spongiotic dermatitis).**

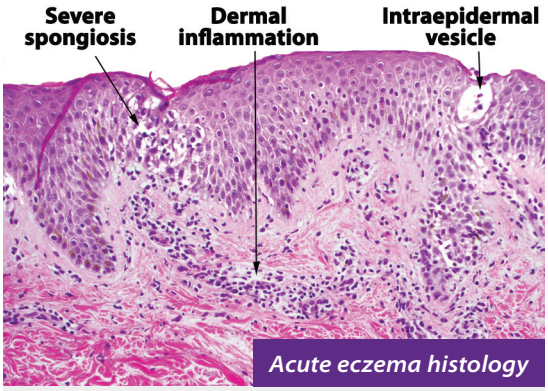
- **Subacute eczema:** In between state that *clinically* presents with **pruritic, scaly and crusted** papules and plaques with mild to moderate **erythema and edema.** Excoriations are common. *Histologically,* there is parakeratosis with mild to moderate spongiosis and dermal inflammation **(subacute spongiotic dermatitis).**

- **Chronic eczema:** *Clinically* presents with **thickened, dyspigmented, dry skin,** often **lichenified and fissured** from chronic rubbing and scratching. Generally, there is mild to absent erythema and edema and no vesiculation. *Histologically,* the epidermis is thickened (acanthotic and hyperkeratotic) with minimal to absent spongiosis and subtle dermal inflammation **(chronic spongiotic dermatitis).**

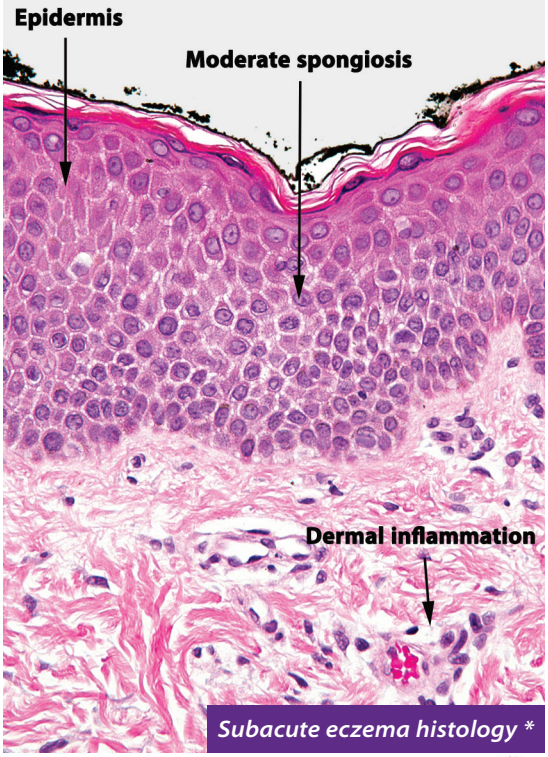
1. ATOPIC DERMATITIS (AD)

- **General:** Most common chronic inflammatory disorder of the skin. Etiology is unknown and many mechanisms have been proposed; recent evidence points to a **dysfunctional skin barrier and immune response** as being key abnormalities. Atopic dermatitis characteristically develops *before* age 5 and subsides by adulthood, but there are many exceptions. It generally follows a **chronic and relapsing course** and is associated with:
  - **Personal and family history of atopy** (eg, asthma, hay fever, allergic rhinitis, urticaria, food allergies).
  - **Frequent skin infections** (eg, molluscum contagiosum, impetigo, eczema herpeticum).

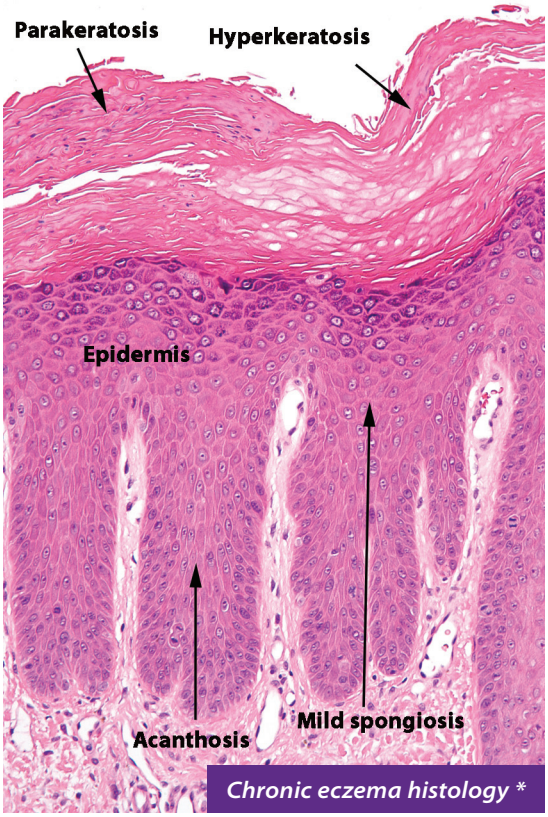
- **Clinical:** Typically varies depending on the patient's age. Postinflammatory hyper- or hypopigmentation and exfoliative erythroderma may occur at any age.
  - **Infancy AD (< 2 years old):** Characterized by acute and subacute eczematous lesions involving the **face (cheeks) and neck** and less commonly the extensor surface of trunk and extremities. The centrofacial and diaper areas are usually spared.



Acute eczema histology

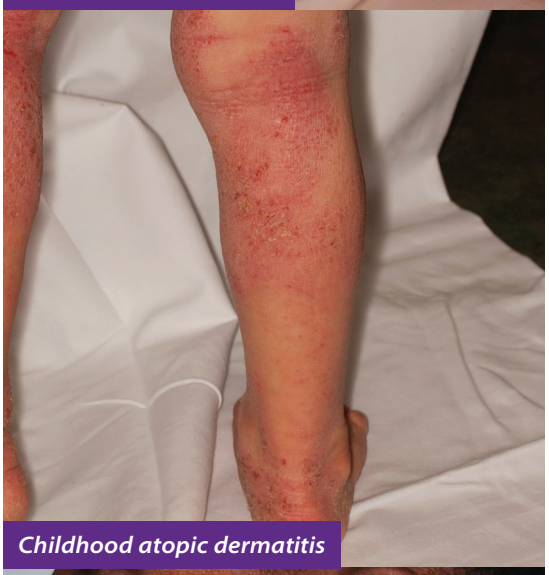


*Subacute eczema histology **

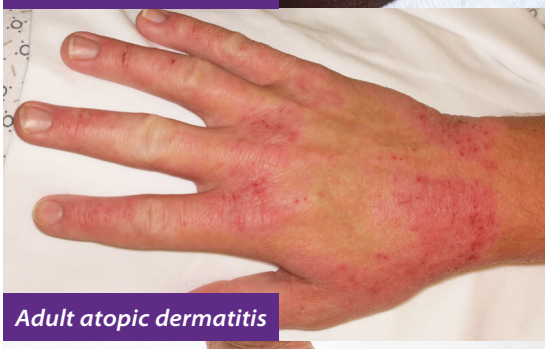


*Chronic eczema histology **


Infant atopic dermatitis


Childhood atopic dermatitis


Pityriasis alba


Adult atopic dermatitis


Atopic dermatitis erythroderma


Lichen simplex chronicus

- **Childhood AD (2 to 12 years old):** Characterized by subacute and chronic eczematous lesions involving the **antecubital and popliteal fossae, perioral and periorbital areas** and **distal extremities** (hands, wrists, ankles and feet). Hypopigmented macules and patches known as **pityriasis alba** are commonly seen on the face and extremities.
- **Adolescent and adult AD (> 12 years old):** Presents similar to childhood atopic dermatitis but with more prominent **eyelid, neck, chest and hand** involvement. Skin is **lichenified, fissured and dry.**

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical. Labs may show high IgE and eosinophilia. Skin biopsy showing acute, subacute or chronic spongiotic dermatitis with occasional eosinophils supports the diagnosis.

- **Treatment**
  - **First line:** Emollients + topical steroids. Oral antihistamines are useful to control pruritus. Cotton clothes are preferred and should be washed with mild detergents.
  - **Second line:** Topical calcineurin inhibitors (tacrolimus or pimecrolimus). Consider phototherapy, methotrexate, mycophenolate mofetil or cyclosporine for recalcitrant or severe disease.

- **USMLE Pearls: Lichen Simplex Chronicus (LSC):** Also known as **neurodermatitis,** it is a secondary process characterized by **thickening, roughening** and **white-to-gray scaling** of the skin due to chronic scratching or rubbing. The skin is often hyperpigmented with prominent white skin markings resembling **"tree bark."** Generally presents in patients with **chronic pruritic disorders** such as atopic and contact dermatitis. Associated with **chronic anxiety** and other **psychiatric conditions.** *Treat* by identifying and controlling the underlying condition and topical steroids.

2. ALLERGIC CONTACT DERMATITIS (ACD)

- **General:** Characterized by a **delayed hypersensitivity reaction** to small antigens penetrating the stratum corneum. Langerhans cells capture these antigens and migrate to nearest lymph nodes to present them to naïve T-cells. Effector T-cells are activated and **proinflammatory cytokines** are released at the site of initial antigen encounter. This initial antigen sensitization may take **1 to 2 weeks** to occur, but on re-exposure, the reaction tends to be *faster* (hours to days) and *more severe*.

- **Clinical:** Presents with acute, subacute and chronic eczematous lesions at sites where the skin comes in contact with the allergen. The dermatitis pattern generally depends on the type of allergen encountered.
  - **Nickel:** Characterized by acute and subacute eczematous lesions **resembling the shape and pattern** of a nickel-containing object or *jewelry*. Commonly occurs at the site of earrings, necklaces, buttons or objects in pockets.
  - **Urushiol:** Oily organic resin found in *poison ivy, poison oak* and *poison sumac*. The classic presentation is **linear streaks of acute eczematous lesions** on the extremities where the skin was in contact with the plant (allergen). The patient history may reveal a recent exposure to one of the above-mentioned poisons during **gardening, camping, hiking** or other outdoor activities.

- **Latex and rubber:** Used in *gloves, shoes, condoms* and *objects*. The classic presentation is **hand or foot dermatitis** after using rubber-containing gloves or shoes. Allergy to latex is most often immediate with contact urticaria and/or anaphylaxis; occurs less frequently as the amount of latex in rubber gloves has been decreased in recent years.
- **Formaldehyde and preservatives:** Found in *cosmetics, shampoos, sunscreens, perfumes* and *lotions*. The dermatitis is usually manifested on the face, body and hands.
- **P-Phenylenediamine (PPD):** Found in *hair dye* and *temporary tattoos*. Manifested with acute and subacute dermatitis in the location of a tattoo or in skin that was in contact with hair dye (scalp, adjoining face, neck and ears).
- **Medications:** Usual culprits are *topical antibiotics* (bacitracin and neomycin) and less frequently, *topical steroids*. Classically presents with acute and subacute eczematous lesions in a patient using one of these medications for **atopic or stasis dermatitis.** These patients will have exacerbation of pre-existing skin lesions and delayed healing secondary to superimposed contact dermatitis.

- **Diagnosis**
  - **Best initial test:** Clinical. Patients often self-diagnose as they relate the skin lesions with a specific allergen. Biopsy showing acute, subacute or chronic spongiotic dermatitis with occasional eosinophils supports the diagnosis.
  - **Most accurate test:** Patch testing.

- **Treatment**
  - **First line:** Identification and avoidance of allergen (diagnostic and therapeutic) + topical steroids. Consider oral antihistamines for pruritus.
  - **Second line:** Oral steroids for recalcitrant or severe disease.

3. IRRITANT CONTACT DERMATITIS (ICD)

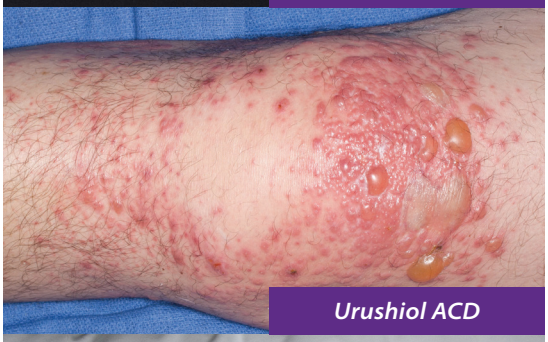
- **General:** Major occupational inflammatory skin disorder produced by the direct **cytotoxic effect of chemicals** and other physical agents on the skin. The most common culprits are:
  - **Water:** Excessive hand washing (eg, healthcare workers)
  - **Solvents, acids** and **alkali chemicals**
  - **Laundry detergents** and **soaps**
  - **Stool and urine** (diaper dermatitis; does not involve skin folds)

- **Clinical:** Typically manifested by **painful (burning),** acute eczematous lesions with or without **ulceration** and **necrosis.** The reaction tends to occur within **minutes to hours** after exposure to irritant, even on first encounter (not a delayed-hypersensitivity). May also present with chronic eczematous lesions from repeated exposure to irritant. ICD occurs most frequently on the **hands;** inflammation usually ceases after removal of irritant.

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical. Skin biopsy showing acute, subacute or chronic spongiotic dermatitis +/- epidermal cell necrosis supports the diagnosis.

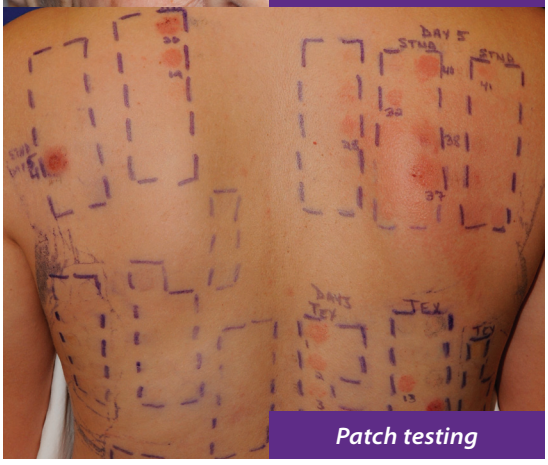

Nickel ACD


Urushiol ACD


Urushiol ACD

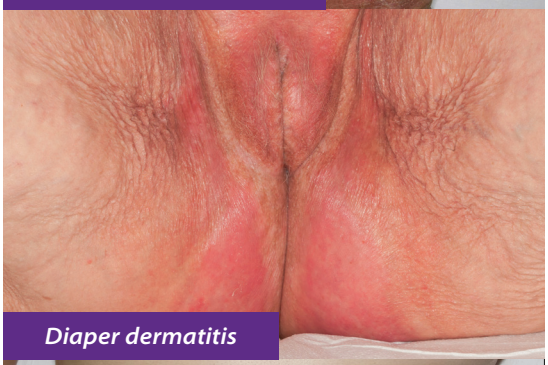

Rubber ACD

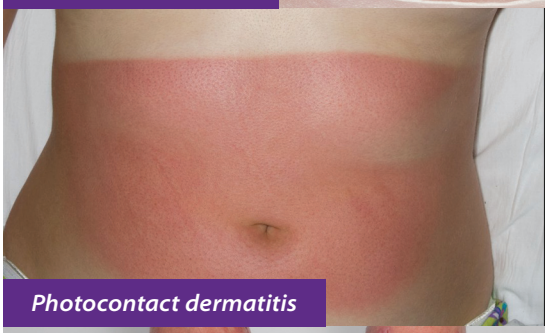

Cosmetic ACD

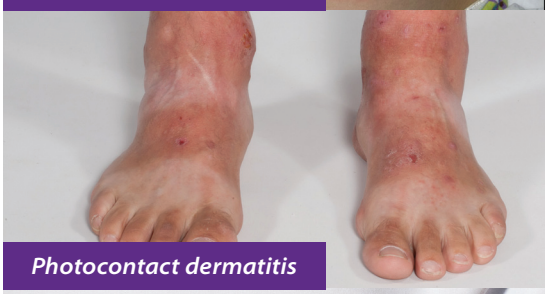

Patch testing


Irritant contact dermatitis


Irritant contact dermatitis


Diaper dermatitis


Photocontact dermatitis


Photocontact dermatitis


Polymorphous light eruption

- **Treatment**
  - **First line:** Identification and avoidance of causal irritant (diagnostic and therapeutic) + emollients.
  - **Second line:** Topical steroids.

4. PHOTOCONTACT DERMATITIS

- **General:** Divided into *phototoxic* and *photoallergic reactions*.
  - **Phototoxic reaction:** Direct tissue or cellular damage caused by UV-light-activated drug metabolites. The reaction may occur on **first encounter** to drug + UV-light; it usually develops within **minutes to hours.** Common offending drugs are **griseofulvin, voriconazole, diuretics, NSAIDS, quinolones, sulfonamides** and **tetracyclines.**
  - **Photoallergic reaction:** UV-light-activated drug acts as a skin antigen leading to a *delayed-type hypersensitivity.* **Re-exposure** to the antigen is **required** for photoallergic reactions to occur; they usually develop within **24 to 72 hours.** Common offending drugs are **sulfonamides, griseofulvin, quinidine, NSAIDS, quinolones** and **topical agents** (eg, sunscreens, fragrances, NSAIDS).

- **Clinical: Phototoxic reactions** burn or sting and resemble exaggerated sunburn; they may heal with desquamation and hyperpigmentation. **Photoallergic reactions** are pruritic and eczematous, with occasional vesiculation. Both occur on sun-exposed areas (face, chest and extremities).

- **Diagnosis**
  - **Best initial test:** Clinical. Biopsy showing acute or subacute spongiotic dermatitis supports the diagnosis.
  - **Most accurate test:** *Photo*patch testing.

- **Treatment**
  - **First line:** Identification and avoidance of offending drug and UV-light + topical steroids and cool compresses.
  - **Second line:** Oral steroids for severe cases.

- **USMLE Pearls: Polymorphous Light Eruption (PMLE):** Different than photocontact dermatitis, it is also referred to as **"sun allergy"** or **"sun poisoning."** PMLE is the *most common* idiopathic photodermatosis, affecting approximately 10% of normal individuals. Characterized by erythematous and pruritic papules, plaques and vesicles developing **within minutes to hours** after UV-light exposure, especially during **summer.** Decreased light sensitization may occur after repeated exposures **(hardening).** *Treat* with photoprotection +/- topical or oral steroids.

5. SEBORRHEIC DERMATITIS (SD)

- **General:** Common chronic and relapsing inflammatory skin disorder that predominantly affects areas **rich in sebaceous glands** (seborrheic distribution) and **body folds.** It is associated with the fungi ***Malassezia furfur*** (formerly known as *Pityrosporum ovale*). Lesions are exacerbated by **stress, immunosuppression** and **humidity.** Severe disease may be associated with **Parkinson disease, HIV infection** and **mood disorders.**

- **Clinical**
  - **Adults:** Characterized by skin inflammation and pruritus with **yellow, flaky, "greasy" scales.** Most commonly affects the **scalp, face** (ears, eyebrows, eyelids, forehead and nasal crease), **chest** and **axillae.** Milder disease presents with **dandruff** of the scalp and other hair-bearing areas (eg, beard). Inflammation of the eyelid commonly occurs **(seborrheic blepharitis).**
  - **Infants:** May affect the **diaper area** and present with acute eczematous lesions *involving* the **inguinal folds.** May coexist with seborrheic dermatitis in other parts of the body (eg, face, retroauricular area and axillae). Often confused with *candidal diaper rash*.
  - **Newborns:** The characteristic lesion is **"cradle cap,"** a **thick, yellow, greasy crust** over the scalp area. May also present in infants.

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical. Skin biopsy showing acute, subacute or chronic spongiotic dermatitis supports the diagnosis. Consider HIV testing in severe and recalcitrant seborrheic dermatitis.

- **Treatment**
  - **First line:** Topical antifungal creams or shampoos such as *zinc pyrithione, ketoconazole, ciclopirox* or *selenium sulfide*. Consider short-term topical steroids for acutely inflamed lesions.
  - **Second line:** Oral antifungals (eg, itraconazole or terbinafine) for recalcitrant or severe disease.

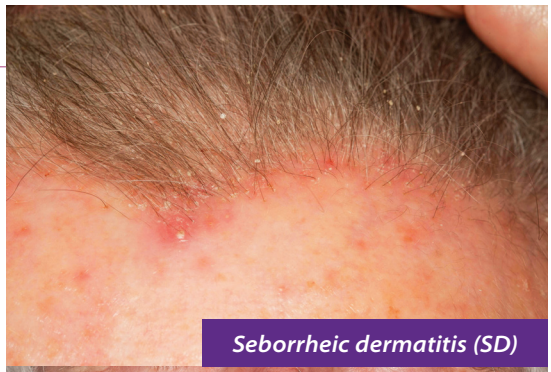
6. DYSHIDROTIC ECZEMA

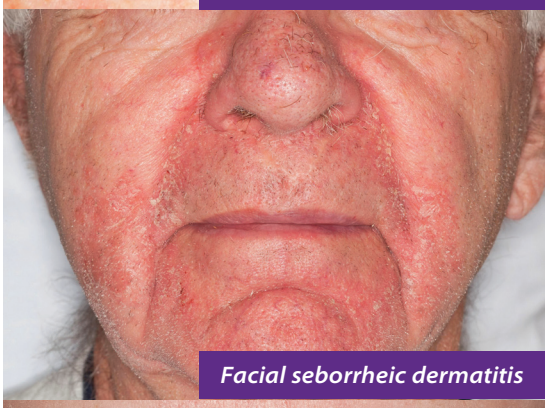
- **General:** Also known as **dyshidrosis** or **pompholyx,** a type of eczema characterized by a **relapsing vesicular eruption** limited to the **hands and feet,** particularly the palmoplantar aspect. The pathogenesis is unknown; however, **hyperhidrosis** exacerbates the disease. Dyshidrotic eczema is associated with:
  - **Family history of atopy** (eg, atopic dermatitis)
  - **Contact dermatitis**
  - **Intravenous immunoglobulin** (IVIG) treatment

- **Clinical:** Characterized by crops of **pruritic, deep-seated, firm** vesicles or bullae on the **palms, soles** and lateral aspects of **fingers and toes.** Outbreaks may occur in waves and usually resolve spontaneously in 2 to 4 weeks.

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical. Skin biopsy showing spongiotic dermatitis with intraepidermal vesicles supports the diagnosis.

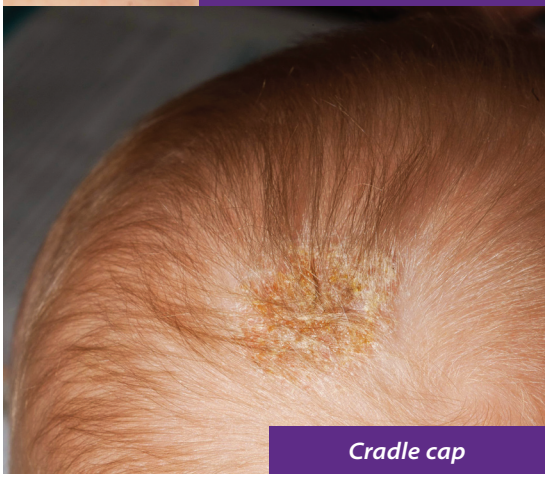
- **Treatment**
  - **First line:** Topical steroids and cool compresses. Consider oral antihistamines for pruritus.
  - **Second line:** Phototherapy or oral steroids for severe flares and recalcitrant disease.

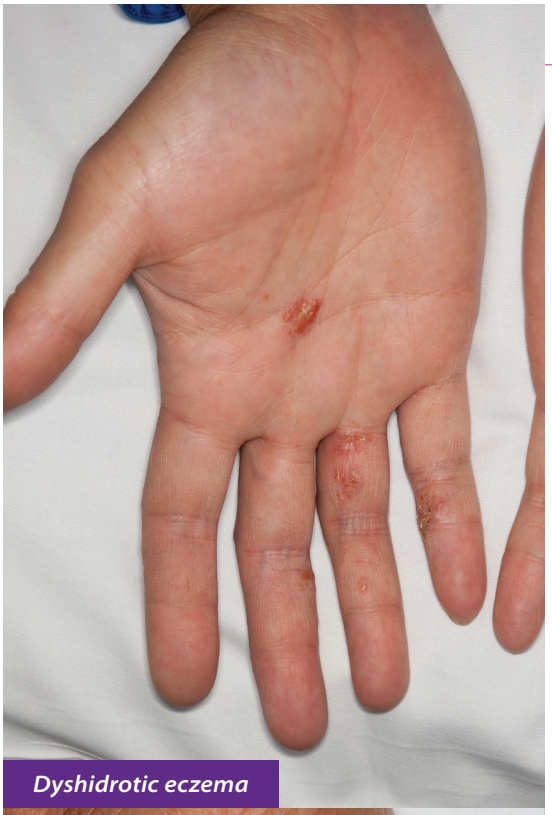

Seborrheic dermatitis (SD)

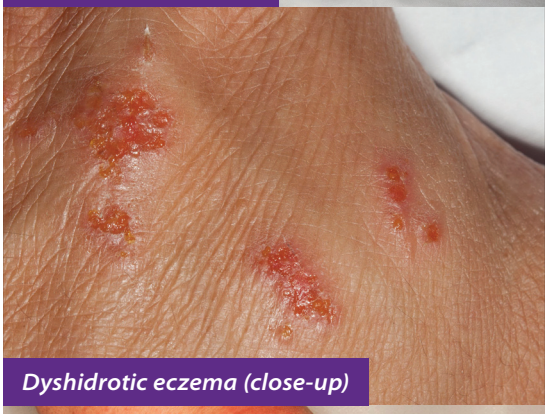

Facial seborrheic dermatitis

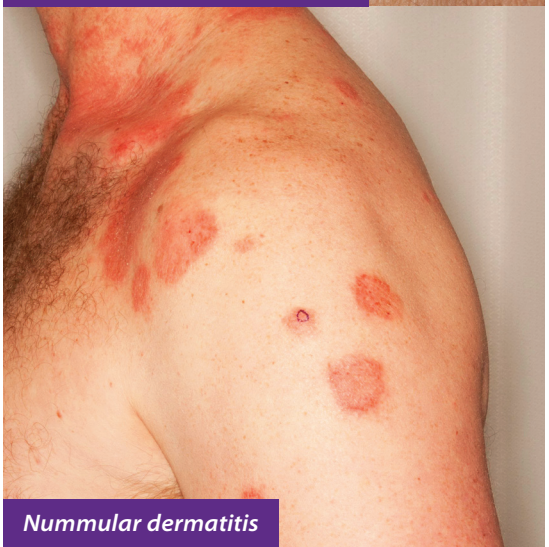

Seborrheic blepharitis

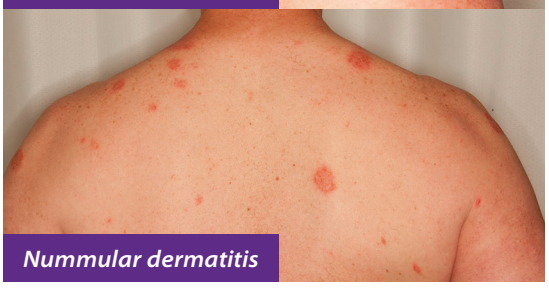

Infant seborrheic dermatitis


Cradle cap


Dyshidrotic eczema


Dyshidrotic eczema (close-up)


Nummular dermatitis


Nummular dermatitis

7. NUMMULAR DERMATITIS

- **General:** Also known as **discoid eczema,** a chronic relapsing form of eczema characterized by **"coin-shaped"** lesions. Nummular dermatitis is more common in adults during the **third to sixth decade** of life and rarely occurs in children. Lesions improve in humid and warm climate. Nummular dermatitis is associated with:
  - **Asthma, atopic dermatitis** and **contact dermatitis**
  - **Xerosis** (dry climate and winter)

- **Clinical:** Characterized by **well-demarcated, round (discoid)** and **intensely pruritic** acute or chronic eczematous scaly plaques ranging from 1 to 4 cm in diameter. **Plaques may have central clearing** and be indistinguishable from tinea corporis. Lesions are most commonly located on the **legs and arms** and usually *spare* the face and scalp. Nummular dermatitis may spontaneously regress and later recur in the same location.

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical. Consider patch testing to exclude contact dermatitis. Skin biopsy showing acute, subacute or chronic spongiotic dermatitis supports the diagnosis.

- **Treatment**
  - **First line:** Emollients + topical steroids or calcineurin inhibitors (eg, tacrolimus).
  - **Second line:** Phototherapy or oral steroids for recalcitrant or severe disease.

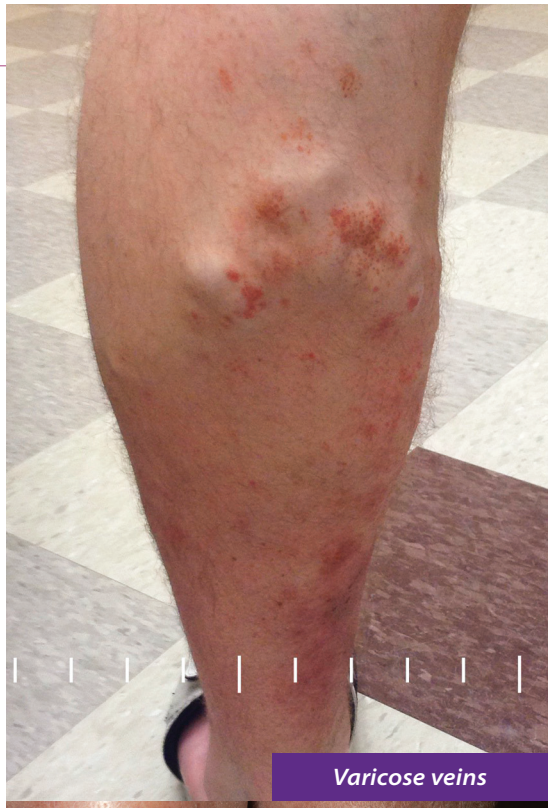
8. STASIS DERMATITIS

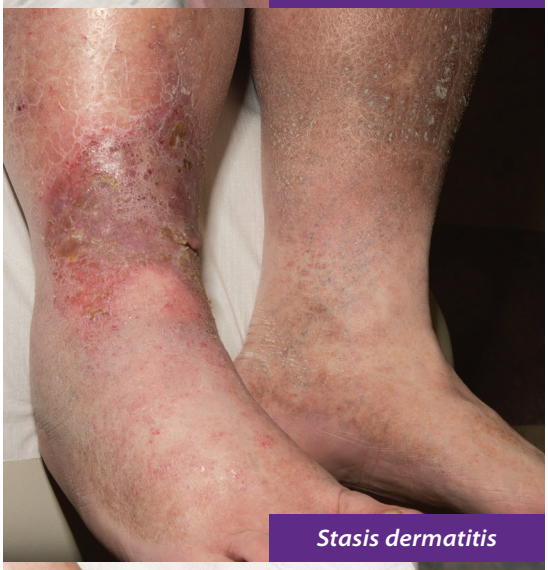
- **General:** Common chronic inflammatory skin disorder mainly affecting the **lower extremities.** Stasis dermatitis is multifactorial and multiple mechanisms have been proposed; **venous hypertension** of the lower extremities secondary to **deep venous valvular insufficiency** is usually the initiating factor. Complications include **infections** (eg, cellulitis), **venous leg ulcerations** and **lipodermatosclerosis.**

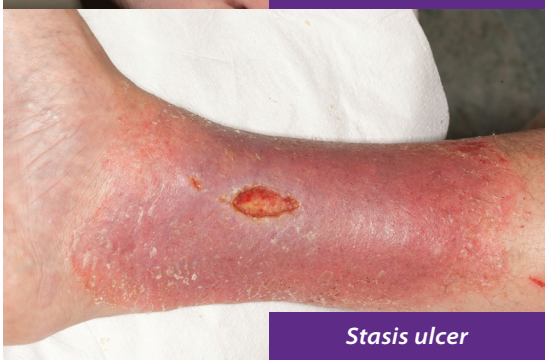
- **Clinical:** Characterized by acute, subacute and chronic eczematous patches and plaques on the distal lower extremities, particularly the medial aspect. **Hyperpigmentation** secondary to hemosiderin deposition and **varicose veins** are commonly seen. Common exacerbating factors include: **chronic deep venous thrombosis** (DVT), **heart failure, pregnancy** and **prolonged periods of standing.**

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical. Consider blood tests and Doppler ultrasonography of the lower extremity to rule out infections and DVT, respectively. Skin biopsy showing acute, subacute or chronic spongiotic dermatitis +/- dilated capillaries and hemosiderin deposition supports the diagnosis.

- **Treatment**
  - **First line:** Emollients + lifestyle modifications (eg, compression stockings or dressings, leg elevation and avoiding prolonged periods of standing). Gentle skin cleansing helps prevent secondary infections.
  - **Second line:** Short-term topical steroids for acutely inflamed lesions. Consider oral or topical antibiotics (eg, mupirocin) for secondary infections (impetiginization).


Varicose veins


Stasis dermatitis


Stasis ulcer

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Chapter 10

INFLAMMATORY DISORDERS OF THE SKIN

1. LICHEN PLANUS (LP)

- **General:** Common papulosquamous inflammatory dermatosis of unknown etiology. Lichen planus slightly increases the risk for developing **squamous cell carcinoma (SCC)** and is associated with **hepatitis C virus (HCV) infection** and **primary biliary cirrhosis.** If it occurs in the scalp, it is called **lichen planopilaris** and may cause **scarring alopecia.** LP lesions are mainly characterized by the **five Ps:**
  - **Papules (or plaques)**
  - **Purple**
  - **Polygonal**
  - **Pruritic**
  - **Peripheral (extremities)**

- **Clinical: Pruritic, scaly** and **violaceous flat-topped** papules or plaques most commonly located in the **oral cavity,** distal extremities **(wrists and ankles)** and **genitals.** Papules often have fine, white lines in a "net-like" or reticular pattern known as **Wickham striae. Nail involvement** most commonly presents with ridging, grooving and color changes. LP may develop secondary to trauma such as scratching (Koebner phenomenon). Lesions may spontaneously regress within a year and recur later in life.

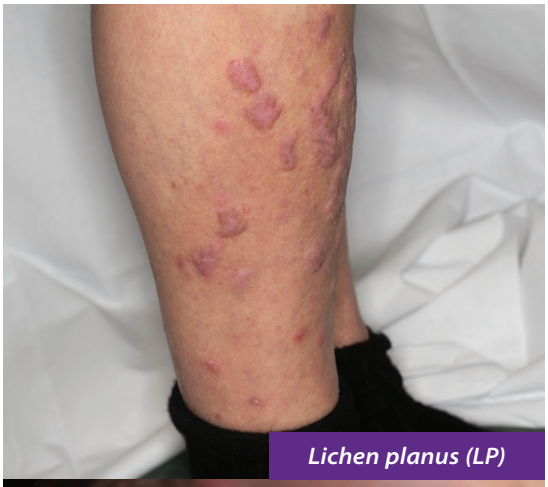
- **Diagnosis**
  - **Best initial test:** Clinical. In patients with widespread disease or risk factors for HCV infection, order hepatitis C serology.
  - **Most accurate test:** Skin biopsy showing a band-like (lichenoid) lymphocytic infiltrate in the upper dermis with degeneration of epidermal basal cells.

- **Treatment**
  - **First line:** Topical or intralesional steroids.
  - **Second line:** Topical calcineurin inhibitors such as tacrolimus or pimecrolimus. Consider oral steroids, oral retinoids (acitretin), mycophenolate mofetil or phototherapy for recalcitrant or severe disease.

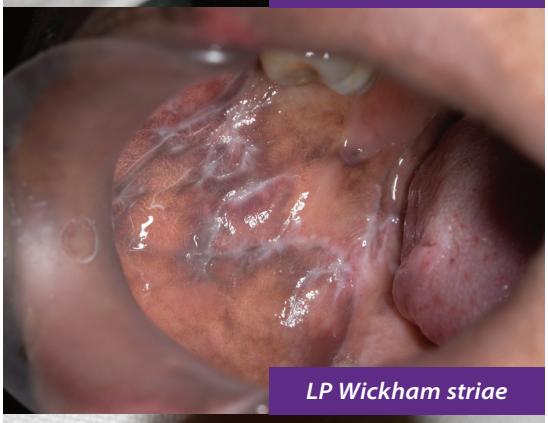
2. LICHEN SCLEROSUS (LS)

- **General:** Female-predominant, chronic inflammatory dermatosis of unknown etiology. Lichen sclerosus mainly affects the anogenital skin of prepubertal girls, **postmenopausal women** or **uncircumcised males,** less commonly can occur on nongenital skin (extragenital LS). Slight increased risk for developing **squamous cell carcinoma (SCC)** in genital LS.

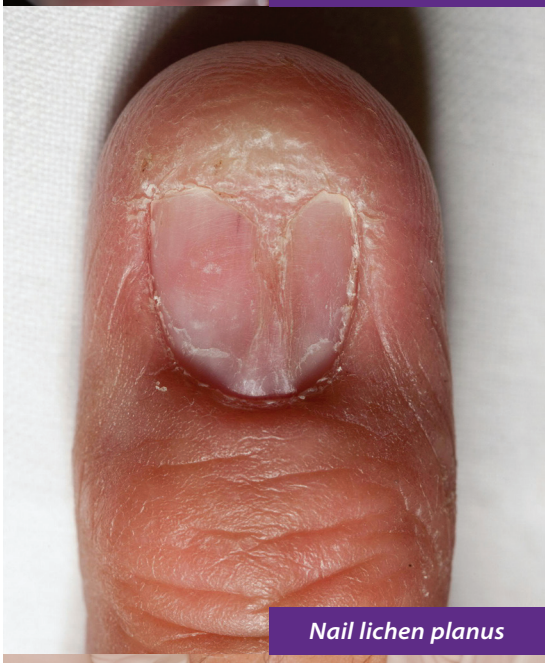
- **Clinical:** Characterized by **thin, atrophic, shiny white** papules and plaques that are often **intensely pruritic.** Genital LS commonly assumes an **"hourglass"** or **"keyhole"** pattern by involving the genital and perianal area simultaneously. Hemorrhagic lesions can be seen and mistaken for **child sexual abuse.** Chronic LS may cause adhesions and scarring and lead to **dysuria, anogenital bleeding, dyspareunia, phimosis** and **genitourinary obstruction.** Differential diagnosis in females includes *atrophic vaginitis,* which also presents with atrophic genital skin, pruritus and dyspareunia; this responds to topical estrogens.



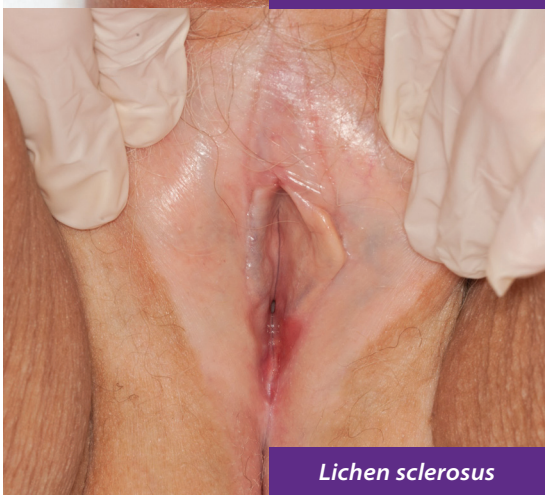
Lichen planus (LP)



LP Wickham striae

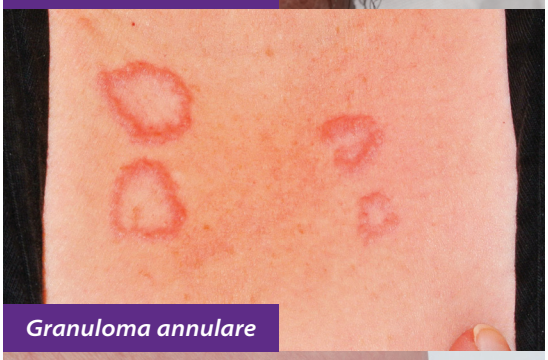


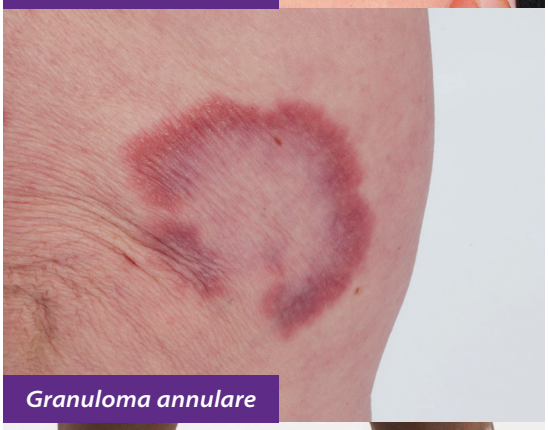
Nail lichen planus

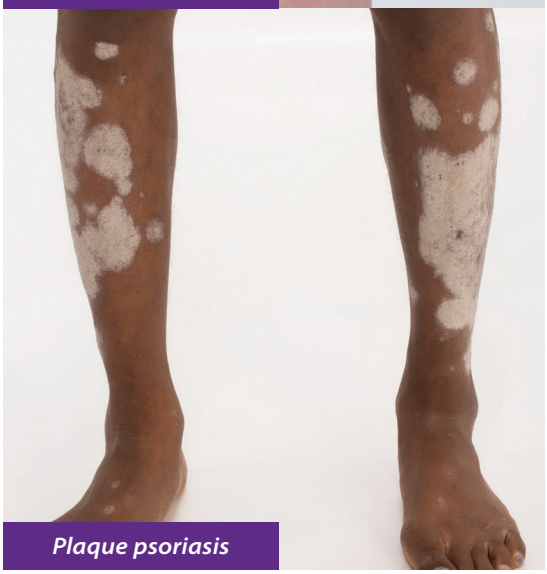


Lichen sclerosus


Lichen sclerosus


Granuloma annulare


Granuloma annulare


Plaque psoriasis

- **Diagnosis**
  - **Best initial test:** Clinical.
  - **Most accurate test:** Skin biopsy showing a thinned epidermis and an edematous and sclerotic papillary dermis with a chronic inflammatory infiltrate beneath.

- **Treatment**
  - **First line:** Potent topical steroids (eg, clobetasol or halobetasol); lubricants may be helpful for dyspareunia.
  - **Second line:** Topical tacrolimus, oral acitretin or phototherapy; circumcision in males may be effective in selected patients.

3. GRANULOMA ANNULARE (GA)

- **General:** Common benign inflammatory dermatosis of unknown etiology. GA affects all age groups and is more common in females. Generalized form may be associated with **dyslipidemia** and **diabetes.**

- **Clinical:** Most commonly presents with localized, small, erythematous papules arranged in a **semi-lunar or annular** configuration. Papules can vary from flesh-colored to reddish-purple. The *center* of the ring-shaped lesion may be **clear, erythematous** or **hyperpigmented.** GA most commonly affects the **dorsal part of distal extremities,** but can occur almost anywhere.

- **Diagnosis**
  - **Best initial test:** Clinical.
  - **Most accurate test:** Skin biopsy showing lymphocytes and histiocytes surrounding a focus of degenerated dermal collagen.

- **Treatment**
  - **First line:** Reassurance. GA tends to resolve spontaneously in weeks to months. Consider potent topical or intralesional steroids for persistent lesions (> 2 years) or cosmetics.
  - **Second line:** Phototherapy, dapsone or isotretinoin for generalized disease.

4. PSORIASIS

- **General:** Chronic relapsing and remitting papulosquamous dermatosis affecting 1 to 3% of the world population. Psoriasis is multifactorial and complex. Overproduction of **inflammatory cytokines** such as **TNF-α, IFN-γ** and **IL-12** may play an important role in pathogenesis. There is a strong genetic HLA relationship and heritability. Psoriasis may be associated with:
  - **Streptococcal infection** (guttate type psoriasis)
  - **HIV infection** (sudden onset and severe psoriasis)
  - **Drugs** (**lithium,** β-blockers, antimalarials and NSAIDs)
  - **Alcoholism, smoking** and **metabolic syndrome**

- **Clinical:** Characterized by **well-demarcated, salmon-colored** papules and plaques commonly covered by adherent **white-to-silvery scales.** The appearance of pinpoint areas of bleeding when scales are scraped off is known as the **Auspitz sign.** Skin lesions may develop at sites of trauma (Koebner phenomenon). Common type of psoriasis are:

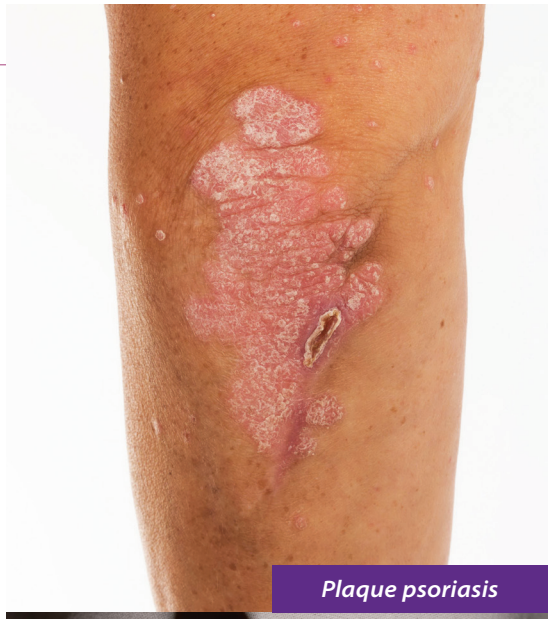
- **Plaque psoriasis:** Most common form of psoriasis. Characterized by symmetrically distributed plaques of different shapes and sizes mainly located on the **scalp** and **extensor surface** of the trunk, knees and elbows. **Psoriatic arthritis** or **nail psoriasis** may precede skin manifestations and be the only sign of psoriasis.
- **Psoriatic arthritis:** Seronegative spondyloarthropathy manifesting with **tender** and **inflamed joints, sacroiliitis, spondylitis** and **dactylitis** ("sausage digits"). **"Pencil-in-cup" deformity** on hand x-ray is typical.
- **Nail psoriasis:** Most commonly presents with **nail pitting** and loosening or separation **(onycholysis).** May manifest as **yellow-brown, thickened** nails that are indistinguishable from onychomycosis.
- **Guttate psoriasis:** Sudden appearance of **multiple, small** and **circumscribed** erythematous papules with silvery scales resembling **"drops."** Guttate psoriasis may occur after **streptococcal infection** (eg, pharyngitis or tonsillitis); treatment of infection may hasten resolution of psoriasis.
- **Inverse psoriasis:** Characterized by **smooth and inflamed erythematous** lesions *with minimal or absent scales*. Lesions are located on **flexural** or **intertriginous areas** (eg, axillae, groin, intergluteal, inframammary). **Differential diagnosis** include: candidal intertrigo, erythrasma, tinea cruris and seborrheic dermatitis.

- **Diagnosis**
  - **Best initial test:** Clinical. Rheumatoid factor (RF) may aid in differentiating rheumatoid arthritis (RA) from *seronegative* psoriatic arthritis. Test for tuberculosis with PPD before starting anti-TNF-α inhibitors.
  - **Most accurate test:** Skin biopsy showing epidermal hyperplasia and parakeratosis, thinned dermal suprapapillary plates with vessels extending proximal to the epidermis and a neutrophilic collection in the stratum corneum **(Munro microabscesses).**

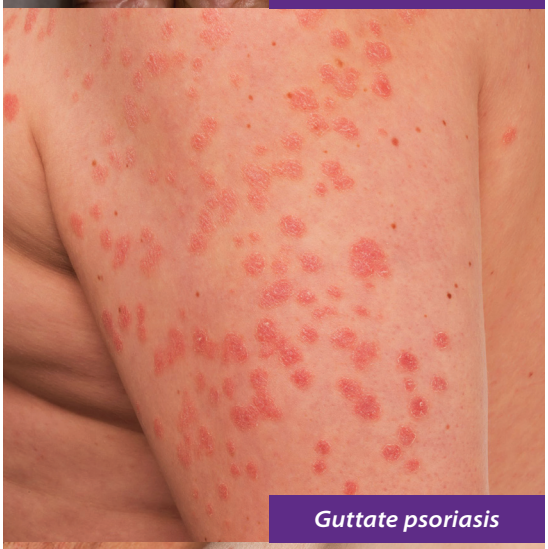
- **Treatment**
  - **First line:** Avoid smoking, alcohol, lithium, β-blockers and antimalarials.
    - **Mild-to-moderate disease (< 10% BSA):** Emollients + topical steroids often combined with *topical vitamin D analogues* (eg, calcipotriene) or *retinoids* (eg, tazarotene). Topical calcineurin inhibitors, coal tar and salicylic acid are alternatives.
    - **Moderate-to-severe disease (> 10% BSA):** Phototherapy (eg, PUVA) or systemic therapy with methotrexate, anti-TNF-α inhibitors (eg, adalimumab, etanercept, infliximab), cyclosporine, retinoids (eg, acitretin) or anti-IL-12/23 (eg, ustekinumab).

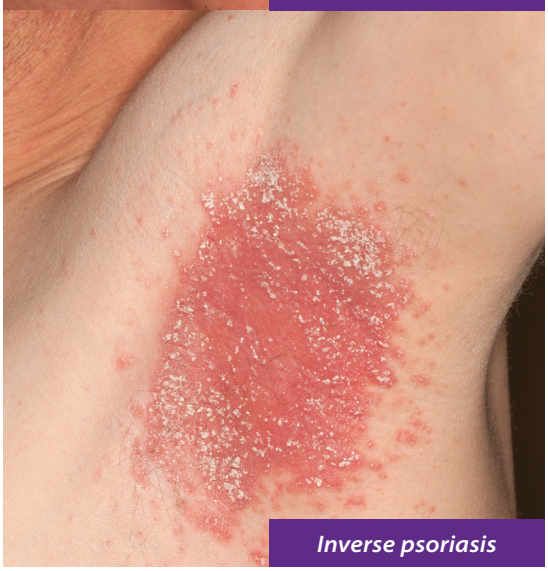
5. PITYRIASIS ROSEA

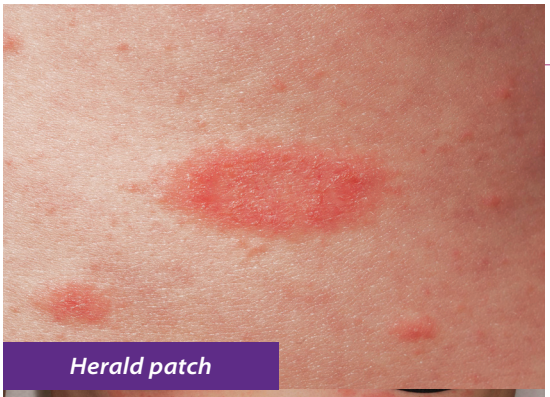
- **General:** Acute papulosquamous inflammatory dermatosis of unknown etiology. The eruption **usually follows a prodrome** of fever, headache, malaise, pharyngitis and lymphadenopathy such as an **upper respiratory tract infection (URTI).** Pityriasis rosea is more common in teenagers and young adults. The eruption is generally **self-limited,** resolving in 4 to 8 weeks. May be associated with ***Human herpesvirus-6*** **(HHV-6)** and **HHV-7.**

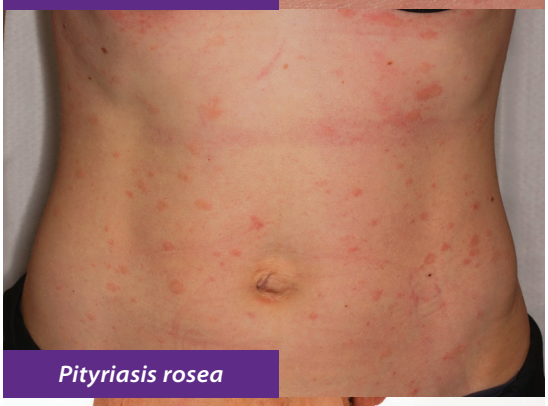

Plaque psoriasis

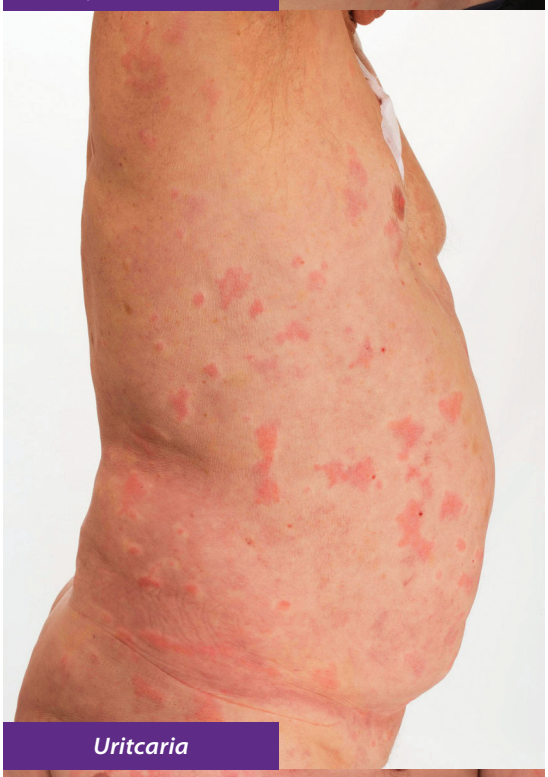

Nail psoriasis

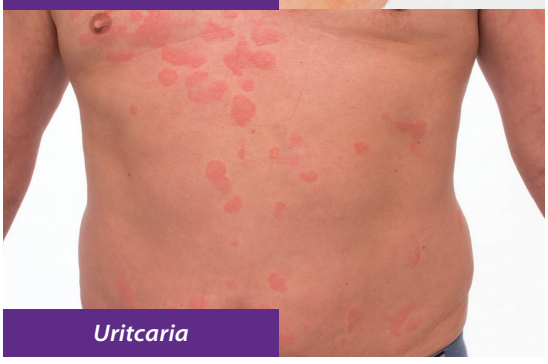

Guttate psoriasis


Inverse psoriasis


Herald patch


Pityriasis rosea


Uritcaria


Uritcaria

- **Clinical:** Begins with a **single,** reddish-pink or hyperpigmented patch known as a **"herald patch."** This patch varies in size from **2 to 6 cm** in diameter and has a characteristic **ring or "collarette" of scale.** One to two weeks later, a generalized, pruritic rash with similar but *smaller* patches develops predominantly on the trunk. The patches have a **central "cigarette paper"** appearance and follow the **skin lines of cleavage,** producing the classic **"Christmas tree" pattern.** Ampicillin may worsen the rash, an effect similar to EBV drug-induced rash.

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical. Consider KOH prep and VDRL to rule out fungal infection (eg, tinea corporis or versicolor) and secondary syphilis, respectively.

- **Treatment**
  - **First line:** Reassurance. Topical steroids and oral antihistamines are useful for pruritus.
  - **Second line:** Phototherapy or acyclovir.

6. URTICARIA

- **General:** Also known as **hives,** a common pruritic dermatosis characterized by epidermal and dermal edema due to release of *vasoactive substances* from **mast cells** and **basophils. Histamine, bradykinin** and **leukotrienes** promote fluid extravasation into the superficial dermis leading to the classic **"wheals"** seen in urticaria. There is usually a family history of **atopic disorders,** such as eczema, asthma and allergic rhinitis. **Dermatographism** or "skin writing" is a type of urticaria that develops after firm stroking of the skin. Urticaria is most commonly **idiopathic,** however, recognized causes are:
  - **Type I hypersensitivity (IgE-mediated):**
    - **Drugs** (eg, NSAIDs, beta-lactams, sulfonamides)
    - **Insect stings** (eg, fire ants, bees, wasps)
    - **Foods** (eg, peanuts, eggs, strawberries, tomatoes, shellfish)
    - **Inhalants** (eg, animal dander, pollen, mold, dust)
  - **Direct mast cell activators:** Vancomycin, radiocontrast media, muscle relaxants (eg, succinylcholine) and opiates (eg, codeine and morphine).
  - **Infections:** Bacterial (eg, *Streptococcus, H. pylori*), parasitic (eg, *Giardia lamblia*) and viral (eg, hepatitis virus, EBV, HIV).
  - **Systemic diseases:** Malignancies, autoimmune thyroiditis, SLE, rheumatoid arthritis and polycythemia.
  - **Physical stimuli:** Pressure, vibration, exercise, sun, heat or cold.

- **Clinical:** Generally divided into **acute urticaria** (< 6 weeks) and **chronic urticaria** (> 6 weeks). Lesions are characterized by **pruritic, erythematous** and **swollen** plaques that develop over minutes to hours and **disappear within 24 hours** ("wheal and disappear"). Plaque sizes and shapes vary greatly. **Common configurations are**: linear, gyrate, map-like and annular often with central clearing. **Systemic symptoms include:** angioedema, wheezes, stridor, respiratory distress, diarrhea, abdominal cramps, hypotension and anaphylaxis.

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical. Challenge test to suspicious triggering agent may elicit diagnosis. *Skin prick testing* and *radioallergosorbent tests* (RASTs) may be useful to identify culprit allergens. Consider blood tests to rule out infections and systemic disorders triggering urticaria. Skin biopsy showing epidermal and superficial dermal edema with mild perivascular inflammation and some eosinophils supports the diagnosis.

- **Treatment**
  - **First line:** Avoid and discontinue triggering agents + H_1-antihistamines (eg, fexofenadine, loratadine). Intramuscular (IM) epinephrine and IV fluids for anaphylaxis.
  - **Second line:** H_2-antihistamines (eg, cimetidine), montelukast, doxepin, cyclosporine, omalizumab or short-course of steroids.

- **USMLE Pearls: Scombroid fish poisoning:** Food-borne illness caused by scombrotoxin (histamine) poisoning from inadequately refrigerated fish. Common culprits are mackerel, tuna, marlin, mahi-mahi, amberjack and bluefish. It presents **within 1-2 hours** of fish consumption with a **nonedematous, pruritic, bright-red eruption** on the **face and upper torso** mimicking urticaria or an allergic reaction. The patient may also complain of headache, dizziness, diarrhea, metallic taste, nausea or vomiting, angioedema, burning sensation, flushing, hypotension and tachycardia. Usually self-limited; first-line therapy is oral or IV antihistamines.

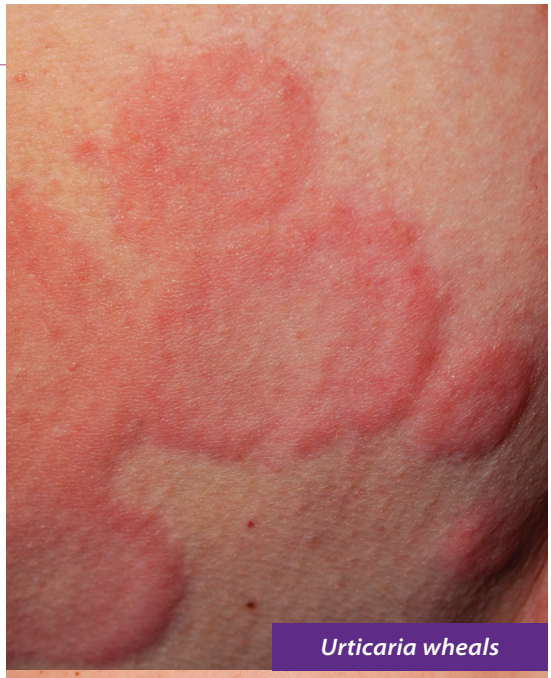
7. MACULOPAPULAR CUTANEOUS MASTOCYTOSIS

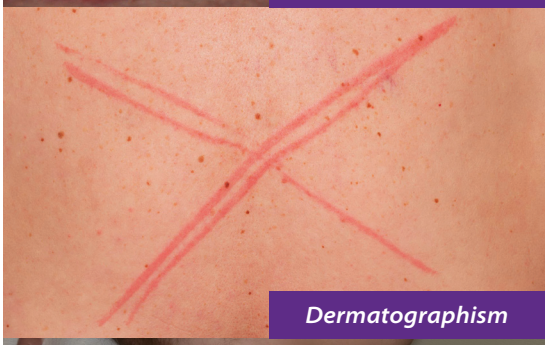
- **General:** Also called **urticaria pigmentosa,** the most common type of cutaneous mastocytosis. Characterized by abnormal **proliferation and accumulation** of mast cells in the skin. Usually affect **children or newborns,** but can occur in adults. May rarely progress to systemic mastocytosis and involve extracutaneous tissue (eg, bone marrow, liver and spleen).

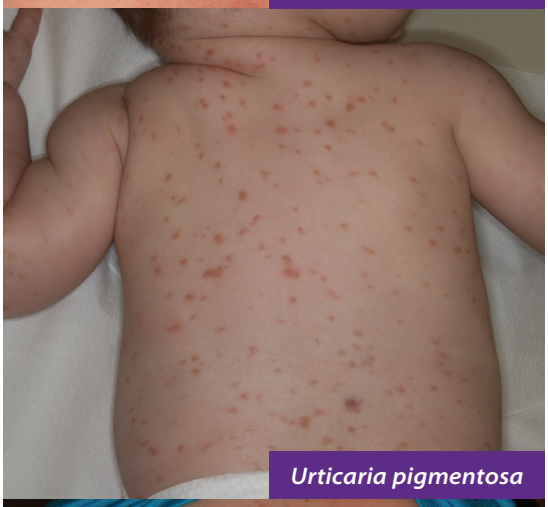
- **Clinical:** Most commonly presents with **circumscribed, reddish-brown, pruritic** macules, papules or plaques involving most of the body but *sparing* the face, scalp, palms and soles. Lesions range in number from a few to hundreds. The classic feature is the **Darier sign,** which is production of localized urticaria (erythema, edema and pruritus) *after* gently stroking or rubbing the skin. **Triggering agents** and **systemic symptoms** are similar to urticaria (discussed above).

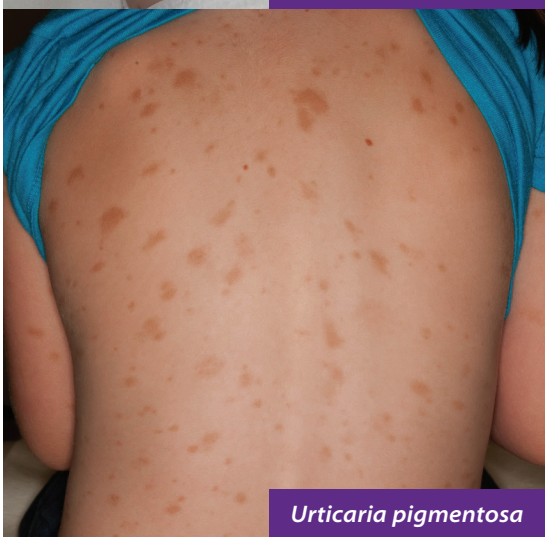
- **Diagnosis**
  - **Best initial test:** Clinical + urine or plasma histamine and serum tryptase levels (markers for mast cell degranulation). Genetic testing for *c-KIT* mutation may aid in diagnosis.
  - **Most accurate test:** Skin biopsy showing multifocal, dense infiltrates of mast cells. Special staining with tryptase, Giemsa, toluidine blue and CD117 (c-KIT) help identify mast cells.

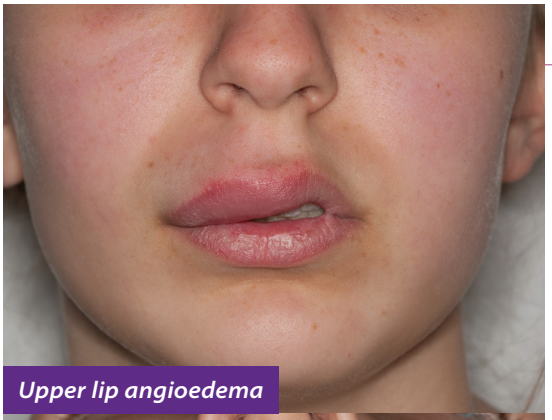
- **Treatment**
  - **First line:** Avoid and discontinue triggering agents + topical steroids and H_1-antihistamines combined with H_2-antihistamines. Consider IM epinephrine and IV fluids for anaphylaxis.
  - **Second line:** Phototherapy, cromolyn sodium or oral steroids.


Urticaria wheals

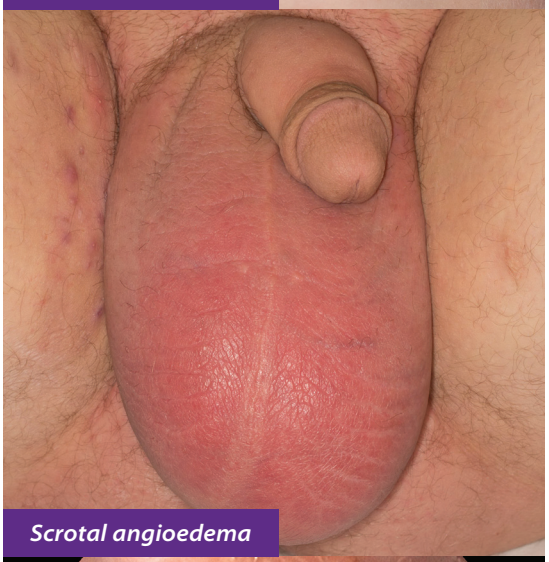

Dermatographism

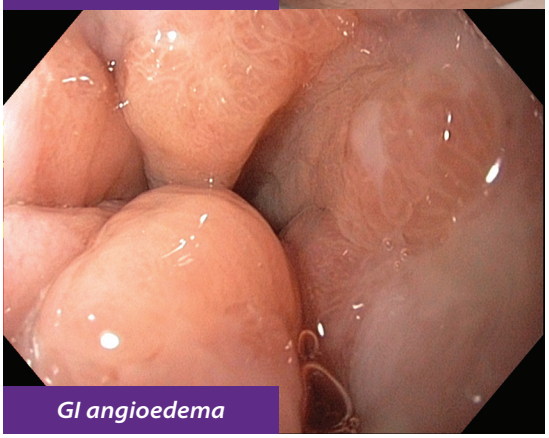

Urticaria pigmentosa


Urticaria pigmentosa


Upper lip angioedema


Upper lip angioedema


Scrotal angioedema


GI angioedema

8. ANGIOEDEMA

- **General:** Proinflammatory and vasoactive actions of **bradykinin, histamine** and **leukotrienes** leading to edema of **deep tissues. Angioedema** and **urticaria** often **coexist,** as many causes of urticaria also lead to high levels of these vasoactive elements. Other important mechanisms that may lead to angioedema are:
  - **ACE-inhibitor induced:** Bradykinin is normally degraded by angiotensin converting enzyme (ACE), also known as *kininase*. When ACE is inhibited, bradykinin levels increase leading to angioedema.
  - **C1-esterase inhibitor (C1-INH) deficiency:** Normally, bradykinin synthesis is regulated by C1-INH. People with *hereditary* or *acquired C1-INH deficiency* will have high levels of bradykinin leading to angioedema.
  - **NSAID induced:** NSAIDs inhibit the prostaglandin pathway and induces the overproduction of *leukotrienes* leading to angioedema.

- **Clinical:** The hallmark of angioedema is **sudden, severe swelling,** often accompanied by **pain (burning)** with or without **pruritus** and **erythema.** Episodes are usually transient lasting 1 to 2 days and may be life-threatening. Common affected sites and symptoms include:
  - **Lips, tongue, uvula and larynx:** Dysphonia, dyspnea and severe airway obstruction.
  - **Gastrointestinal:** Abdominal pain, nausea, vomiting, diarrhea and bowel obstruction.
  - **Genitals:** Genitourinary obstruction.

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical. *Skin prick testing* and *radioallergosorbent tests* (RASTs) may be useful to identify culprit allergens. C1-INH and C4 levels may be low in C1-INH deficiency. Skin biopsy showing edema in deep reticular dermis and subcutaneous or submucosal tissue supports the diagnosis.

- **Treatment**
  - **First line:** Avoid and stop triggering agents.
    - **Mild-to-moderate disease:** H_1-antihistamines (eg, cetirizine).
    - **Moderate-to-severe disease:** Assess airway, breathing and circulation + IV antihistamines and steroids. Consider IM epinephrine and intubation for severe airway compromise. *Hereditary C1-INH deficiency* is generally refractory to these medications; use C1-INH concentrate, ecallantide, icatibant or danazol.

Chapter 11

INHERITED SKIN DISORDERS

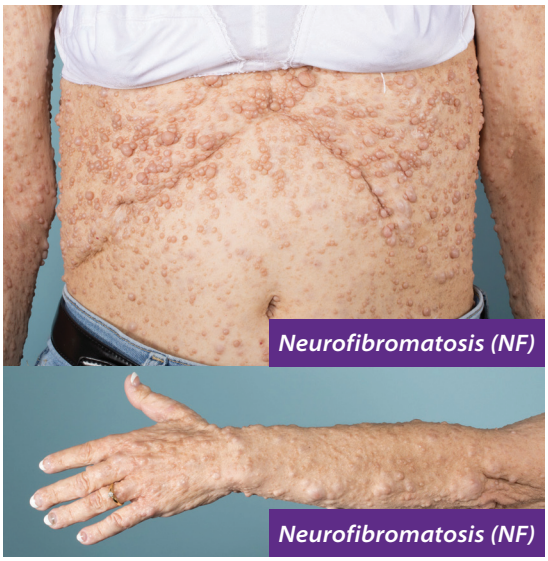
Table 11.1. Neurofibromatoses Diagnostic Criteria

Neurofibromatosis Type 1 (NF-1) *	Neurofibromatosis Type 2 (NF-2) **
1) ≥ **6 café-au-lait spots** (hyperpigmented macules) ○ ≥ 5 mm in diameter in pre-pubertal children ○ ≥ 15 mm in diameter in post-pubertal children 2) > **2 axillary or inguinal freckles**	1) **Bilateral vestibular schwannomas**
3) ≥ **2 typical neurofibromas** or **one plexiform neurofibroma** 4) **Optic nerve glioma** 5) ≥ **2 iris hamartomas** (Lisch nodules)	2) **A first-degree relative with NF-2** AND **Unilateral vestibular schwannoma** OR **Any two of:** Meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
6) **Sphenoid dysplasia** or typical **long-bone abnormalities**, such as pseudarthrosis	3) **Unilateral vestibular schwannoma** AND **Any two of:** Meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
7) **First-degree relative with NF-1**	4) **Multiple meningiomas** AND **Unilateral vestibular schwannoma** OR **Any two of:** Schwannoma, glioma, neurofibroma, cataract

*** Clinical diagnosis of NF-1** requires that an individual present with **at least 2 of 7** of the above-mentioned criteria.
**** Clinical diagnosis of NF2** requires that an individual present with **at least 1 of the 4** clinical scenarios mentioned above.

1. NEUROFIBROMATOSES

- **General:** *Autosomal dominant* group of genetic disorders that affect **bones, soft tissue, skin** and **nervous system.** Classified into *neurofibromatosis type 1* (NF-1) and *neurofibromatosis type 2* (NF-2).
  - **Neurofibromatosis type 1 (NF-1):** Also known as **peripheral NF** or **von Recklinghausen disease,** fairly common neurocutaneous disorder occurring in 1:3000 births. It is caused by *NF-1* gene mutation on chromosome 17 leading to decreased production of the tumor suppressor protein **neurofibromin.** NF-1 is associated with: **pheochromocytomas, Chiari type-1 malformation** and **gastrointestinal stromal tumors** (GIST).
  - **Neurofibromatosis type 2 (NF-2):** Also known as **central NF** or **bilateral acoustic neurofibromatosis,** rarer neurocutaneous disorder occurring in 1:50,000 births. It is caused by *NF-2* gene mutation on chromosome 22 leading to decreased production of the tumor suppressor protein **merlin.**

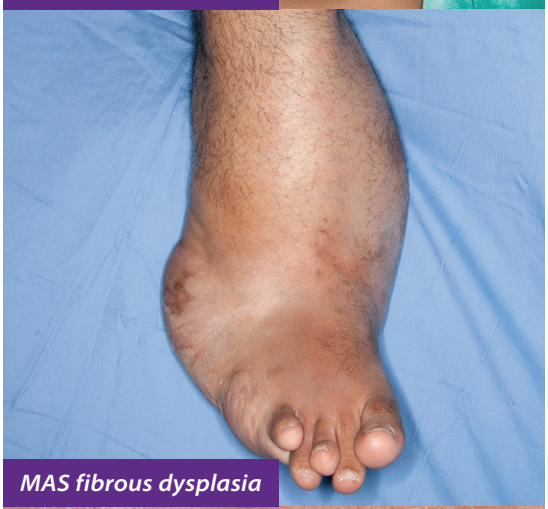

Neurofibromatosis (NF)

Neurofibromatosis (NF)


NF axillary freckles


NF café-au-lait spots


MAS fibrous dysplasia


MAS fibrous dysplasia


MAS oral hyperpigmentation

- **Clinical**
  - **Neurofibromatosis type 1 (NF-1):** Characterized by hyperpigmented macules known as **café-au-lait spots** and multiple cutaneous **neurofibromas. Axillary and inguinal freckles** are common and become more prominent as the patient ages. Other common manifestations of NF-1 are:
    - **Bone dysplasia** and **scoliosis.**
    - **Optic nerve gliomas** and **iris hamartomas** (Lisch nodules).
  - **Neurofibromatosis type 2 (NF-2):** Neurofibromas and café-au-lait spots may affect the skin, but NF-2 patients tend to have *minimum* or *absent* cutaneous involvement. NF-2 is characterized by **hearing loss, tinnitus** and **balance problems** secondary to **vestibular schwannomas** (acoustic neuromas). Other common manifestations of NF-2 are:
    - Gliomas and **meningiomas.**
    - Hydrocephalus, seizures and cranial nerves and motor defects.
    - Juvenile **cataracts** and **subcapsular lenticular opacities.**

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical. Genetic molecular testing for *NF-1* and *NF-2* gene mutations is helpful when positive (most specific). If symptomatic, order brain MRI to detect **intracranial tumors.** If patient has hypertension, consider urinary or plasma *free metanephrines* to screen for **pheochromocytoma.** For NF-1, slit-lamp eye examination for **Lisch nodules.** For NF-2, eye examination for **lenticular opacities.**

- **Treatment**
  - **First line:** Annual routine examination to detect and minimize complications. There is no cure.
  - **Second line:** Surgical excision for painful and large neurofibromas or schwannomas.

2. MCCUNE-ALBRIGHT SYNDROME (MAS)

- **General:** Genetic disorder that mainly affects the **skin, bones** and **endocrine system.** An activating mutation of the *GNAS1* gene leads to prolonged activation of the Gs-alpha protein and persistent high levels of intracellular cAMP. MAS is associated with:
  - **Hyperthyroidism**
  - **Hypophosphatemic rickets**
  - **Acromegaly** and **Cushing syndrome**

- **Clinical**
  - **Skin:** Café-au-lait macules are usually **unilateral** and **do not cross** the midline. These pigmented macules often have irregular borders resembling the **"coast of Maine"** compared with the smooth border café-au-lait spots typical in NF-1 (resembling the **"coast of California"**). Contrary to NF-1, MAS lacks axillary and inguinal freckling. Later in life, **oral hyperpigmentation** may occur similar to that seen in Peutz-Jeghers syndrome and Addison disease.
  - **Bones:** Polyostotic fibrous dysplasia may result in severe **disfigurement** and multiple **pathological fractures.** Clinically presents with bone pain, palpable masses and gait abnormalities.

- **Endocrine:** Gonadotropin-independent **precocious puberty** is the hallmark of MAS. More common in girls, clinically presents with early vaginal bleeding, breast enlargement, public hair and tall stature for age.

- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + order estrogen, testosterone, TSH, GH, cortisol and phosphate to identify underlying endocrine syndromes. Genetic testing of affected tissue for the *GNAS1* gene mutation may be helpful in confirming diagnosis.

- **Treatment**
  - **First line:** Precocious puberty and pathological fractures may respond to aromatase inhibitor (anastrazole) and bisphosphonates, respectively.
  - **Second line:** Orthopedic surgery for severe bone dysplasia.

3. STURGE-WEBER SYNDROME (SWS)

- **General:** Also known as **encephalotrigeminal angiomatosis,** fairly rare neurocutaneous vascular disorder characterized by **angiomas** in the **leptomeninges, brain** and **facial skin.** It is caused by an activating mutation in the *GNAQ* gene that results in failure of the cephalic vascular plexus to regress during neural tube development.

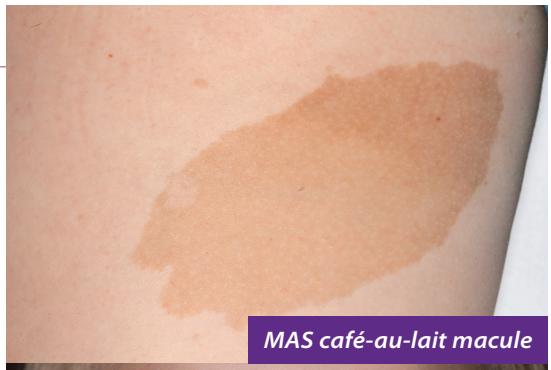
- **Clinical:** The classic birthmark lesion is a **facial red irregular patch** known as **"nevus flammeus"** or **"port-wine stain;"** it is caused by overabundance and dilation of cutaneous capillaries usually involving the **ophthalmic (V1)** and **maxillary (V2)** distributions of the trigeminal nerve. Ipsilateral capillary-venous malformation may affect the brain and eye leading to **seizures, stroke-like episodes, developmental delays, mental retardation, glaucoma, visual loss** and buphthalmos.

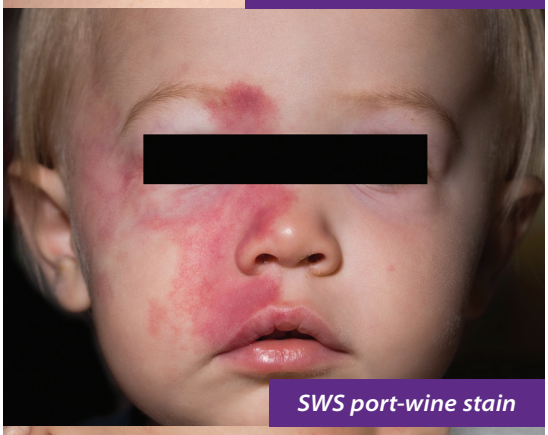
- **Diagnosis**
  - **Best initial and most accurate test:** Clinical. Brain imaging (eg, MRI, angiography) may reveal vascular malformations and *"tram track"* calcifications (also seen in tuberous sclerosis). Yearly ocular tonometry to detect glaucoma.

- **Treatment**
  - **First line:** *Anticonvulsants* for seizure control, *antiglaucoma agents* (eg, beta-blockers drops) for intraocular pressure control and *laser therapy* for port-wine stain.
  - **Second line:** Brain or eye surgery for intractable seizures and glaucoma, respectively.

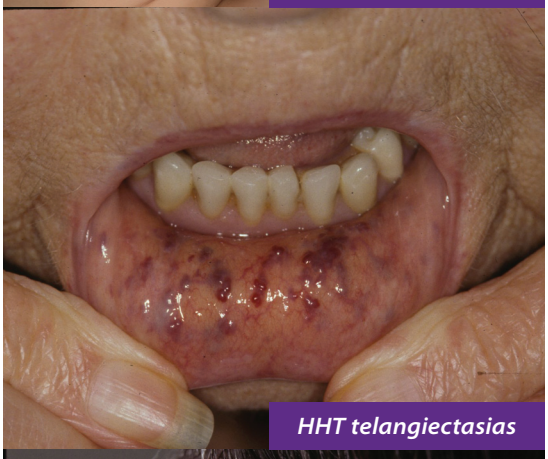
4. HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)

- **General:** Also known as **Osler-Weber-Rendu syndrome,** an *autosomal dominant* vascular disorder resulting in **telangiectasias** and **arteriovenous malformations** (AVMs) throughout the body. A genetic mutation encoding proteins such as blood vessel TGF-β receptor leads to abnormal angiogenesis. Family history is important for diagnosis.


MAS café-au-lait macule


SWS port-wine stain


SWS port-wine stain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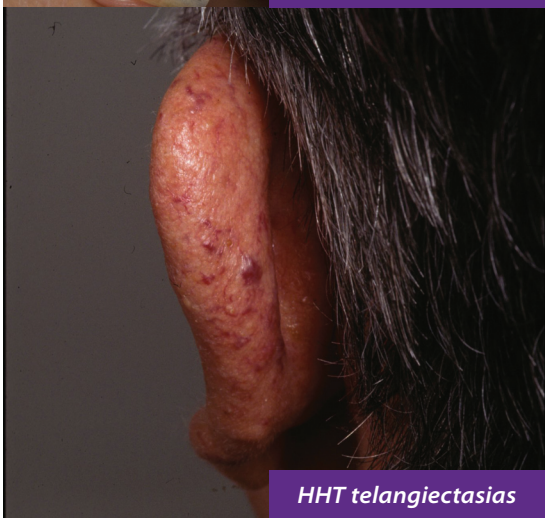
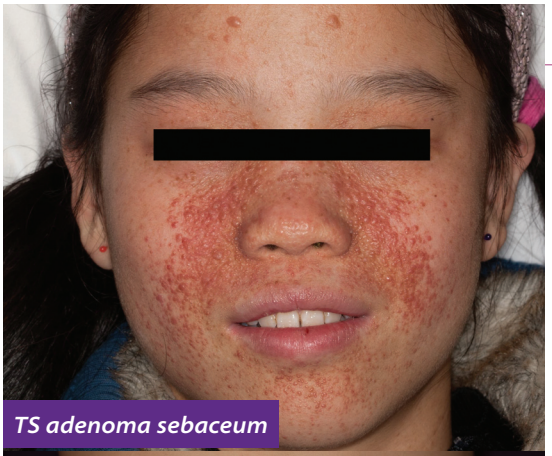
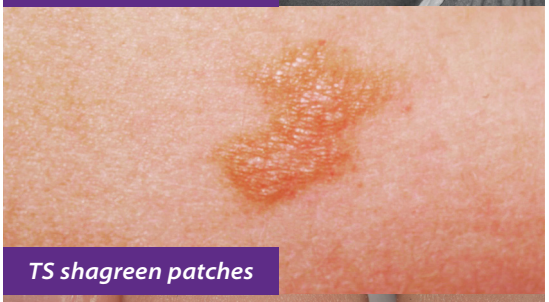
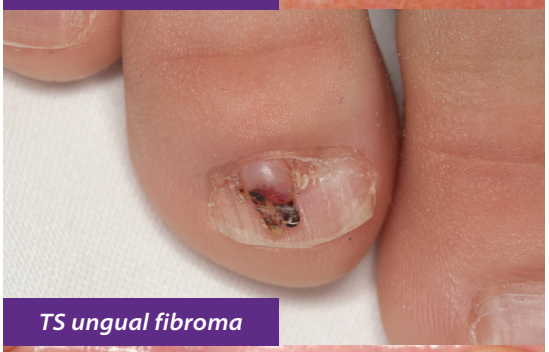

HHT telangiectasias


TS adenoma sebaceum


TS ash leaf spots


TS ash leaf spots


TS shagreen patches


TS ungual fibroma


TS gingival fibroma

- **Clinical**
  - **Skin:** Numerous telangiectasias and AVMs present as dark-red linear or circular papules involving mucous membranes or any part of the body.
  - **Respiratory tract:** Recurrent epistaxis, hemoptysis, dyspnea, fatigue and cyanosis.
  - **GI tract and liver:** GI bleeding, portal hypertension and high-output cardiac failure (large AVMs).
  - **Brain:** Headaches, seizures and strokes.

- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + molecular genetic testing for causative gene mutations *(ACVRL1, ENG* and *SMAD4).* CBC may show iron-deficiency anemia. Consider endoscopy, urinalysis and CT scan or MRI to identify internal AVMs.

- **Treatment**
  - **First Line:** Observation.
  - **Second line:** RBC transfusion for symptomatic anemia. Consider hemostasis procedures (eg, endoscopy, embolization) for active bleeding refractory to medical management.

5. TUBEROUS SCLEROSIS (TS)

- **General:** *Autosomal dominant* neurocutaneous disorder with **hamartomatous malformations** affecting many organ systems in the body. It is caused by a mutation in **TSC1 or TSC2** genes responsible for the production of tumor suppressor proteins **hamartin** and **tuberin,** respectively. A *hamartoma* is a benign focal malformation composed of tissue elements normally found at the anatomic site of growth. The classic *tuberous sclerosis complex (TSC) triad* is **mental retardation, intractable epilepsy** and **facial angiofibromas** (formerly called **adenoma sebaceum**).

- **Clinical**
  - **Skin:** The hallmark lesion is the presence of **multiple cutaneous angiofibromas** that present as reddish maculopapular lesions in **facial skin,** usually in a butterfly distribution. Other important cutaneous manifestations are:
    - **Ash leaf spots:** Single or multiple circumscribed hypomelanotic macules; subtle ones may be detected with Wood's lamp examination.
    - **Shagreen patches:** Thickened, pebbly, flesh-colored skin with orange-peel texture, usually located on the lower back.
    - **Ungual and gingival fibromas:** Smooth, firm and circumscribed flesh-colored fibrous outgrowth commonly located inside or around the nail and gums.
  - **Brain:** Cortical tubers are potato-like nodules in the brain that calcify and sclerose. Characteristic manifestations are **developmental delays, intractable seizures, intellectual deficit, stroke-like episodes** and **gait abnormalities.** Subependymal nodules and giant astrocytomas are also common and may result in **obstructive hydrocephalus.**
  - **Kidney:** Autosomal dominant polycystic kidney disease (ADPKD), **angiomyolipomas (AMLs)** and **renal cell carcinoma (RCC).** These lesions can present clinically with hematuria, flank pain, UTIs, retroperitoneal hemorrhage, hypertension and renal failure.

- **Heart:** Cardiac rhabdomyomas, most common in young children, can lead to **valvular dysfunction, systemic embolization,** arrhythmias and cardiomyopathy.

- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + *TSC1* and *TSC2* gene mutation testing. Consider extensive imaging (eg, echocardiography, renal ultrasound, brain MRI) to identify visceral hamartomas; EEG for seizures.

- **Treatment**
  - **First line:** Rapamycin or sirolimus (mTOR inhibitors). Anticonvulsants for seizure control.
  - **Second line:** Surgical treatment for symptomatic hamartomas, intractable seizures or malignancies.

6. ICHTHYOSIS

- **General:** Group of inherited or acquired skin disorders characterized by **abnormal keratinization.** Ichthyosis is mainly divided into:
  - **Ichthyosis vulgaris:** *Autosomal dominant,* **most common** form of ichthyosis (95%) occurring in 1:300 people. It is associated with **loss of filaggrin,** an epidermal barrier protein that protects against water loss and skin infections. Usually presents in the first years of life and *spares* the flexural surfaces. Associated with **atopic dermatitis** and tends to be milder than other types.
  - **X-linked ichthyosis:** *X-linked disease,* second most common ichthyosis occurring in 1:1500 males. It is caused by a **deficiency of steroid sulfatase (STS).** Presents as early as birth and spares the palms and soles. Associated with **corneal opacities, prolonged labor** and **cryptorchidism.**
  - **Lamellar ichthyosis:** *Autosomal recessive,* rare form of ichthyosis. It is caused by a mutation in keratinocyte **transglutaminase 1 gene.** It usually presents at birth with a thick membrane covering most of the body, termed **collodion membrane.** Associated with **bilateral ectropions** and **corneal ulcerations.**

- **Clinical:** The characteristic finding in all ichthyoses is **thickened, dry, scaly skin** that **resembles fish scales** along with prominent skin markings. Patients often complain of painful skin fissuring, especially during cold weather. When it severely affects the whole body, it resembles **lizard skin.** Ectropion of the eyelids can lead to **severe keratitis.**

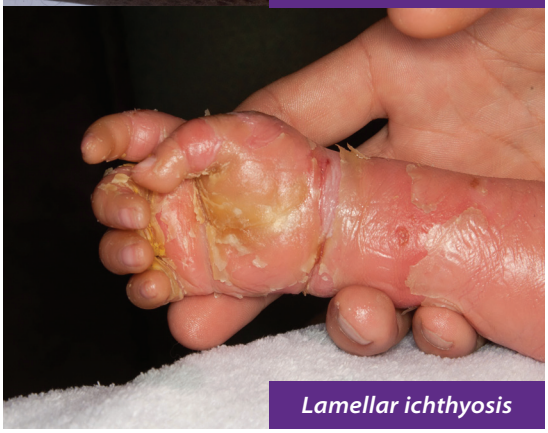
- **Diagnosis**
  - **Best initial test:** Clinical. High-resolution prenatal ultrasound may be helpful in detecting congenital ichthyosis syndromes.
  - **Most accurate test:** Genetic testing for specific mutations + skin biopsy if indicated. Ichthyosis vulgaris will show prominent hyperkeratosis and absent granular layer.

- **Treatment**
  - **First line:** Emollients + topical retinoids.
  - **Second line:** Oral retinoids.


Ichthyosis vulgaris


X-linked ichthyosis


Ichthyosis (close-up)


Lamellar ichthyosis

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Chapter 12

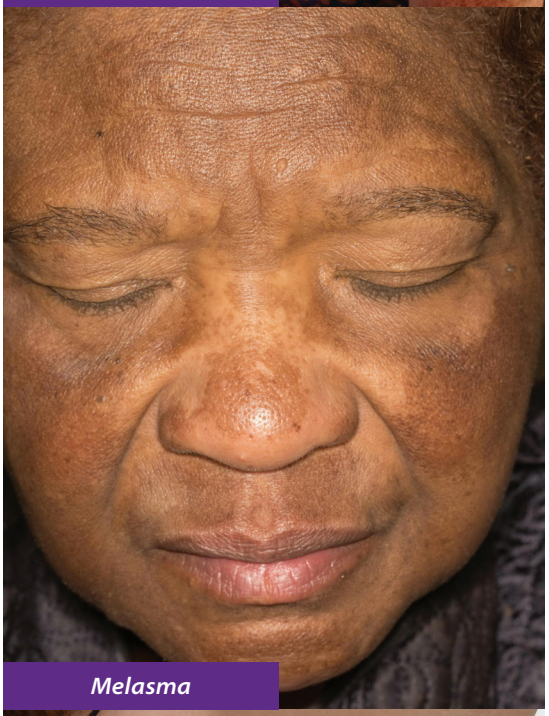
MELANOCYTIC SKIN DISORDERS

Table 12.1. Melanocytic Skin Disorders Summary

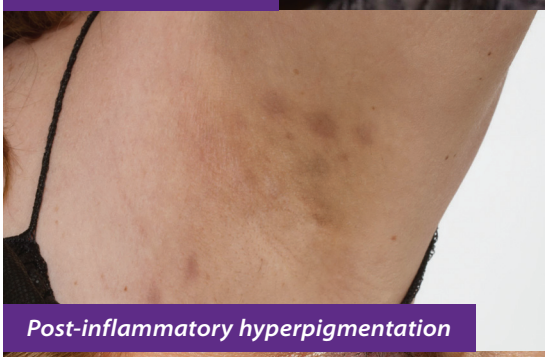
Melanocytic Lesion	Pathogenesis	Clinical Appearance	Characteristics/Associations
Ephelides (Freckles)	**Normal number of melanocytes** with increased melanin production (melanogenesis).	Well-circumscribed, evenly pigmented, small **(1 to 4 mm)**, tan-to-brown macules on sun-exposed skin (face, forearms, upper back).	Become prominent and **increase in number with sun exposure** Marker of sun-damaged skin Regress during winter and with aging
Melasma (Mask of Pregnancy)		Symmetric, hyperpigmented tan-to-brown patches primarily on the **centrofacial areas** (forehead, cheeks, nose, upper lip and chin).	Female predominant (90%) **Africans**, Hispanics and Asians **Worsened by:** UV-light, pregnancy and hormonal therapy
Lentigo Simplex (Juvenile Lentigo)	**Increased number of melanocytes and melanin.** Do not form nests.	**Circumscribed**, **evenly pigmented**, brown-to-black small macule with **regular borders**. Can affect mucous membranes and palmoplantar skin.	Mainly in **young patients** Can be a sign of genetic disorders **Not sun-induced**
Solar Lentigo (Senile Lentigo)		Tan-to-brown-black, small macules with **regular or irregular borders**, usually homogenous but can have **mottled appearance**.	Mainly in **elderly patients** Incidence increases with aging **Sun-induced**
Junctional Nevus	Benign neoplastic *melanocytic nests* in **DEJ only**.	Evenly pigmented, **brown-to-black**, **circumscribed** *macule* with regular borders.	Can be present early in life Number peaks around age of 30 Can disappear with aging **Influenced by environmental factors:** sun-exposure, increased hormonal levels, skin injury and immunosuppression
Compound Nevus	Benign neoplastic *melanocytic nests* in **DEJ + dermis**.	Evenly pigmented, **tan-to-brown**, **dome-shaped** papule frequently surrounded by macular pigmentation.	
Intradermal Nevus	Benign neoplastic *melanocytic nests* in **dermis only**.	**Skin-colored-to-light-brown**, **dome-shaped** *papule* with regular borders.	
Atypical Nevus (Dysplastic Nevus)	**Proliferating melanocytes** with some degree of **atypical** architecture +/- cytology.	Brown-to-black *macule* and/or *papule* that may have **irregular borders**, **uneven pigmentation**, **asymmetric shape** and **size** > **6mm** in diameter.	**Dysplastic nevus syndrome** Not a definitive melanoma precursor

*Ephelides (freckles) **

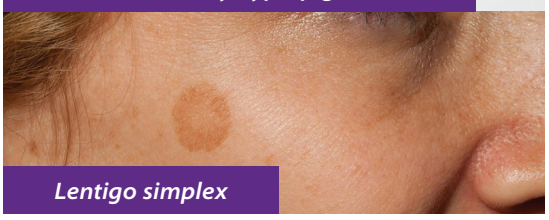
*Ephelides (freckles) **



Melasma



Post-inflammatory hyperpigmentation



Lentigo simplex

1. EPHELIS (PLURAL EPHELIDES)

- **General:** Also known as **freckles,** a benign melanocytic skin disorder characterized by a **normal number of melanocytes** with increased melanogenesis. Commonly appear during childhood in **fair-skinned** and **red-haired individuals.** Freckles become prominent and increase in number with sun exposure and may regress during winter and with aging.

- **Clinical:** Characterized by asymptomatic, **well-circumscribed** and **evenly pigmented tan-to-brown** macules ranging from **1 to 4 mm** in diameter. Most commonly located on **sun-exposed areas** (face, forearms and upper back).

- **Diagnosis**
  - **Best initial test:** Clinical.
  - **Most accurate test:** Skin biopsy showing focal increased melanin deposition in basal keratinocytes.

- **Treatment**
  - **First line:** Avoid and protect from sun.
  - **Second line:** Hydroquinone and/or tretinoin cream (poor response).

2. MELASMA

- **General:** Also known as **chloasma** or **mask of pregnancy,** a benign facial melanocytic skin disorder characterized by a **normal number of melanocytes** with increased melanogenesis. Melasma is seen almost exclusively in **female patients** (9:1) and favors darker skin types. May be associated with **autoimmune thyroid diseases** and **medications** (eg, OCPs, phenytoin and phototoxic drugs).

- **Clinical:** Characterized by **symmetric** and **patchy tan-to-brown** hyperpigmentation most commonly located on the **centrofacial areas** (forehead, cheeks, nose, upper lip and chin). Melasma may gradually regress or resolve, but often persists indefinitely. Hyperpigmentation is worsened by **UV-light, pregnancy** and **hormonal therapy** (induce melanogenesis).

- **Diagnosis**
  - **Best initial test:** Clinical.
  - **Most accurate test:** Skin biopsy showing increased melanin deposition in all epidermal layers and increased melanophages in the upper dermis.

- **Treatment**
  - **First line:** Avoid and protect from sun + discontinue culprit medication (eg, OCPs).
  - **Second line:** Hydroquinone, topical tretinoin and/or chemical peels.

- **USMLE Pearls: Post-Inflammatory Hyperpigmentation (PIH):** Hyperpigmented patches located in **sites of previous skin inflammation.** The inflammatory process (likely through cytokines) promotes production and deposition of melanin. It may be primarily within the epidermis or dermis. Pigmentation varies from tan-to-dark brown **(epidermal PIH)** or gray-to-blue/brown **(dermal PIH)** and may darken on sun exposure. PIH generally resolves in months to years, but can persist indefinitely. Hydroquinone or tretinoin cream may be used to lighten persistent lesions.

3. LENTIGO (PLURAL LENTIGINES)

- **General:** A benign melanocytic skin disorder characterized by an **increased number of melanocytes** and accumulation of melanin within keratinocytes. The melanocytes **do not** form nests. Lentigines are very common in young and elderly individuals, especially in whites.

- **Clinical**
  - **Lentigo simplex:** Also known as **simple lentigo** or **juvenile lentigo,** it is usually present at **birth** or appears during **childhood; not sun-induced.** Lentigo simplex is characterized by an asymptomatic, **circumscribed, brown-to-black** small macule ranging from 1 to 6 mm in diameter. Pigmentation is **evenly distributed and borders are regular.** Generalized lentigines may be a **sign of genetic disorders** (eg, xeroderma pigmentosum).
  - **Solar lentigo:** Also known as **liver spot** or **senile lentigo.** Almost exclusively seen in **elderly individuals** (90%), lesions gradually **increase in number with aging.** Characterized by tan-to-brown-black small macules with regular or irregular borders that may merge to form large patches. Lesions are **sun-induced** and commonly appear on the upper chest and back, face and extremities.

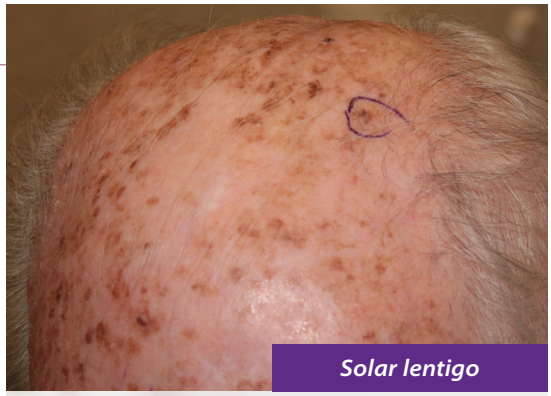
- **Diagnosis**
  - **Best initial test:** Clinical. Dermoscopy may aid in differentiating benign from malignant melanocytic lesions. If there is suspicion for melanoma, perform an excisional biopsy with 1 to 3 mm margins.
  - **Most accurate test:** Skin biopsy showing normal melanocytic proliferation and increased melanin deposition in basal keratinocytes and within dermal melanophages.

- **Treatment**
  - **First line:** Observation and prevention with sun protection.
  - **Second line:** Tretinoin and/or hydroquinone creams (poor response).

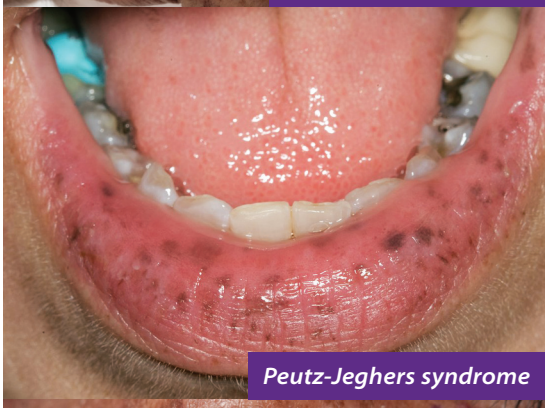
- **USMLE Pearls: Peutz-Jeghers Syndrome:** *Autosomal dominant* disease characterized by childhood **lentigines** commonly on the **oral mucosa and lips,** but can occur anywhere (eg, face, hands, genitals). Other common manifestations are **GI bleeding, obstruction** and **intussusception** secondary to **hamartomatous polyps in the small bowel.** There is a slight increased risk of developing **pancreatic, colon** and breast cancer. **Addison disease** and **McCune-Albright syndrome** are other pathologies that may have oral pigmentation.

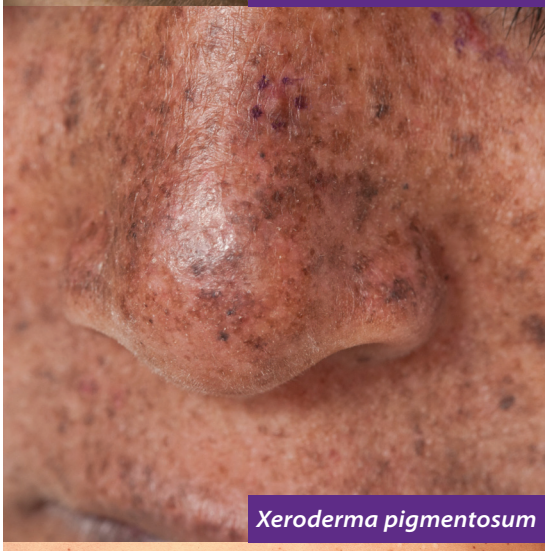
- **USMLE Pearls: Xeroderma Pigmentosum:** *Autosomal recessive* genetic disorder with numerous lentigines at a young age. The **nucleotide excision repair enzyme** is defective; therefore, **DNA damage** produced by UV-light cannot be repaired. Progressive DNA mutations result in premature photodamage and childhood **BCCs, SCCs and melanomas.** *Treatment* is avoiding and protecting from sun. Photograph all melanocytic lesions and schedule annual skin examinations to monitor evolution.

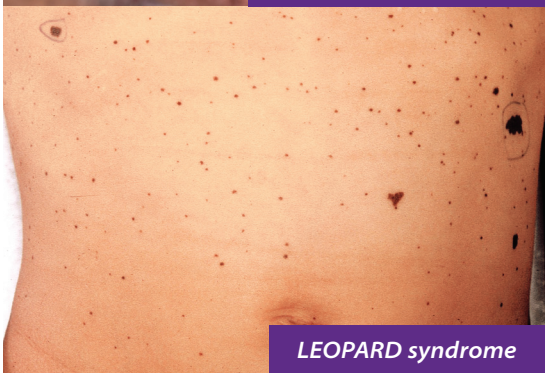
- **USMLE Pearls: LEOPARD Syndrome:** *Autosomal dominant* disorder with variable penetrance that presents with numerous lentigines at a young age. Main features are:
  - **L**entigines
  - **E**lectrocardiographic conduction abnormalities
  - **O**cular hypertelorism

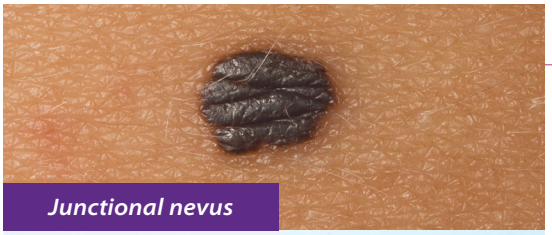

Solar lentigo

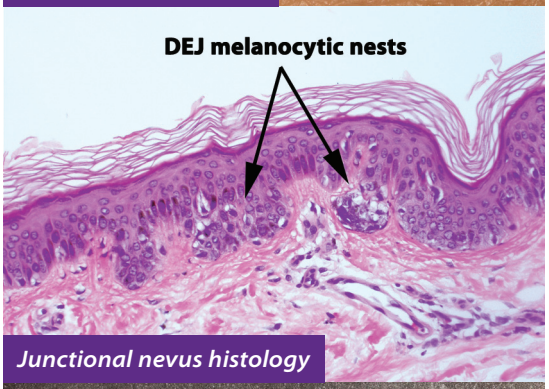

Solar lentigo


Peutz-Jeghers syndrome

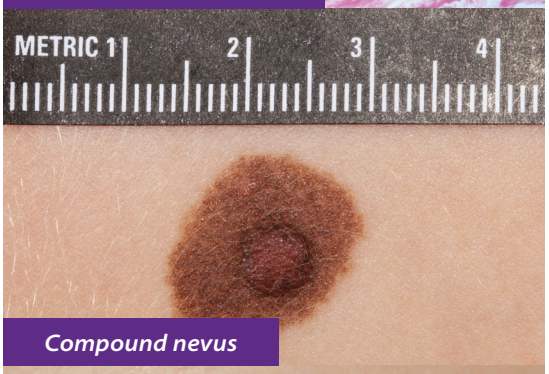

Xeroderma pigmentosum


LEOPARD syndrome

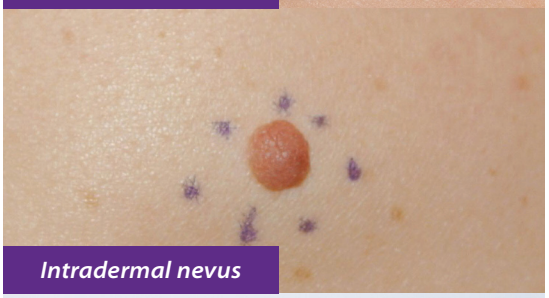

Junctional nevus

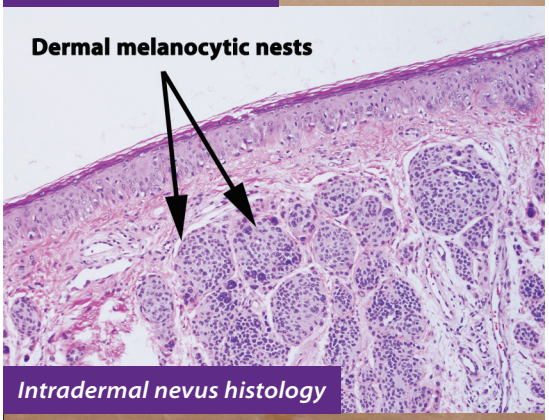


Junctional nevus histology

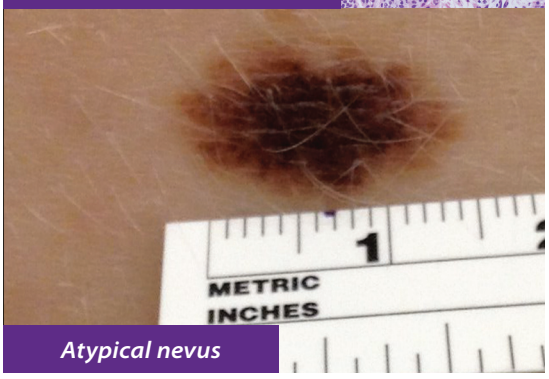


Compound nevus


Intradermal nevus



Intradermal nevus histology



Atypical nevus

- Pulmonary stenosis
- Abnormalities of genitalia
- Retardation of growth
- Deafness

4. MELANOCYTIC NEVUS (PLURAL NEVI)

- **General:** Also known as **nevocellular nevus** or **"mole,"** a melanocytic skin disorder characterized by **benign proliferation of *melanocytic nests* in the epidermis and/or dermis.** A combination of environmental and genetic factors are thought to play a role in nevi development, especially **sun exposure** and ***BRAF* gene mutation.** It is hypothesized that nevi usually follow a standard progression, initially developing in the basal epidermis **(junctional nevi)** and subsequently migrating to the dermis **(compound nevi)** until being completely in the dermis **(dermal nevi).** As they move down to the dermis, they lighten in color and become raised (papular).

- **Clinical:** Most commonly seen in whites, who have an average of 15 to 20 nevi. Most acquired melanocytic nevi are asymptomatic and rarely display the **ABCDE** warning signs. As a general rule, their clinical appearance is mainly determined by the melanocytic nest location. The four main types are:
  - **Junctional nevus:** Melanocytic nests are confined to the **DEJ,** clinically presents as a circumscribed, evenly pigmented **brown-to-black** *macule* with regular borders.
  - **Compound nevus:** Develops when a junctional nevus acquires a dermal component. Melanocytic nests are confined to the **DEJ and dermis,** clinically presents as an evenly pigmented, **tan-to-brown** dome-shaped *papule* surrounded by a *macular* pigmentation.
  - **Intradermal nevus (IDN):** Occurs when a compound nevus loses its junctional component. The melanocytic nests are confined to the **dermis,** clinically presents as a **skin-colored-to-light-brown** dome-shaped *papule* with regular borders. More common in adults. Lesions may regress in the elderly.
  - **Atypical nevus (dysplastic or Clark nevus):** Melanocytic proliferation with a degree of **atypical cytology and/or architecture.** Histologically, may be defined as mild, moderate or severe. Characterized by a brown-to-black *macule* and/or *papule* that may have **irregular borders, uneven pigmentation, asymmetric shape** and **size > 6mm** in diameter (displays some **ABCDE** warning signs). May be associated with **dysplastic nevus syndrome,** an *autosomal dominant* disease with > 50 atypical nevi and increased risk of developing melanoma.

- **Diagnosis**
  - **Best initial test:** Clinical. Dermoscopy may aid in differentiating benign from malignant melanocytic lesions. If there is suspicion for melanoma, perform an excisional biopsy with 1 to 3 mm margins.
  - **Most accurate test:** Skin biopsy to evaluate melanocyte cytology and nests architecture and distribution.

- **Treatment**
  - **First line:** Observation (annual skin examinations) for **benign nevi.** Biopsy proven **atypical nevi** may be excised based on severity.

5. VITILIGO

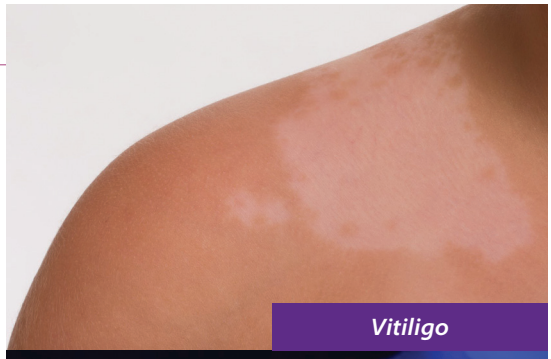
- **General:** An acquired, chronic and progressive melanocytic skin disorder characterized by **loss of function and destruction of melanocytes.** The result is absent melanin production with **depigmented** macules and patches. Affects approximately 1% of the general population with average age of onset between 10 and 30 years of age. Vitiligo is difficult to treat and can be **associated with autoimmune conditions** such as:
  - **Autoimmune thyroid disease** (most common)
  - **Pernicious anemia** (vitamin B12 deficiency)
  - **Type 1 diabetes mellitus**
  - **Addison disease**
  - **Alopecia areata**
  - **Systemic lupus erythematosus** (SLE)
  - **Inflammatory bowel disease** (IBD)

- **Clinical:** Localized to extensive areas of well-demarcated, **amelanotic, white "chalk–colored" macules and patches** surrounded by normal-appearing skin. Hair depigmentation may occur and result in patches of **white or gray hair.** Lesions greatly vary in size and shape. Their behavior is unpredictable. Vitiligo usually affects:
  - **Darker pigmented skin:** Face, nipples, dorsal hands, axillae and anogenital area.
  - **Around body orifices:** Eyes, mouth, anus and umbilicus.
  - **Acral areas and extensor surfaces:** Elbows, knees, hands and feet; lesions develop after trauma **(Koebner phenomenon).**

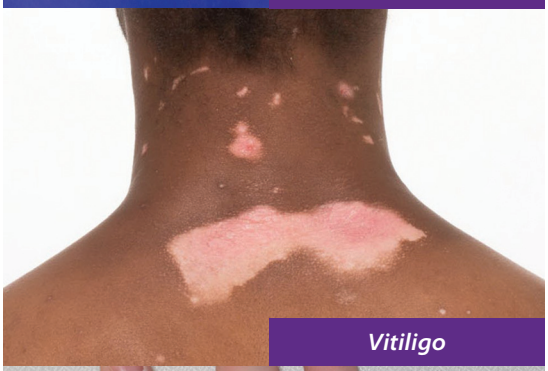
- **Diagnosis**
  - **Best initial test:** Clinical. Wood's lamp examination reveals intense *blue-white fluorescence* in depigmented areas. Investigate for associated autoimmune disorders (eg, TSH).
  - **Most accurate test:** Skin biopsy showing absence of melanocytes and epidermal melanin.

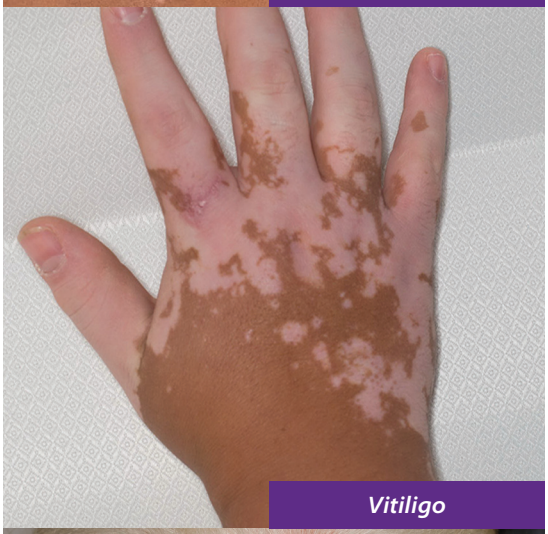
- **Treatment**
  - **First line:** Cosmetic camouflage, phototherapy, topical steroids or calcineurin inhibitors for limited skin involvement. Consider observation for small lesions.
  - **Second line:** Oral steroids for rapidly progressive disease. Consider total depigmentation therapy for extensive skin involvement.

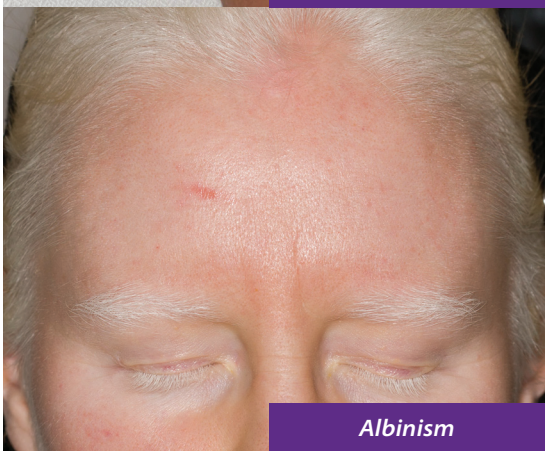
- **USMLE Pearls: Albinism:** A group of hypomelanotic disorders characterized by **partial or total absence of melanogenesis.** Melanocytes are present, but they have reduced or absent melanin. **Oculocutaneous albinism (OCA)** is the most common group; the majority of OCA types are due to defective or missing **tyrosinase enzyme** in the melanin synthesis pathway. Patients generally have **photosensitive skin** prone to sunburn and cancer. Lack of melanin in the eyes may result in impaired vision, photophobia, strabismus and nystagmus. **Hermansky-Pudlak syndrome** (most common in Puerto Rico) and **Chédiak-Higashi syndrome** are disorders leading to albinism secondary to defective melanosome biogenesis (abnormal lysosome-related organelles). Additional features include **bleeding tendency** and **recurrent infections.**


Vitiligo


Vitiligo Wood's lamp


Vitiligo


Vitiligo


Albinism

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Chapter 13

PREMALIGNANT AND MALIGNANT SKIN DISORDERS

Table 13.1. Premalignant Lesions and Squamous Cell Carcinoma (SCC) Summary

Disease	Degree of Malignancy	Common Location(s)	Clinical Presentation
Actinic Keratosis	Squamous dysplasia	**Sun-exposed areas** (head, neck and limbs)	Erythematous, flat-to-thickened lesions with **sandpaper texture** and **central white scale**.
Actinic Cheilitis	Squamous dysplasia	**Lips**	Same as actinic keratosis, but on the **lips**.
Bowen Disease	SCC in situ	**Sun-exposed areas** (head, neck and limbs)	Same as actinic keratosis but patches are **larger**, **redder** and with **more scales** and **crust**.
Erythroplasia of Queyrat	SCC in situ	**Penile glans or prepuce** **Vaginal vulva or labia**	Well-demarcated, **velvety**, **bright-red**, **painless** papule or plaque.
Bowenoid Papulosis	SCC in situ	**Anogenital area**	Small, **flesh-colored-to-reddish-brown flat** or **warty** lesions.
Keratoacanthoma	Well-differentiated SCC	**Sun-exposed areas** (head, neck and limbs)	Dome-shaped, flesh-colored "**volcano-like**" tumor with **raised edges** and a **central keratin horn**.
Squamous Cell Carcinoma (SCC)	Poorly differentiated or invasive SCC	**Sun-exposed areas** (head, neck and limbs)	Papular or nodular nonhealing lesion that **ulcerates**, **bleeds** and **crusts**.

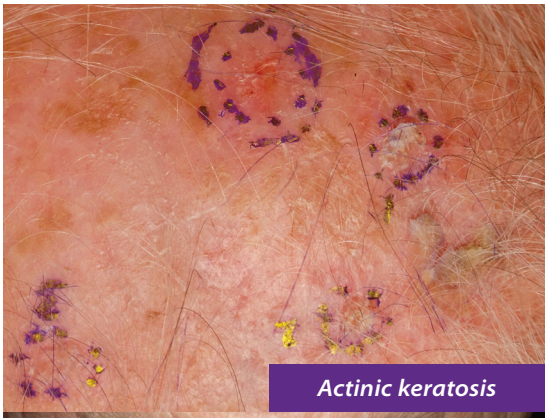
1. ACTINIC KERATOSIS (AK)

- **General:** Also known as **solar or senile keratosis.** Fairly common cutaneous lesion often seen in elderly white individuals. These **premalignant** lesions are **squamous dysplasia,** a precursor of squamous cell carcinoma (SCC). Associated with:
  - **Prolonged sun exposure** (eg, cyclists, farmers, mail carriers, lifeguards).
  - **Arsenic** and **hydrocarbons exposure.**
  - **Immunosuppression** (eg, drugs, malignancies, organ transplant, dialysis).

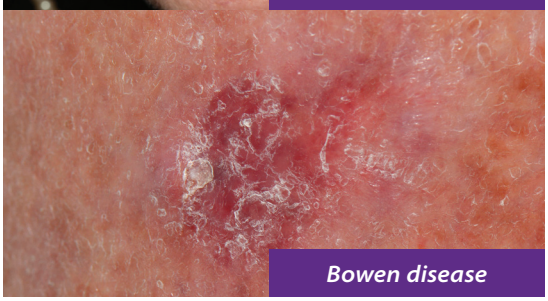
- **Clinical:** Flesh-colored to erythematous, circumscribed, flat-to-thickened macules and papules with **sandpaper texture** and **central white scales.** Lesions are often multiple and occur almost exclusively on **sun-exposed skin** (eg, face, scalp, back of neck, dorsum of hands and arms). If the lesion is located on the **lips,** it is called **actinic cheilitis.** AKs tend to recur when scraped off.

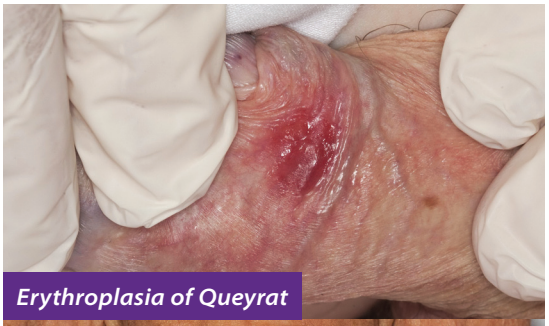
- **Diagnosis**
  - **Best initial test:** Clinical.
  - **Most accurate test:** Skin biopsy showing atypical keratinocytes in the basal layer and some scattered in upper epidermal layers, but not involving full thickness or going beyond the epidermis.

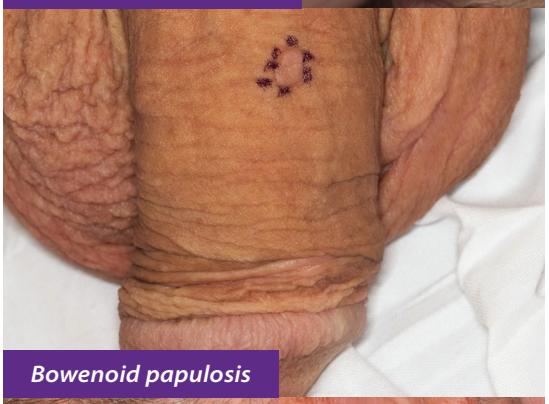
- **Treatment**
  - **First line:** Cryotherapy for limited number of lesions or topical 5-fluorouracil (5-FU) for diffuse involvement (patients can use 5-FU at home).
  - **Second line:** Imiquimod (interferon inducer).

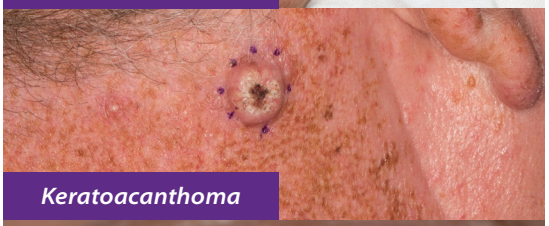

Actinic keratosis

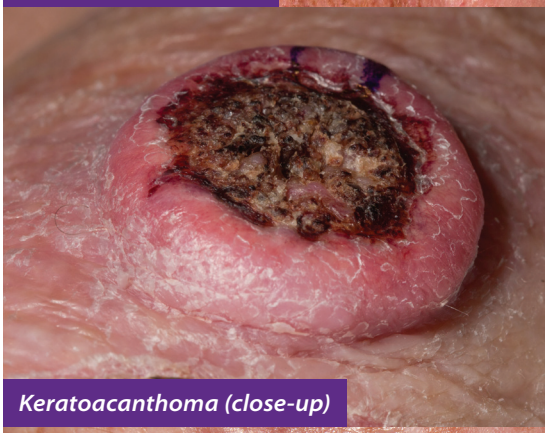

Actinic cheilitis

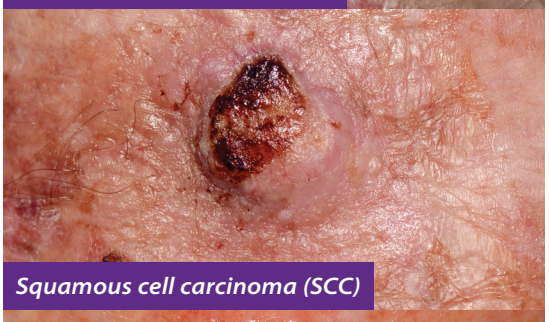

Bowen disease

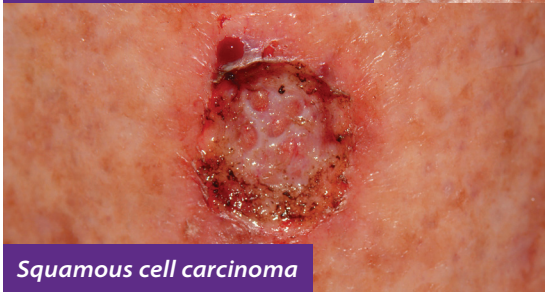

Erythroplasia of Queyrat


Bowenoid papulosis


Keratoacanthoma


Keratoacanthoma (close-up)


Squamous cell carcinoma (SCC)


Squamous cell carcinoma

- **USMLE Pearls: Bowen disease:** This lesion is also known as **squamous cell carcinoma in situ (SCCIS);** the earliest form of SCC. Clinically, Bowen disease may appear similar to actinic keratosis, however the **size, erythema and degree of scale** may be more pronounced. *Histologically*, atypical keratinocytes involve the **full thickness** of the epidermis without going beyond the DEJ.

- **USMLE Pearls: Erythroplasia of Queyrat:** A variant of Bowen disease with involvement usually **limited to the penis or vagina.** Characterized by a well-demarcated, **velvety, bright-red** and **painless** papule or plaque. These lesions are associated with an **uncircumcised penis** and underlying **HPV** (types 16, 18, 31, 35) infection.

- **USMLE Pearls: Bowenoid papulosis:** Also SCCIS and appears histologically similar to *Bowen disease* and *erythroplasia of Queyrat*. The main difference among these three diseases is the clinical presentation. Bowenoid papulosis presents with small **tan-to-red-brown flat or warty** lesions around the **anogenital area,** most commonly on the **penile shaft** or **vaginal labia.** Associated with underlying **HPV** and often diagnosed as condyloma acuminata. *Diagnose* bowenoid papulosis, erythroplasia of Queyrat and Bowen disease with skin biopsy and *treat* with 5-FU, cryotherapy, laser ablation, surgical excision or Mohs micrographic microsurgery.

2. KERATOACANTHOMA (KA)

- **General:** Malignant, low-grade and **well-differentiated SCC.** Rarely will this tumor progress to invasive SCC or metastasize. Same risk factors as SCC (discussed below).

- **Clinical:** The characteristic lesion is a **dome-shaped,** flesh-colored, **crateriform** or **"volcano-like"** tumor with **raised edges** and a **central keratin horn.** Keratoacanthomas usually range from 1 to 2 cm in diameter and develop unusually rapidly over **2 to 8 weeks.** Commonly appear on **sun-exposed areas** such as the limbs, head and neck. KAs may spontaneously regress over 6 to 12 months and leave a depressed annular scar.

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical + skin biopsy showing a keratin-filled central crater with infiltrating, well-differentiated atypical squamous nests.

- **Treatment**
  - **First line:** Surgical excision with clear margins.
  - **Second line:** Cryotherapy, intralesional 5-fluorouracil (5-FU) or methotrexate for nonsurgical candidates.

3. SQUAMOUS CELL CARCINOMA (SCC)

- **General:** Second most common malignant skin cancer after basal cell carcinoma (BCC). Derived from **epidermal keratinocytes** and often arises from precursor lesions such as actinic keratosis, Bowen disease, or bowenoid papulosis. Good prognosis with **< 1% chance of dying** of the disease. Important risk factors are:

- **Chronic UV-light exposure** (most common)
- **Tobacco** and **alcohol** (synergistic effect)
- **High-risk HPV infection** (16, 18, 31, 35 subtypes)
- **Immunocompromised state** (eg, transplant, drugs, dialysis)
- **Lichen planus** and **lichen sclerosus**
- **Hydrocarbons, arsenic, pitch** and **coal tar exposure**
- **Xeroderma pigmentosum**
- **Chronically inflamed or scarred tissue** (eg, third-degree burns, chronic osteomyelitis, chronic ulcers). Also known as **Marjolin ulcer.**

- **Clinical:** Presentation varies greatly; typically characterized by a scaly, erythematous papule, plaque or nodule that may **ulcerate, bleed** and become **tender.** Occurs almost exclusively on **sun-exposed areas** such as head, neck and limbs. A general rule is that SCC commonly affects the **lower part of the face,** but it can occur almost anywhere.

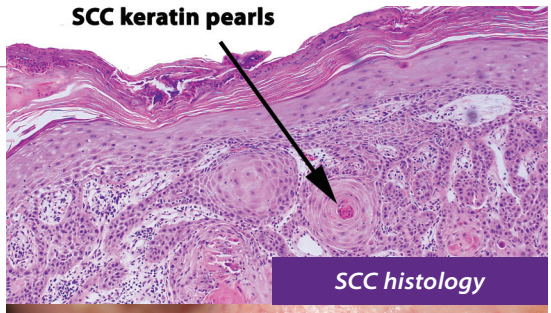
- **Diagnosis**
  - **Best initial and most accurate test:** Skin biopsy showing nests of atypical squamous cells arising from the epidermis and extending into the dermis producing *keratin pearls.*

- **Treatment**
  - **First line:** Curettage and electrodessication, surgical excision or Mohs micrographic microsurgery with clear margins.
  - **Second line:** Radiation therapy for nonsurgical candidates.

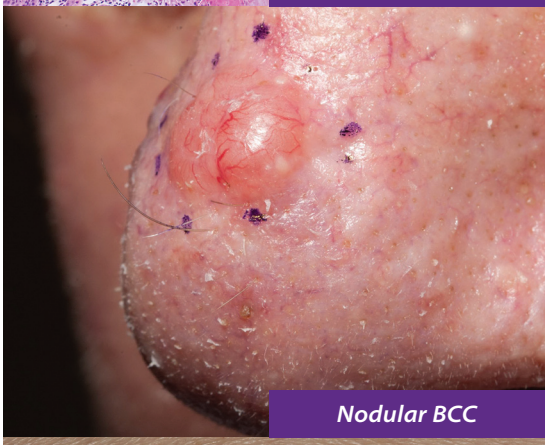
4. BASAL CELL CARCINOMA (BCC)

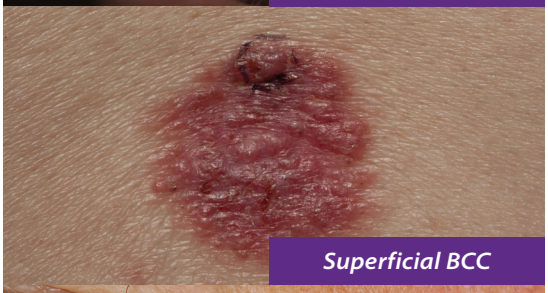
- **General:** Most common malignant skin tumor **(80%).** BCCs are derived from the **basal cells of the epidermis.** Locally aggressive and infiltrating cancer that may rarely invade nerves, bones, vessels or metastasize. Most commonly affects fair-complexioned individuals with chronic sun exposure (eg, cyclists, farmers, lifeguards, mail carriers).

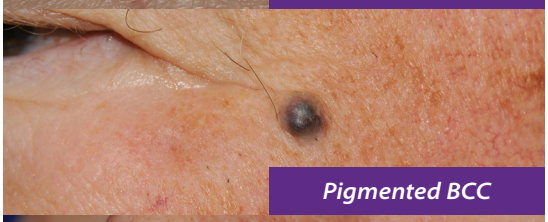
- **Clinical:** BCC clinical presentation depends on the subtype. The usual clinical scenario is a white patient with one of the lesions described below in the inner canthus of the eye, alae of the nose or on the upper lip. A general rule is that **BCC favors the upper lip and above,** but it can occur almost anywhere.
  - **Nodular BCC:** Most common BCC variant **(> 60%)** and most common cancer on the face. Classic appearance of a **round, pearly** and **translucent flesh-colored papule** with **telangiectasias.** May outgrow its blood supply to form an **ulcer with rolled-up borders.**
  - **Micronodular BCC:** Aggressive variant of BCC. Clinically, may appear similar to *nodular BCC* but may be more difficult to treat.
  - **Superficial BCC:** Scaly, **reddish** and irregular **well-circumscribed patch or plaque** that bleeds and may ulcerate. Usually located on the trunk or shoulders. This subtype of BCC can be confused clinically with *SCCIS* or *annular dermatoses* (eg, tinea corporis, nummular eczema).
  - **Pigmented BCC:** May appear similar to a *nodular BCC* or *superficial BCC* but with a **brown-to-black pigmentation.** This subtype of BCC can be confused clinically with melanoma.



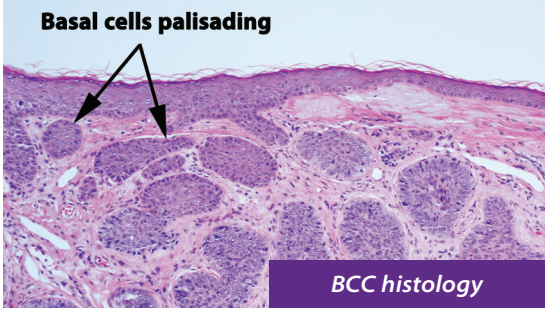
SCC histology


Nodular BCC

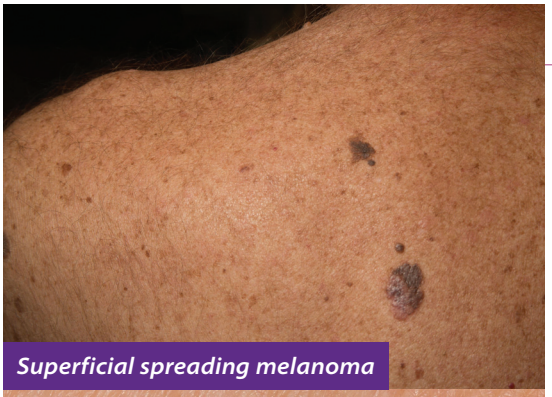

Superficial BCC

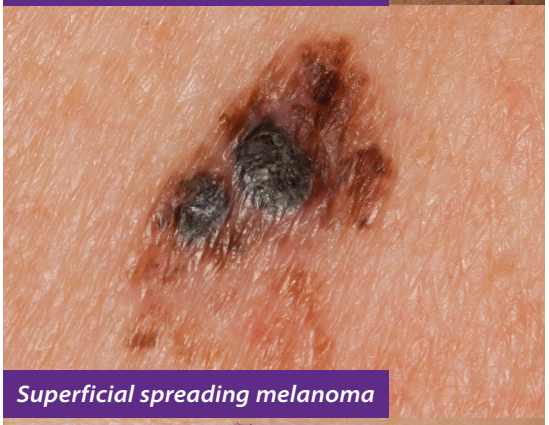

Pigmented BCC

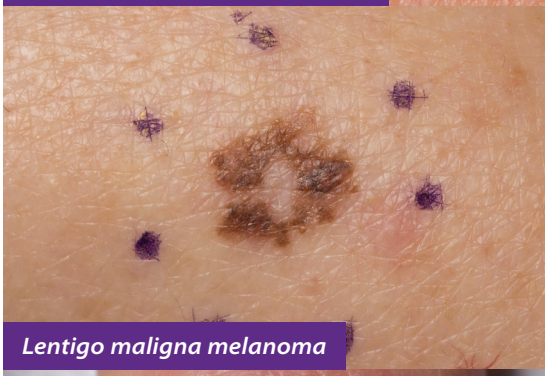

Sclerosing BCC



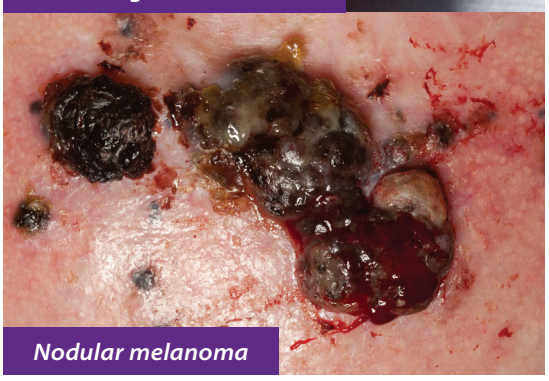
BCC histology


Superficial spreading melanoma


Superficial spreading melanoma


Lentigo maligna melanoma


Acral lentiginous melanoma


Nodular melanoma

- **Morpheaform (sclerosing) BCC:** Appears as a **yellow-to-whitish** scar-like area that is **flat** or **slightly depressed** and **firm** in comparison to the surrounding tissue. This lesion may have telangiectasias and rarely bleeds or ulcerates.
- **Infiltrative BCC:** An **aggressive variant** characterized by infiltrative, vertical basaloid tumor strands penetrating into the dermis.

- **Diagnosis**
  - **Best initial and most accurate test:** Skin biopsy showing multifocal nests of *palisading* basaloid cells extending into the dermis.

- **Treatment**
  - **First line:** Electrodessication and curettage, surgical excision or Mohs micrographic microsurgery.
  - **Second line:** Some BCCs may be amenable to topical 5-FU, imiquimod, cryotherapy or radiation therapy. **Vismodegib,** a small molecule inhibitor of the *smoothened receptor,* may be appropriate for select patients with locally advanced or metastatic BCC.

5. MELANOMA

- **General:** Malignant and aggressive tumor due to uncontrolled and malignant growth of melanocytes. Associated with ***BRAF, KIT*** and ***CDKN2A*** gene mutations. Most rapidly increasing cancer worldwide and leading cause of death secondary to skin cancer. More prevalent in **whites** with a median age of diagnosis at around 50 years of age. Melanoma may be **prevented** with sun-protective behaviors and annual skin checks. Most important risk factors are:
  - **Prolonged sun exposure** (most important), tanning booth usage and history of blistering sunburns
  - **Previous melanoma** or strong family history
  - Light complexion, light eyes and blonde or red hair
  - **Dysplastic nevus syndrome**
  - **Xeroderma pigmentosum**
  - **Immunodeficiency**

- **Clinical:** **ABCDE** criteria for malignancy screening: **A**symmetry of shape, **B**order irregularity, **C**olor variation, **D**iameter > 6 mm and **E**volution.
  - **Radial (horizontal) growth phase:** Initial phase of invasion with **minimal** metastatic potential. Melanocytes proliferate within the epidermis and along the DEJ but stay *within* the papillary dermis. The three main subtypes that exhibit initial radial growth are:
    - **Superficial spreading melanoma (SSM):** Irregular, flat or slightly elevated, **brown-to-black** lesion with varying nodularity (displays **ABCDE** warning signs). Affects intermittently sun-exposed areas such as the **lower extremities in women** and **upper back in men.**
    - **Lentigo maligna melanoma (LMM):** Common in elderly patients and mainly appears on chronically sun-damaged skin. Characterized by a **brown-to-black** macule or patch with **irregular pigmentation and borders.** Carries a good prognosis due to a **long and slow radial growth phase** lasting over 15 to 20 years.
    - **Acral lentiginous melanoma:** Most common subtype in **African Americans and Asians.** Not related to sun exposure. Usually located on the **palms, soles or subungual** and may be confused with other benign entities (eg, subungual hematoma, nevi). **Hutchinson sign**

refers to dark pigmentation at proximal nailfold and indicates nail matrix involvement. Poor prognosis often due to delayed diagnosis.

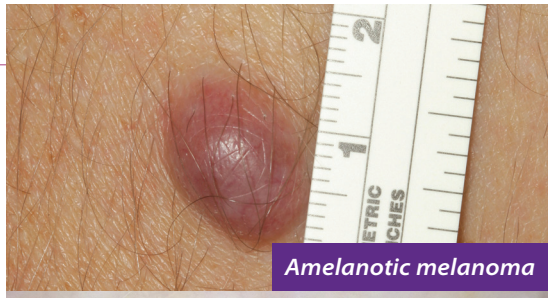
- **Vertical growth phase:** Final phase of invasion with **high potential for metastasis.** Penetration of malignant cells into the underlying reticular dermis. May spread to local lymph nodes and internal organs via lymphatics or bloodstream, respectively. In this phase of evolution, the cancer is usually thickened and raised.
  - **Nodular melanoma:** Presents as a dark brown-to-black, **dome-shaped papule or nodule** that rapidly changes in size and shape. Lesions are **aggressive** and usually **ulcerate, bleed** and **crust.** Nodular melanoma skips the radial growth and goes straight to vertical growth **(worst prognosis).** The **amelanotic variant** is flesh-colored and lacks pigmentation; it often goes unnoticed for years and may be confused with a BCC or pyogenic granuloma.

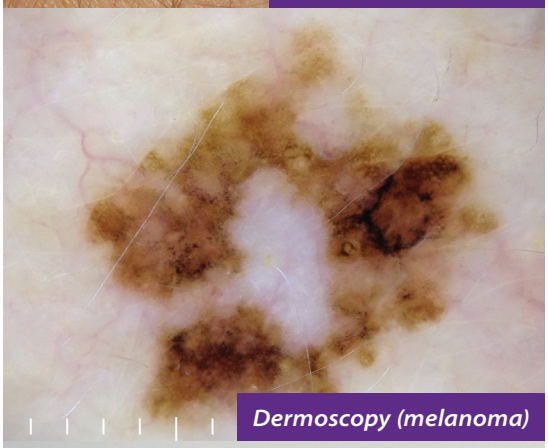
- **Diagnosis**
  - **Best initial test:** Clinical + **excisional biopsy** with 1 to 3 mm margins. Excisional biopsy allows for evaluation of *Breslow depth, presence of ulceration, mitosis count* and *lymphatic/vessel invasion*. If the lesion is **> 1 mm deep,** a sentinel lymph node biopsy **(SLNB)** should be considered. Dermoscopy examination may provide clues to differentiate benign from malignant melanocytic lesion.
  - **Most accurate test:** Skin biopsy showing atypical and infiltrating melanocytic nests proliferating through epidermis and dermis. Special stains used to differentiate melanocytes from keratinocytes include **S-100, HMB-45 and Melan-A.**

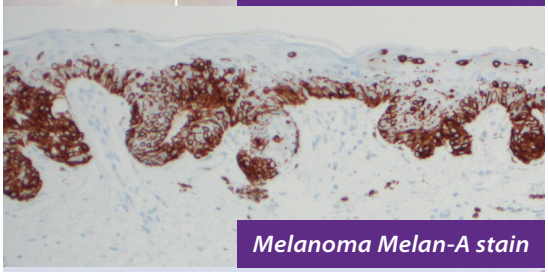
- **Treatment**
  - **First line:** Early **wide local excision (WLE)** *with* **narrow margins** is the standard initial treatment (narrow margins = **1 to 2 cm,** wide margins = **3 to 5 cm**).
    - **Excisional margins** are *based on thickness*:
      - **Melanoma in situ:** WLE with **0.5 cm** margins.
      - **< 1mm thick:** WLE with **1 cm** margins.
      - **1 to 2 mm thick:** WLE with **1 to 2 cm** margins.
      - **> 2 mm thick:** WLE with **2 cm** margins.
    - **Systemic medications:** For unresectable or metastatic melanoma, systemic therapy may be considered:
      - **Dacarbazine** (alkylating agent)
      - **Vemurafenib** (BRAF inhibitor)
      - **Ipilimumab** (CTLA-4 inhibitor)
      - **Pembrolizumab** (PD-1 inhibitor)
      - **Trametinib** (MEK inhibitor)

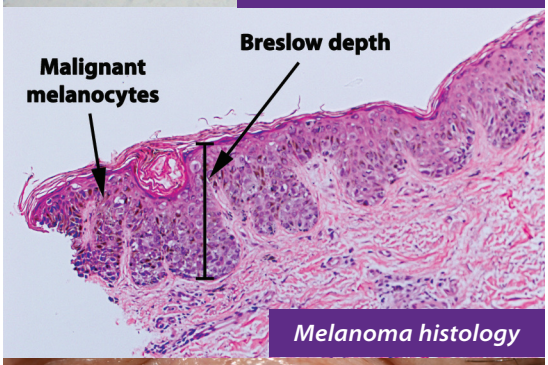
- **USMLE Pearls: Breslow depth:** Measures **depth of invasion,** the most important histologic determinant of **prognosis.** Defined as the vertical measure (mm) from the *top of the granular layer to the deepest point of tumor* involvement. The second most important prognostic factor is the *presence of ulceration* on histology. The **Clark level** is a measure indicative of the **anatomical level of invasion** (eg, epidermis, reticular dermis) and is used less frequently, as it has less prognostic significance.

- **USMLE Pearls:** Look for a patient that had a melanocytic lesion excised > 10 years ago **(melanoma).** The patient now presents to the physician with a new melanocytic lesion in a very unusual location such as the genitals, eye or GI tract. This is most likely a recurrence of melanoma after 10 years.

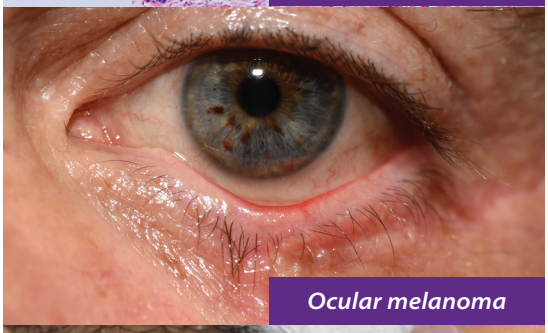

Amelanotic melanoma

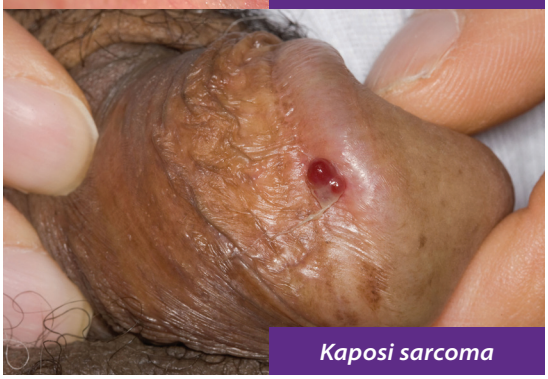

Dermoscopy (melanoma)


Melanoma Melan-A stain

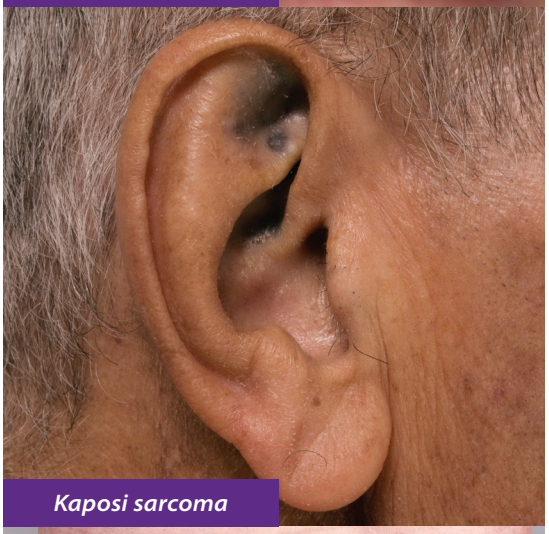


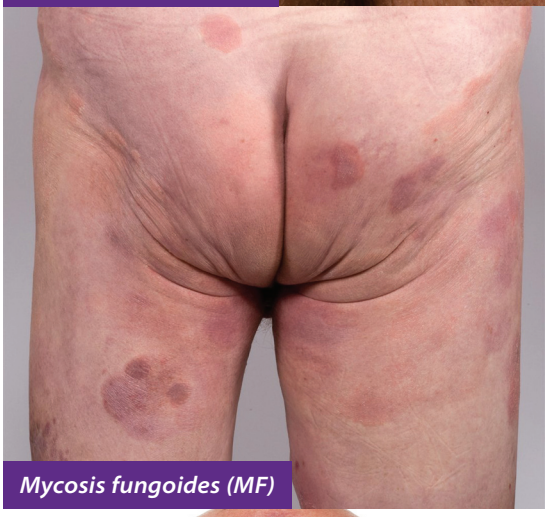
Melanoma histology


Ocular melanoma


Kaposi sarcoma


Kaposi sarcoma


Kaposi sarcoma


Mycosis fungoides (MF)


Mycosis fungoides (MF)

6. KAPOSI SARCOMA (KS)

- **General:** Malignant tumor derived from **endothelial cells** or primitive mesenchymal cells. Considered an **AIDS-defining lesion;** the *most common* cancer in HIV patients. **HHV-8** is found in all types of KS tissue. Commonly affect people of **Mediterranean or African origin** and patients with **lymphoma** or **immunosuppression** (eg, transplant, dialysis, HIV).

- **Clinical:** Characterized by a flat-to-raised, **reddish-purple-to-black** lesion that evolves into a plaque, nodule or ulcer. Lesions are **highly vascular** and prone to bleeding. Most commonly affect the **skin,** followed by the **GI tract.** Kaposi sarcoma is often confused with hemangiomas or bacillary angiomatosis *(B. henselae).*

- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + skin biopsy showing atypical spindle cells and extensive vessel proliferation with RBCs extravasation into the dermis. Stains positive for **HHV-8.** Consider testing for HIV (ELISA) if the patient has any risk factors.

- **Treatment**
  - **First line:** Radiation therapy, surgical excision or intralesional interferon, bleomycin or cisplatin. If HIV+, optimize therapy to increase CD4+ count (KS may regress with antiretroviral therapy).
  - **Second line:** Vinblastine or liposomal doxorubicin. Establish baseline cardiac function with MUGA scan or echocardiography before initiating doxorubicin therapy, as it is cardiotoxic.

7. CUTANEOUS T-CELL LYMPHOMA (CTCL)

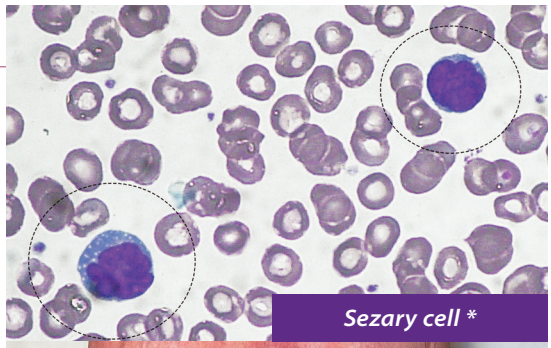
- **General:** Lymphoproliferative disorder with **neoplastic T-cells** infiltrating the dermis and epidermis. The most common T-cell lymphoma immunophenotype is the **CD4+ type.** There are many CTCL subtypes, but the most important ones are:
  - **Mycosis fungoides (MF):** The name is a misnomer; it has nothing to do with a fungus. It is the *most common* primary cutaneous T-cell lymphoma (CTCL). MF is a chronic and slowly progressive neoplastic disorder of **memory Th cells.** It is mainly divided into three stages: **patch, plaque** and **tumor.**
  - **Sézary syndrome:** Aggressive form of MF with whole skin involvement **(erythroderma)** plus a **leukemic phase** with circulating malignant T-cells. These circulating T-cells have a characteristic **cerebriform nucleus** and are called **Sézary cells.**

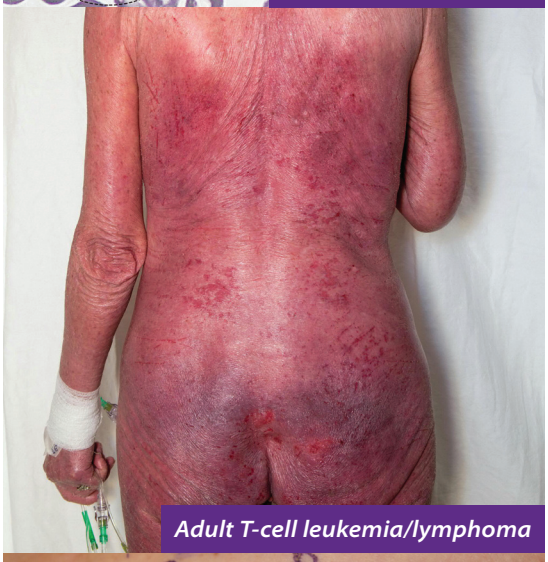
- **Clinical:** Most commonly affects people 40 to 60 years old. Starts with **nonspecific,** often asymptomatic, erythematous, annular macules and/or patches on any part of the skin. These lesions may evolve into well-defined, **red-to-purple plaques, ulcers** and/or **tumors.** The disease can affect the whole skin and disseminate to lymph nodes, lung, liver and spleen. Diagnosis may be delayed, as lesions often resemble eczema or psoriatic plaques.

- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + skin biopsy showing a band-like lymphocytic infiltration with **Pautrier microabscesses** and neoplastic cells invading the epidermis (epidermotropism). Other useful tests include *flow cytometry* to identify CD4+ clones and *peripheral smear* to detect atypical **cerebriform T-cells** in Sézary syndrome.

- **Treatment**
  - **First line:** Depends on staging. Psoralens with UV-A (PUVA), narrow-band UV-B, radiation therapy, topical steroids, topical retinoids or topical alkylating agents for early stage MF.
  - **Second line:** Single agent chemotherapy, oral retinoids (eg, isotretinoin, bexarotene) or photophoresis for advanced MF.

- **USMLE Pearls: Adult T-cell Leukemia/Lymphoma (ATLL):** Rare **aggressive** subtype of CTCL with poor prognosis. Associated with underlying retroviral infection with *Human T-lymphotropic virus 1* **(HTLV-1).** This virus is endemic in **Japan,** the **Caribbean** and South and Central America. ATLL severely affects the **skin** and may also involve **bones,** leading to hypercalcemia. The circulating malignant T-cells have a characteristic multilobulated nucleus that resembles a **cloverleaf.**


Sezary cell *


Adult T-cell leukemia/lymphoma

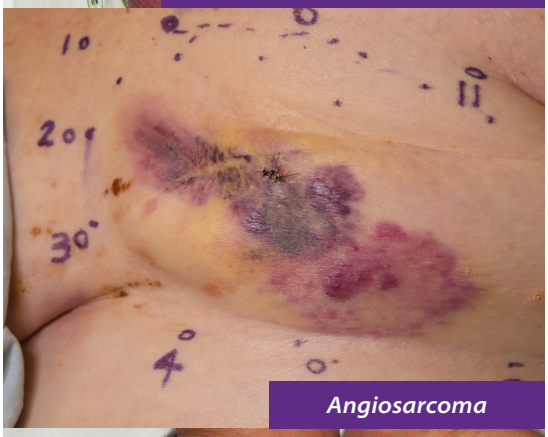
8. ANGIOSARCOMA

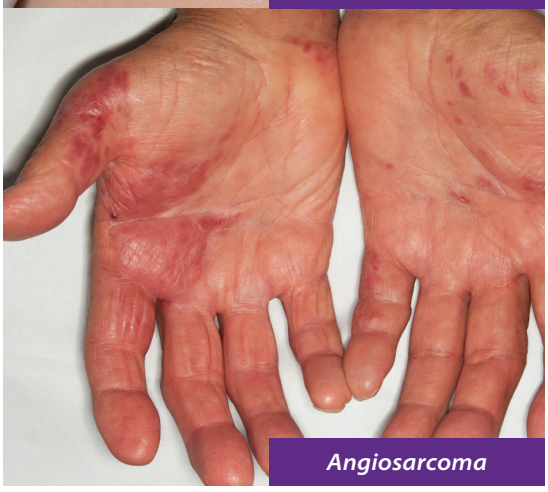
- **General:** Also known as **hemangiosarcoma** or **lymphangiosarcoma,** an uncommon malignant neoplasm derived from the **endothelial cells** of *blood vessels* and/or *lymphatics*. Most commonly occurs in the **skin** and **soft tissues,** but may occur in any organ, such as the liver, breast or spleen. Poor prognosis, as diagnosis is often delayed due to subtle physical findings. When angiosarcoma develops as a complication of chronic lymphedema, it is known as **Stewart-Treves syndrome.** Important risk factors are:
  - **Chronic lymphedema** (eg, post-radical mastectomy)
  - **Radiation therapy** (eg, past lymphoma treated with radiation)
  - **Chronic foreign bodies** (eg, plastic, metal)
  - **Arsenic** and **vinyl chloride exposure**

- **Clinical:** Single or multiple, **blue-black-to-red** macules, papules, plaques, patches or nodules that may **ulcerate and bleed.** Most commonly located on the **head and neck area of an elderly patient,** but can occur anywhere. May be confused with other vascular pathologies such as Kaposi sarcoma or hemangioma.

- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + skin biopsy showing dermal infiltration by proliferating vascular spaces lined by atypical endothelial cells.

- **Treatment**
  - **First line:** Surgical excision followed by radiation therapy.
  - **Second line:** Chemotherapy (eg, paclitaxel).


Angiosarcoma


Angiosarcoma

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Chapter 14

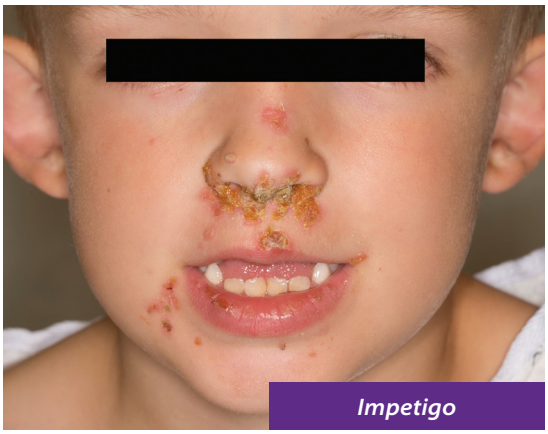
SELECTED BACTERIAL INFECTIONS

Table 14.1. Staphylococcus and Streptococcus Skin Infections Summary *(Refer to Appendix I for Bacterial Classification)*

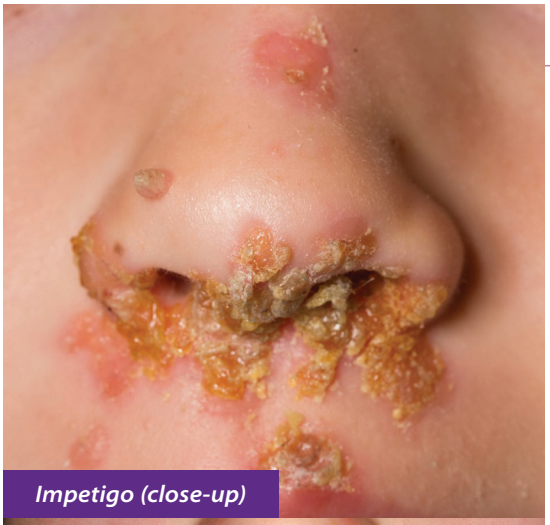
Disease	Most Common Pathogen	Level of Invasion	Method of Invasion	Unique Characteristics
Impetigo "school sores"	*Staphylococcus aureus*	Epidermis	Direct +/– toxin	**Yellow-to-golden honey-colored crust** over an erythematous erosion.
Follicular infection	*Staphylococcus aureus*	Hair follicle	Direct	**Follicular distributed** red papules, pustules and/or nodules +/– purulent follicles.
Erysipelas	*Streptococcus pyogenes*	Superficial dermis	Direct	Bright red, tender, swollen and indurated **plaques with sharply demarcated and advancing raised borders** +/- lymphangitis.
Cellulitis	*Streptococcus pyogenes* (adults) *Staphylococcus aureus* (children)	Deep dermis + subcutaneous tissue	Direct	Erythematous, tender, swollen **plaques with poorly demarcated and flat borders** +/– lymphangitis.
Necrotizing fasciitis (NF)	**Type I NF:** Polymicrobial **Type II NF:** *Streptococcus pyogenes*	Subcutaneous tissue + fascia	Direct +/– toxin	**Necrosis** **Palpable crepitus** **Pain out of proportion** to clinical findings initially.
Scarlet fever	*Streptococcus pyogenes*	Systemic	Direct and toxin	**Strep throat** + **strawberry tongue** + **circumoral pallor** + "**sandpaper" texture rash**. "**Pastia lines**" (accentuation of the rash on the skin folds).
Staphylococcal "scalded skin" syndrome	*Staphylococcus aureus*	Systemic	Toxin	**Desquamating sheets of skin** in a young patient. **Positive Nikolsky sign**.
Toxic shock syndrome	*Staphylococcus aureus*	Systemic	Toxin	**Systemic symptoms** with internal organ involvement (elevated LFTs, BUN, Cr, etc). **Retained foreign body** (eg, tampon, sutures, nasal packing).

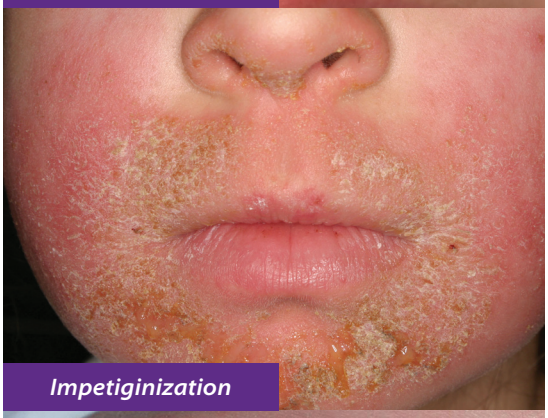
1. IMPETIGO

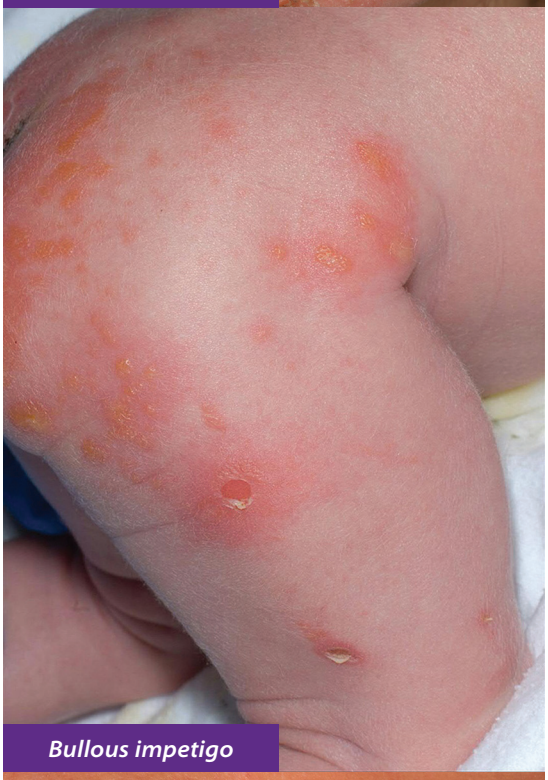
- **General:** Highly contagious *superficial* bacterial skin infection most commonly caused by the gram-positive cocci, ***Staphylococcus aureus,*** followed by ***Streptococcus pyogenes.*** The infection is limited to the **upper epidermis** and **does not** go beyond the DEJ. Most common bacterial infection in children and most prevalent in humid and poor areas. The term **"impetiginization"** is used when impetigo occurs at a site of pre-existing skin injury (eg, erosions, eczema, scratches). **Bullous impetigo** is a rarer clinical variant caused by ***S. aureus;*** **exfoliative toxin** produced *locally* by the bacteria target **desmoglein-1** and disrupts epidermal desmosomes leading to *non-sterile* intraepidermal bullae formation.

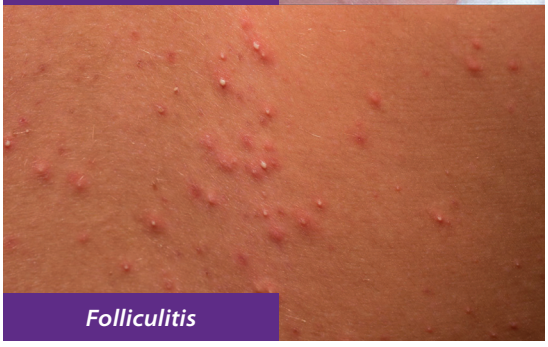


Impetigo


Impetigo (close-up)


Impetiginization


Bullous impetigo


Folliculitis

- **Clinical:** Usually begins with an erythematous macule, papule or pustule that evolves into a short-lived, **fragile vesicle or bulla.** Once they rupture, the content dries up, leaving the classic **yellow-to-golden "honey-colored" crust** over an erythematous erosion. Commonly affect the **extremities, face** (eg, nose, mouth, chin) or a **preexisting skin wound.** Generally, there is regional lymphadenopathy *without* systemic symptoms.

- **Diagnosis**
  - **Best initial test:** Clinical. When in doubt, a quick diagnosis may be elicited by swabbing the lesion and Gram staining; *S. aureus* will show as gram-positive cocci in **clusters** and *S. pyogenes* as gram-positive cocci in **chains.**
  - **Most accurate test:** Bacterial culture of infected tissue or exudate from an intact vesicle or bulla.

- **Treatment**
  - **First line:** Topical mupirocin or retapamulin for limited disease. Remove crust by soaking to allow penetration of creams.
  - **Second line:** Oral dicloxacillin or cephalexin for unresponsive or severe disease. If **MRSA,** use oral clindamycin or trimethoprim-sulfamethoxazole (TMP-SMX).

- **USMLE Pearls: Post-Streptoccocal Glomerulonephritis (PSGN):** Nephritis occurring as a sequela of *S. pyogenes* **throat or skin infection** (eg, impetigo, scarlet fever). PSGN is **not prevented** by antibiotic treatment; it carries a good prognosis in children but a bad one in adults (many of them progress to chronic renal failure). **PSGN** occurs *2 to 4 weeks after* strep infection, **do not** confuse with **IgA nephropathy** (Berger disease), which occurs *only days after* an URTI or throat infection **(synpharyngitic).** *Diagnose* with urinalysis showing **proteinuria** and **dysmorphic RBCs.** *Treat* by controlling edema and blood pressure with diuretics and low-salt diet plus penicillin for those with positive throat culture. Also remember that **acute rheumatic fever (ARF)** occurs **only after streptococcal pharyngitis** (not skin infection) and may be prevented by prompt antibiotic administration.

2. FOLLICULAR INFECTION

- **General:** Infection of the *superficial* or *deep* hair follicle most commonly caused by the coagulase- and catalase-positive bacterium, ***Staphylococcus aureus.*** Commonly affects the face, chest, back, axillae and buttocks. Severity varies by **depth** and **size** of infection.

- **Clinical**
  - **Folliculitis:** Mildest form, infection of the **superficial hair follicle.** Characterized by follicular distributed red papules and/or pustules ranging from **1 to 3 mm** in diameter. May occur after using **hot tubs** or **whirlpools,** in which case the usual pathogen is ***P. aeruginosa*** **("hot tub folliculitis").**
  - **Furuncle (boil):** Deeper infection of the hair follicle with **walled-off collection of pus.** Characterized by an erythematous area surrounding a **tender, fluctuant, red nodule** ranging from 1 to 2 cm in diameter.

- **Carbuncle:** Same as furuncle, except **larger** and **deeper nodule** (subcutaneous tissue). Caused by **merging of furuncles.** Characterized by a **tender, raised, erythematous nodule with multiple purulent draining follicles.**

- **Diagnosis**
  - **Best initial test:** Clinical.
  - **Most accurate test:** Bacterial culture of infected tissue or exudate.

- **Treatment**
  - **First line**
    - **Folliculitis:** Antibacterial washes (eg, chlorhexidine, triclosan), topical mupirocin or clindamycin.
    - **Furuncle and carbuncle:** Incision and drainage (I&D).
  - **Second line**
    - **Folliculitis:** Oral dicloxacillin, TMP-SMX or cephalexin for recalcitrant or severe disease.
    - **Furuncle and carbuncle:** I&D plus systemic antibiotic with **MRSA** coverage (doxycycline, clindamycin or TMP-SMX) for complicated cases.

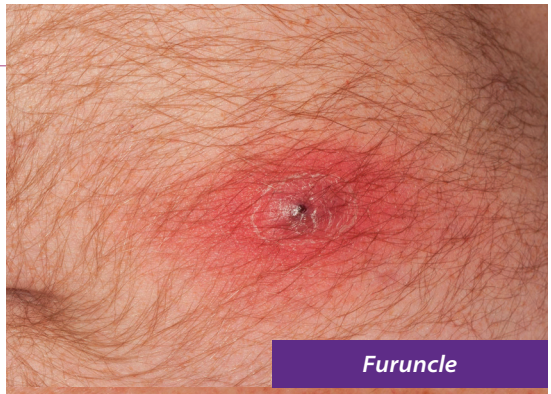
3. ERYSIPELAS

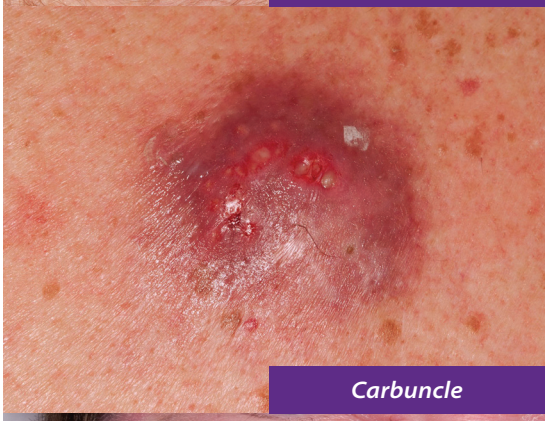
- **General:** Bacterial skin infection most commonly caused by the coagulase and catalase-negative bacterium, ***Streptococcus pyogenes*** and less commonly by ***Staphylococcus aureus*.** Erysipelas is a *superficial* variant of cellulitis mainly involving the **upper dermis** with prominent superficial lymphatic involvement; if left untreated, it may cause lymphangitis and rarely bacteremia or sepsis.

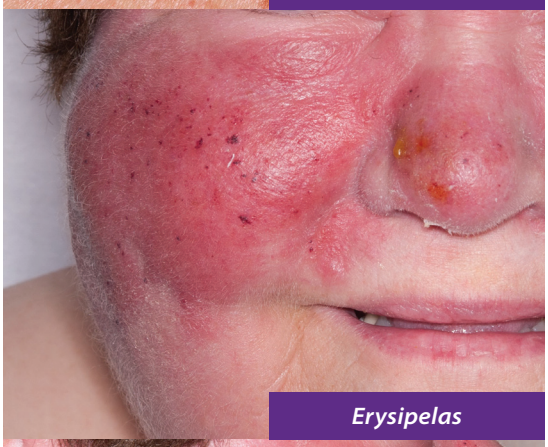
- **Clinical:** Most commonly affects the **legs,** followed by the **face,** but can occur anywhere. Look for a patient with the sudden onset of a **bright red, tender, swollen and indurated** ("peau d'orange") **plaque** on the **leg** or **face.** The erysipelas plaque is **sharply demarcated** with **advancing raised borders,** as opposed to cellulitis (less raised and poorly defined borders). Patients are usually febrile and complain of headaches, myalgias and chills.

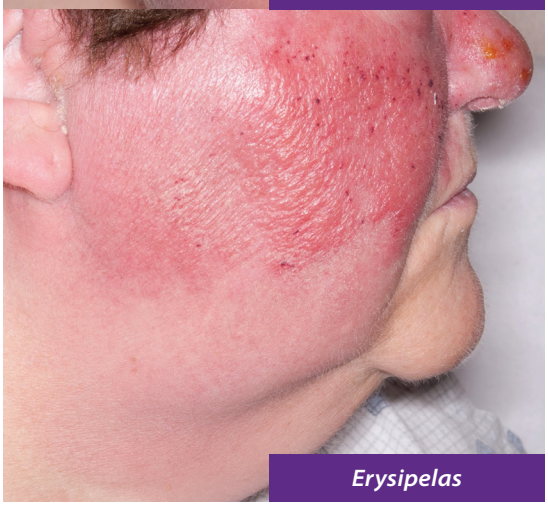
- **Diagnosis**
  - **Best initial test:** Clinical. High anti-DNase B and ASO titers indicate *S. pyogenes* as the most likely culprit.
  - **Most accurate test:** Bacterial culture of infected tissue obtained by saline lavage needle aspiration or skin biopsy.

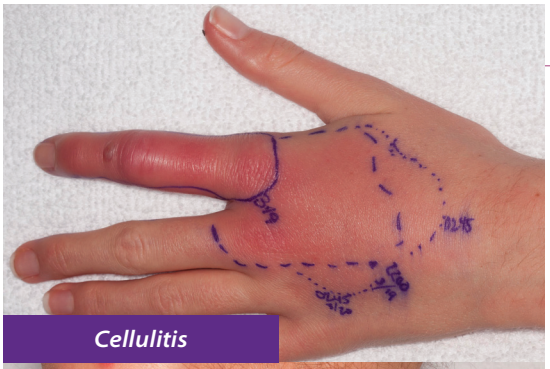
- **Treatment**
  - **First line:** Oral penicillin, amoxicillin or erythromycin. If **MRSA,** use doxycycline, clindamycin or TMP-SMX.
  - **Second line:** IV ceftriaxone or cefazolin for severe or recalcitrant disease. If **MRSA,** use vancomycin, linezolid, ceftaroline, daptomycin, dalbavancin or tigecycline.

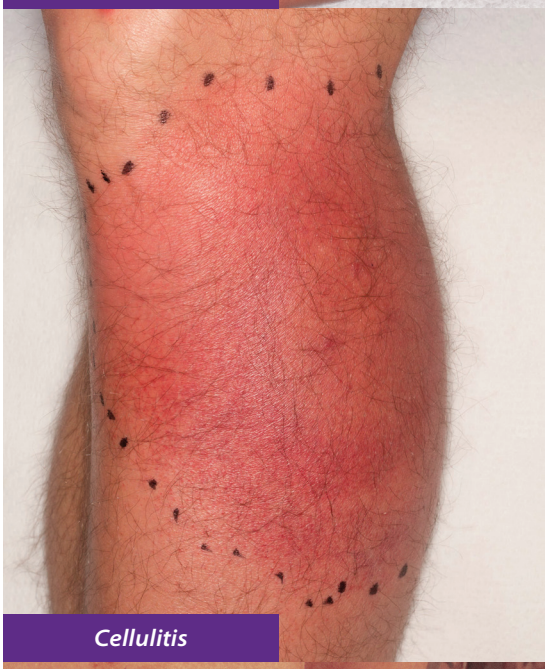

Furuncle

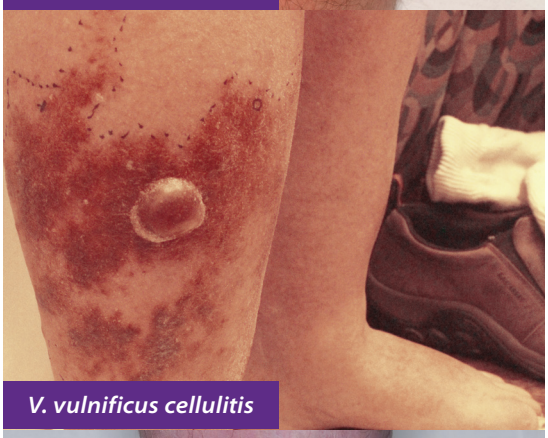

Carbuncle

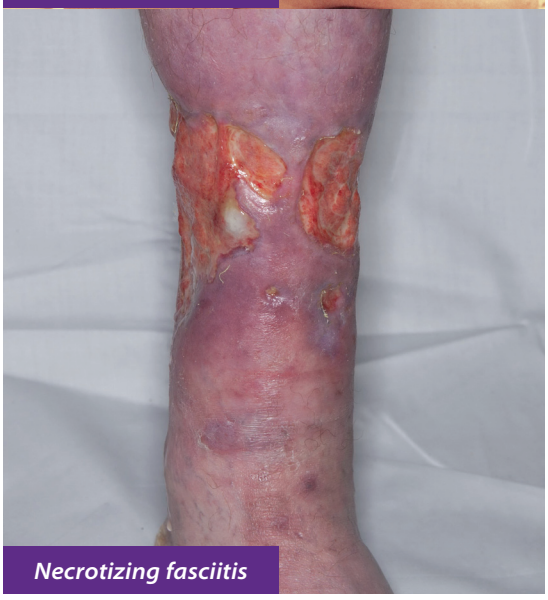

Erysipelas


Erysipelas


Cellulitis


Cellulitis


V. vulnificus cellulitis


Necrotizing fasciitis

4. CELLULITIS

- **General:** Deep bacterial skin infection most commonly caused by ***Streptococcus pyogenes*** and ***Staphylococcus aureus*.** The infection is **deeper than erysipelas,** mainly involving the **deep dermis** and **subcutaneous tissue.** If left untreated, it may spread to dermal lymphatics and blood to cause lymphangitis, bacteremia or sepsis. The bacterium usually enters through a **skin defect** (eg, laceration, tinea pedis lesion, stasis ulcer, insect bite, puncture wound).

- **Clinical:** Fevers, chills and malaise often precede the development of an **erythematous, tender, warm and swollen plaque** (typically unilateral). Cellulitis is clinically similar to erysipelas, except the plaque is **flatter** with **poorly demarcated borders.** Most commonly affects the **lower extremities,** where it may be confused with thrombophlebitis, DVT, stasis dermatitis or a ruptured Baker cyst.

- **Diagnosis**
  - **Best initial test:** Clinical. Blood cultures have very low yield but can be useful if positive.
  - **Most accurate test:** Bacterial culture of infected tissue obtained by saline lavage needle aspiration or skin biopsy.

- **Treatment**
  - **First line:** Oral dicloxacillin, clindamycin or cephalexin. If **MRSA,** use oral doxycycline, clindamycin or TMP-SMX.
  - **Second line:** IV oxacillin, nafcillin or cefazolin for severe or recalcitrant disease. If **MRSA,** use vancomycin, linezolid, ceftaroline, daptomycin, dalbavancin or tigecycline.

- **USMLE Pearls:** ***Vibrio vulnificus*:** Gram-negative, rod-shaped bacterium that causes a **severe type of cellulitis** that often progresses to **necrotizing fasciitis.** Presents with tender, erythematous plaques and large **hemorrhagic bullae** accompanied by fever, chills, **hypotension** and **septic shock.** It occurs in patients exposed to **raw seafood** (eg, oyster) or to **contaminated seawater** with an open wound. Tends to affect immunocompromised patients or those with underlying **liver cirrhosis,** particularly those with **hemochromatosis.** *Treat* with doxycycline. (**Note**: ***Yersinia*, *Listeria*** and ***V. vulnificus*** are iron-loving bacteria and have a predilection for patients with iron overload).

5. NECROTIZING FASCIITIS (NF)

- **General:** Severe, life-threatening and rapidly progressive necrotizing bacterial infection of the **subcutaneous tissue** and **fascia.** Broadly divided into *necrotizing fasciitis type I* and *type II.* **Type I NF** is polymicrobial (including streptococci, *S. aureus, E. coli, Bacteroides* and *Clostridium* sp.) while **Type II** is caused by group A streptococci. The infection spreads through fascial planes to involve adjacent muscles and full thickness skin. **Poor prognosis** and **high mortality** if left untreated. There is usually a **portal of entry** such as a penetrating injury (eg, nail), postsurgical wound or insect bite. When necrotizing fasciitis occur on the perineum or genitalia, it is known as **Fournier gangrene.**

- **Clinical:** Characterized by a **rapid onset** of tender, swollen, erythematous-to-violaceous skin with secondary **bullae, necrosis** and/or **palpable crepitus** (gas). Classically, there is initially **severe pain out of proportion to physical exam.** Often accompanied by **severe systemic findings** such as fevers, chills, weakness, confusion and shock.

- **Diagnosis**
  - **Best initial test:** Clinical. If suspicion is high, **surgical debridement** is both *diagnostic and therapeutic* and should not be delayed. Labs may show high WBCs and CPK levels and imaging (x-ray, CT scan or MRI) may reveal **subcutaneous gas.**
  - **Most accurate test:** Bacterial culture of infected tissue obtained by surgical debridement.

- **Treatment**
  - **First line:** *Surgical debridement* + IV fluids + a carbapenem or beta-lactam/beta-lactamase combination:
    - Ampicillin/sulbactam
    - Ticarcillin/clavulanic acid
    - Piperacillin/tazobactam
  - **Second line:** Clindamycin (often added for antitoxin effect). IV penicillin if *S. pyogenes* is confirmed (Type II NF). Hyperbaric oxygen therapy may be helpful for anaerobes.

6. SCARLET FEVER

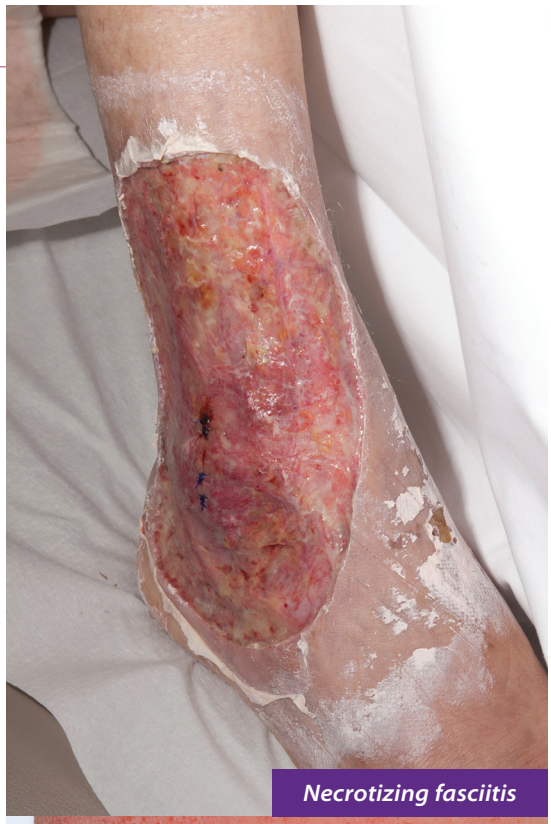
- **General:** Bacterial syndrome caused by infection with the gram-positive cocci **group A β-hemolytic streptococcus** (GABHS). Scarlet fever is characterized by the *triad* of **pharyngitis, fever** and an **erythematous rash** caused by circulating **erythrogenic toxin.** Spreads by respiratory droplets and is more common in school-aged children.

- **Clinical:** Begins with an **exudative pharyngitis** and flu-like symptoms. This is followed by an erythematous **"sunburn-like"** and **petechial** eruption that begins on the head and neck and generalizes to the body. The rash has a **"sandpaper" texture,** is accentuated on skin folds **(Pastia lines)** and *spares* the mouth, producing **circumoral pallor.** The classic sign is a red, beefy tongue with white exudate and prominent papillae known as **"strawberry tongue."** The exanthem ends with **desquamation** and heals without scarring. Scarlet fever clinical presentation is similar and often confused with Kawasaki disease (discussed in chapter 19).

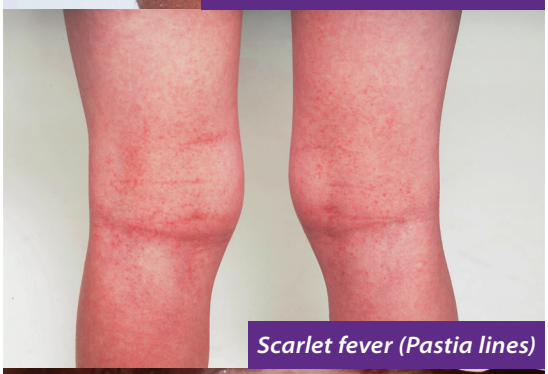
- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + rapid strep test and throat/nose bacterial culture.

- **Treatment**
  - **First line:** Penicillin V + symptomatic care.
  - **Second line:** Amoxicillin (erythromycin if allergic to penicillin).

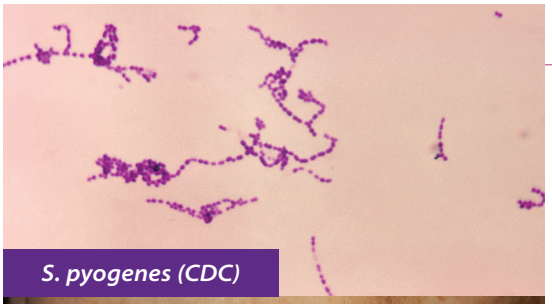
- **USMLE Pearls: Acute Rheumatic Fever (ARF):** Systemic disease affecting the **heart, CNS, joints** and **skin** that occurs as a sequela of **streptococcal pharyngitis.** Most commonly affects the **mitral valve,** followed by the **aortic valve,** which may result in stenosis or regurgitation. The characteristic rash of ARF is **erythema marginatum,** an

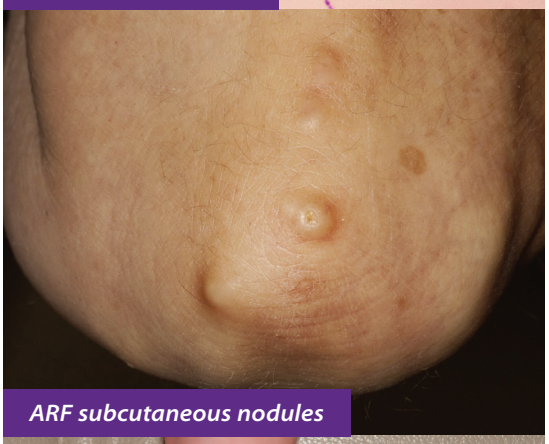

Necrotizing fasciitis

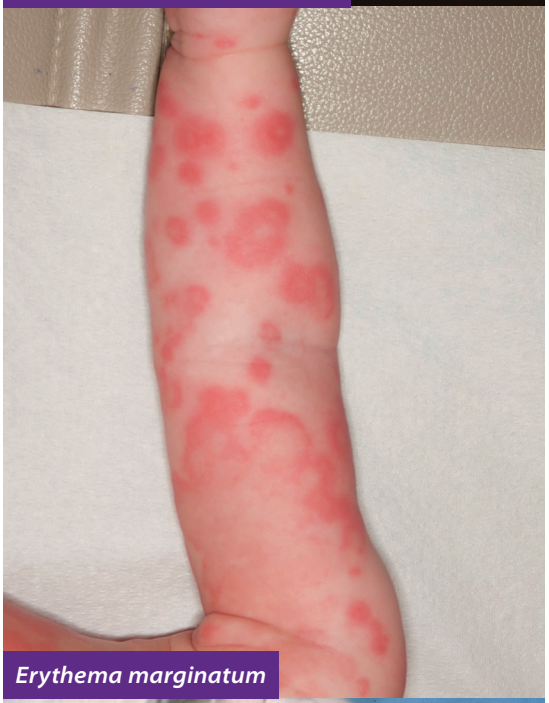

Scarlet fever rash (close-up)

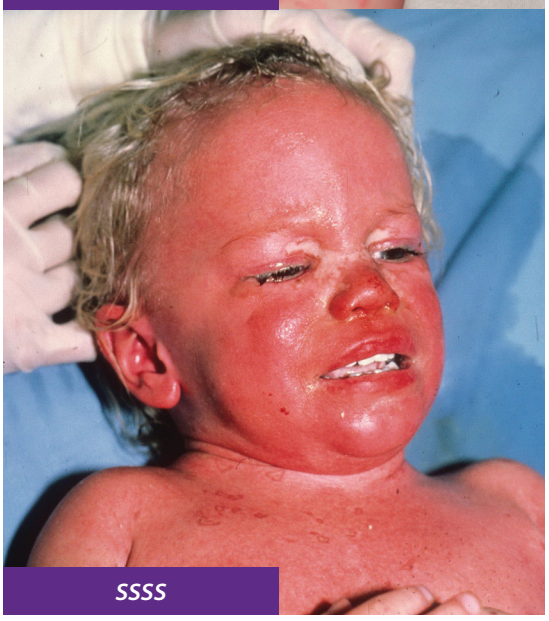

Scarlet fever (Pastia lines)


Strawberry tongue


S. pyogenes (CDC)


ARF subcutaneous nodules


Erythema marginatum


SSSS

erythematous, serpiginous or annular maculopapular rash with advancing raised borders and central clearing. *Diagnosis* of ARF requires evidence of **streptococcal infection** (ASO titers or throat culture) + **2 major** Jones criteria or **2 minor and 1 major** criteria. **Major Jones criteria** can be remembered by using the mnemonic **SPACE:**

- **S**ubcutaneous nodules
- **P**ancarditis (myocarditis, pericarditis and/or endocarditis)
- **A**rthritis
- **C**horea
- **E**rythema marginatum

Acute episodes of ARF are **treated with penicillin** regardless of throat culture results. For **prophylaxis** after first episode, **IM penicillin G is given every 4 weeks;** duration depends on the initial presentation. For the three different scenarios, use whichever prophylaxis is longer.

- **ARF without carditis:** Penicillin for 5 years or until 21 years old.
- **ARF with carditis and no residual heart or valve disease:** Penicillin for 10 years or until 21 years old.
- **ARF with carditis and residual heart or valve disease:** Penicillin for 10 years or until 40 years old.

7. STAPHYLOCOCCAL SCALDED SKIN SYNDROME (SSSS)

- **General:** Bacterial blistering skin syndrome caused by the gram-positive cocci, ***Staphylococcus aureus.*** Circulating **exfoliative toxin** produced by *S. aureus* target **desmoglein-1** and disrupts epidermal desmosomes leading to *sterile* intraepidermal bullae formation. SSSS usually occur in **newborns, young children** and rarely in immunocompromised adults or those with chronic renal failure.

- **Clinical:** Starts with flu-like symptoms and a macular erythema that is accentuated in flexural folds. The rash is followed by the development of **large, flaccid bullae** that rupture to leave **extensive erosions** and **denuded skin.** Classically, the epidermis sloughs off with gentle manual traction **(positive Nikolsky sign). Conjunctivitis** may occur but other mucosal surfaces are spared. In children, SSSS usually follows a benign course with normal BP and **no** liver, renal, GI or CNS involvement, as opposed to SJS/TEN or toxic shock syndrome (TSS).

- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + *S. aureus* exotoxin detection via serum PCR. Occasionally, *S. aureus* may be isolated from the original focus of infection (eg, nares, throat, umbilicus). Blisters *do not* contain the organism; do not culture (compare to bullous impetigo). Skin biopsy showing epidermal separation at the level of the stratum granulosum without an inflammatory infiltrate supports the diagnosis.

- **Treatment**
  - **First line:** Fluids and electrolytes + skin care + IV oxacillin, nafcillin or cefazolin.
  - **Second line:** IV vancomycin, linezolid, daptomycin or ceftaroline for severe disease.

8. TOXIC SHOCK SYNDROME (TSS)

- **General:** Multisystemic bacterial disease most commonly caused by **staphylococcal** production of *toxic shock syndrome toxin-1* (TSST-1). This exotoxin acts as a **superantigen** by triggering clonal T-cell expansion and **uncontrollably stimulating** the release of **cytokines** and **chemokines** in a nonantigen-specific manner. A rarer and more severe clinical variant of TSS is caused by *Streptococcus pyogenes.*

- **Clinical:** Begins with sudden onset of high fever followed by **systemic symptoms** such as diarrhea, myalgia, hypotension and a **diffuse desquamating sunburn-like rash** involving the **palms and soles.** Look for a patient with **retained foreign body,** such as a woman wearing a **tampon,** a patient with **nasal packing** or a wound with **retained sutures.** Severe disease has multi-organ involvement:
  - **Renal:** High BUN and Cr.
  - **Lung:** Respiratory failure and pleural effusion.
  - **GI tract:** Nausea, vomiting and diarrhea.
  - **Hepatic:** High AST, ALT and total bilirubin.
  - **Blood:** Leukocytosis, high CPK, thrombocytopenia and low Ca^{+}.
  - **CNS:** Confusion, stupor, seizures and coma.

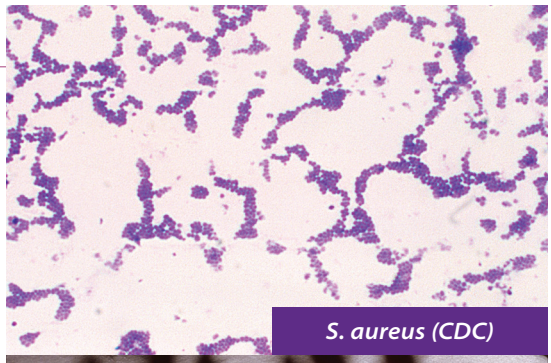
- **Diagnosis**
  - **Best initial test:** Clinical + labs to detect internal organ damage.
  - **Most accurate test:** Bacterial culture of infected tissue and testing serum for specific *S. aureus* exotoxins.

- **Treatment**
  - **First line:** Elimination of foreign body + IV fluids and vasopressors + IV clindamycin *and* oxacillin, nafcillin or cefazolin.
  - **Second line:** IV vancomycin, linezolid, daptomycin, tigecycline or ceftaroline for recalcitrant disease.

- **USMLE Pearls: Bacterial Endocarditis:** Most commonly caused by ***S. aureus*** or ***S. viridians*.** One of the most feared complications is **mycotic embolisms,** which is when infective tissue sloughs off the valves and enters the systemic circulation. This can go to the brain and cause a **stroke** or block an artery to cause severe ischemia **(acute limb ischemia).** *Diagnosis* requires **positive blood cultures** plus visualization of **valvular lesions** on echocardiogram. Most important cutaneous manifestations are:
  - **Osler nodes:** Red-purple raised painful nodes on the hands and feet, classically on the volar surface of fingers and toes.
  - **Janeway lesions:** Painless red macules on the palms and soles.
  - **Roth spots:** Retinal hemorrhages with clear center.
  - **Subungual "splinter" hemorrhages** and **petechial lesions.**

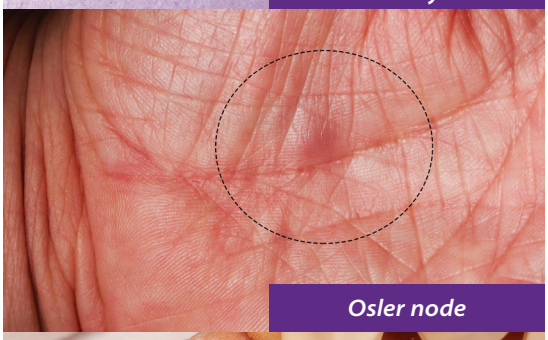
9. LYME DISEASE

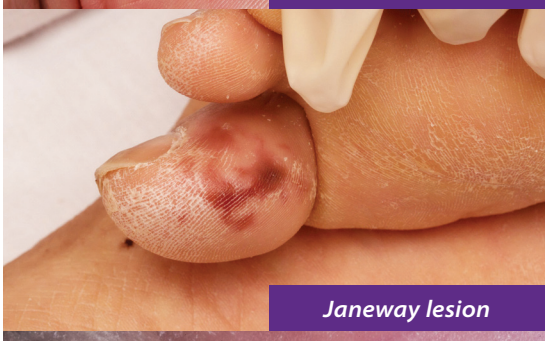
- **General:** Multisystemic bacterial infection caused by the spirochete ***Borrelia burgdorferi*. Most common vector-borne disease in the US**, transmitted by the **deer tick,** *Ixodes scapularis* or *I. pacificus*. The tick needs to be attached **more than 24 hours** to transmit the spirochete. Most common in summer during **outdoor activities** (eg, hiking and camping), particularly in upper Midwest (eg, Minnesota, Wisconsin) and Northeast US (eg, Massachusetts, Vermont, Connecticut, New York, Maryland, Maine).

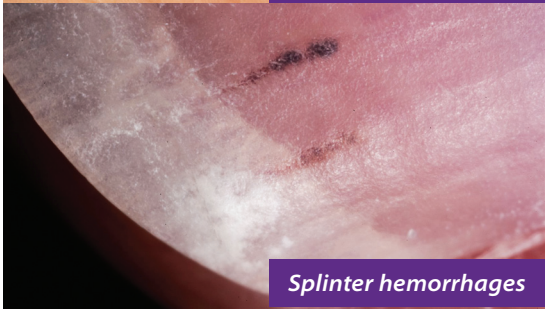

S. aureus (CDC)

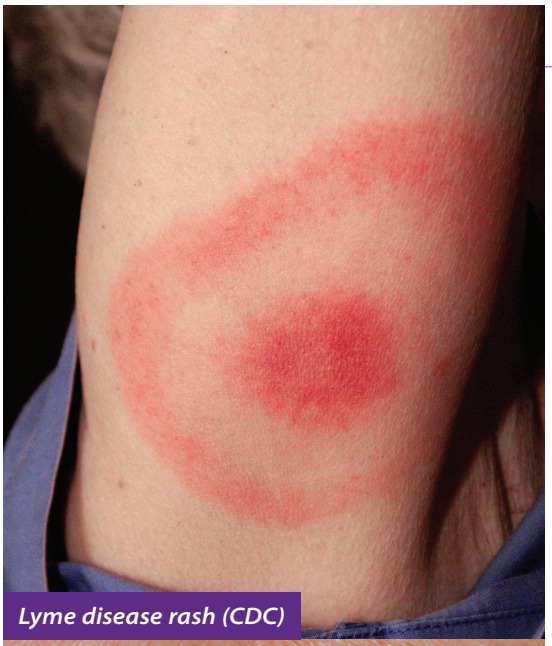

Toxic shock syndrome

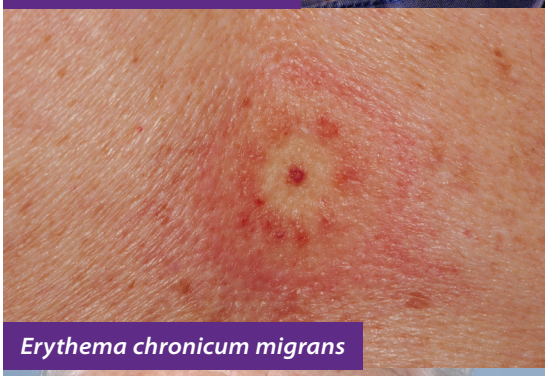

Toxic shock syndrome


Osler node


Janeway lesion


Splinter hemorrhages


Lyme disease rash (CDC)


Erythema chronicum migrans


Lyme disease (Bell palsy)


Ixodes scapularis (CDC)

- **Clinical:** Depends on the *stage of disease.*
  - **Primary:** Occurs about 7 days after the tick bite, begins with flu-like symptoms such as fever, myalgias, fatigue, photophobia and headache. The hallmark of this stage is **erythema chronicum migrans,** a circular, **"target-like,"** erythematous patch with **central clearing.** The rash progressively enlarges to approximately 5 to15 cm in diameter. It **does not** always have the classic central clearing or "bull's-eye" appearance.
  - **Secondary (early disseminated):** Develops weeks after the tick bite, characterized by internal organ involvement:
    - **Cardiac:** Myocarditis, pericarditis, arrhythmias or heart block.
    - **Neurologic:** Bell palsy, aseptic meningitis, encephalopathy or peripheral neuropathy.
    - **Musculoskeletal:** Migratory polyarthritis.
  - **Tertiary (latent or chronic):** Develops months to years after the initial tick bite, presents with **arthritis** and **subacute encephalitis** with memory and mood changes.

- **Diagnosis**
  - **Best initial test:** Clinical; some patients may recall the tick bite. Presence of *erythema chronicum migrans* is confirmatory. Diagnose atypical cases with ELISA and confirmatory Western blot. Arthrocentesis, lumbar puncture and ECG are useful for arthritis, meningitis and cardiac complications, respectively.
  - **Most accurate test:** Skin biopsy or saline lavage needle aspirate from erythema migrans leading edge for PCR or microscopic examination of *B. burgdorferi* spirochetes.

- **Treatment**
  - **First line:** Inspect and remove tick with tweezers + oral doxycycline. Amoxicillin for pregnant women and children under 8 years.
  - **Second line:** IV ceftriaxone for cardiac and neurologic symptoms *excluding* Bell palsy. Consider cardiac pacing for third-degree or severe atrioventricular (AV) block.

- **USMLE Pearls:** ***Ixodes scapularis*** (deer tick): Same vector for babesiosis, a hemolytic disease caused by the protozoan ***Babesia microti*****. Babesiosis** presents with a **flu-like illness** and **malaria-like hemolysis.** The characteristic feature is that RBCs will have the organism inside in a **"Maltese cross"** configuration. The deer tick can also cause **tick-borne paralysis.** This presents with an **ascending flaccid paralysis** similar to Guillain-Barré syndrome (GBS). The main difference is that the **CSF protein level is normal** in tick-borne paralysis and elevated in GBS. *Treat* by carefully inspecting the body and **removing the tick.**

10. ROCKY MOUNTAIN SPOTTED FEVER (RMSF)

- **General:** Tick-borne vasculitis caused by the gram-negative intracellular bacterium, ***Rickettsia rickettsii*****.** Mainly transmitted by the bite of the **dog tick,** *Dermacentor variabilis;* this is also one of the known tick-borne vectors of *Francisella tularensis.*

- **Clinical:** Patients typically present with fever, headache, myalgia and gastrointestinal symptoms (+/- known tick exposure). After 3 to 5 days

erythematous macules develop on the **wrists and ankles,** including the **palms and soles.** This rash then **spreads centripetally** to involve the proximal extremities and trunk, becoming papular and then classically **petechial.** RMSF can be **complicated** by encephalitis, cardiac arrhythmias, noncardiogenic pulmonary edema and rarely disseminated intravascular coagulation (DIC).

- **Diagnosis**
  - **Best initial test:** Clinical. Labs may show thrombocytopenia, leukopenia or leukocytosis, anemia and elevated BUN, Cr and LFTs. *R. rickettsii* antibody detection by indirect immunofluorescence assay (IFA) also exists, but takes 14 to 21 days to become positive, making it less diagnostically useful.
  - **Most accurate test:** Skin biopsy of infected tissue showing *R. rickettsii* bacteria using special immunohistochemical stains.

- **Treatment**
  - **First line:** Oral doxycycline, even in children less than 8 years old. Chloramphenicol for pregnant patients; may lead to gray baby syndrome if administered late in pregnancy.
  - **Second line:** IV doxycycline for severe disease.

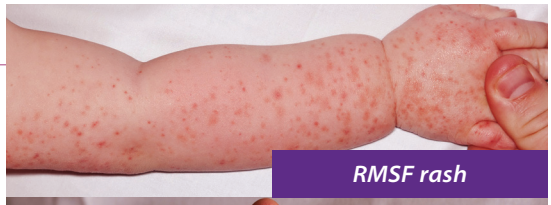
- **USMLE Pearls: Tularemia (Ulceroglandular Disease):** Gram-negative bacterial infection caused by ***Francisella tularensis.*** Common in **butchers** and individuals who are in direct contact with **rabbits** and **squirrels.** Presents with flu-like symptoms, lymphadenopathy and a painful red papule that slowly evolves into a well-defined **punched-out ulcer.** Lymph nodes may become fluctuant and suppurate. *Treat* with streptomycin or a quinolone.

- **USMLE Pearls: Meningococcemia:** Bacterial infection caused by the aerobic gram-negative diplococcus, ***Neisseria meningitidis.*** Presents with **fever, meningitis** and a **petechial eruption,** typically on the trunk and extremities. However, it can **involve the palms and soles,** like RMSF. Endotoxin release by the bacterium provokes a disseminated inflammatory process with **multi-organ failure** (eg, adrenal), **shock** and **widespread purpura.** *Treat* promptly with **IV ceftriaxone** (penicillin for susceptible isolates). **Remember:** Measles, syphilis, Kawasaki disease, hand-foot-mouth disease and endocarditis skin manifestations may also *involve* palms and soles.

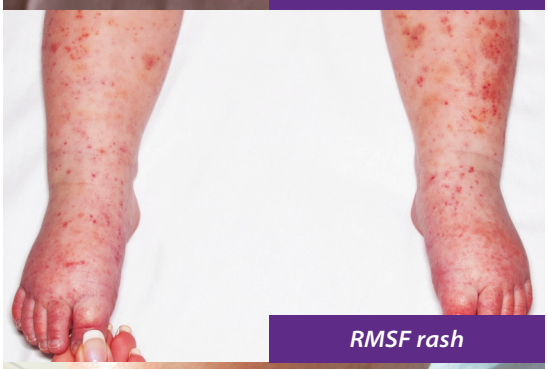
11. ERYTHRASMA

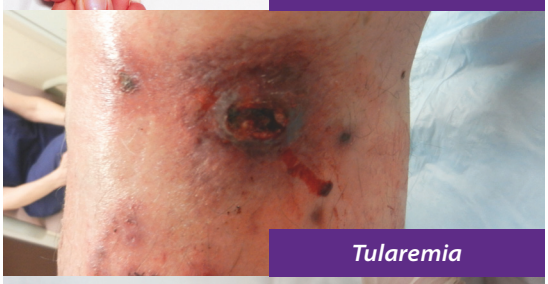
- **General:** Common *superficial* bacterial skin infection caused by the gram-positive bacillus, ***Corynebacterium minutissimum.*** The bacterium mainly affects the **stratum corneum,** where it produces excessive amounts of **coproporphyrin-III.** Associated with humid environment, excessive sweating, poor hygiene and diabetes.

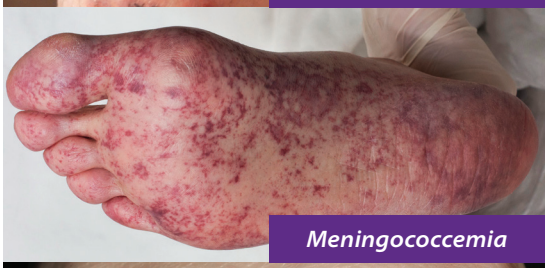
- **Clinical:** Well-demarcated, erythematous-to-brown patches with fine scales on **intertriginous areas** (eg, axillae, groin, inframammary crease, between digits). In **between the toes,** it presents with **skin maceration** and **scales** mimicking tinea pedis fungal infection. Erythrasma may also be **confused** with candidal intertrigo.


RMSF rash

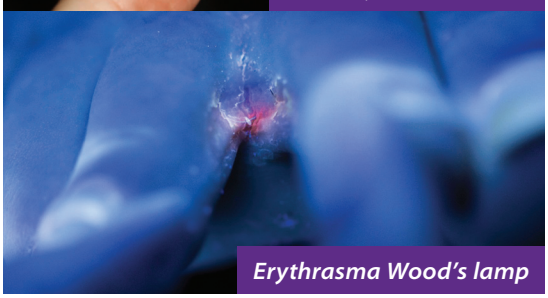

RMSF rash

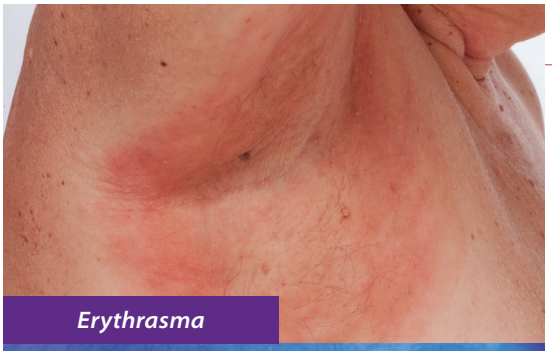

RMSF rash


Tularemia

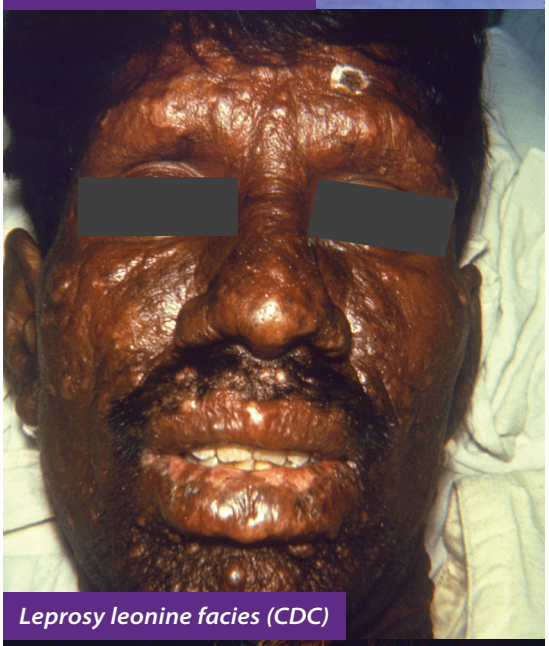

Meningococcemia

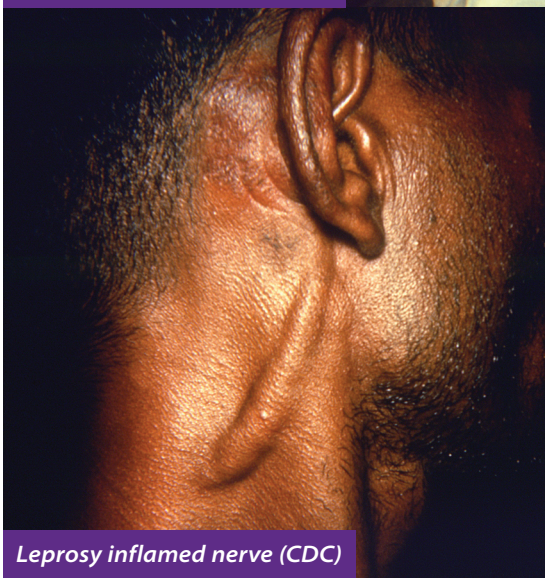

Erythrasma


Erythrasma Wood's lamp


Erythrasma


Erythrasma Wood's lamp


Leprosy leonine facies (CDC)


Leprosy inflamed nerve (CDC)

- **Diagnosis**
  - **Best initial test:** Clinical + Wood's light examination demonstrating *coral-red fluorescence* (coproporphyrin-III deposition).
  - **Most accurate test:** Bacterial culture of infected tissue (eg, scales).

- **Treatment**
  - **First line:** Topical erythromycin or clindamycin.
  - **Second line:** Oral erythromycin or tetracycline for severe or recalcitrant disease.

12. LEPROSY (HANSEN DISEASE)

- **General:** Chronic, granulomatous bacterial infection caused by the acid-fast intracellular bacilli, ***Mycobacterium leprae.*** Typically affects cooler areas of the body, mucous membranes, **bones** and **peripheral nerves.** Rare in the US; cases are mainly limited to **immigrants** or **tourists** coming from developing world (eg, Asia, Africa, Central and South America). Infects primarily humans, but the organism is also found in armadillos and monkeys. Broadly divided in two major forms:
  - **Tuberculoid type (paucibacillary):** Occurs in patients with **intact cellular immunity,** mainly a **Th1 response.** Granulomas are present with very few acid-fast bacilli (AFB). **Lepromin skin test positive.**
  - **Lepromatous type (multibacillary):** Occurs in patients with **low cellular immunity,** mainly a **Th2 response.** Absence of granulomas but numerous AFB in macrophages. **Lepromin skin test negative.**

- **Clinical:** Both types of leprosy affect the **peripheral nerves** and can present with **neuropathies** such as **claw hand** (ulnar nerve), **facial palsy** (CN-VII), **foot drop** (peroneal nerve) or **wrist drop** (radial nerve). Nerves can be so inflamed that they can be palpated externally.
  - **Tuberculoid type: ≤ 5 lesions** in total. Characterized by *well-demarcated*, *asymmetrically* distributed, erythematous patches and **hypopigmented anesthetic macules.** Severe disease may result in chronic ulcers and **auto-amputation of digits.** Absent sensation leads to permanent deformities secondary to chronic trauma.
  - **Lepromatous type: ≥ 6 lesions** in total. Characterized by *poorly defined*, *symmetrically* distributed erythematous and hypopigmented macules, plaques and nodular lesions. Facial involvement results in **loss of eyebrows and eyelashes,** dystrophic **perforated nose** and **thickened forehead,** leading to the classic **leonine facies.** Sensation is usually preserved.

- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + Ziehl-Neelsen or Fite stained tissue showing *M. leprae* acid-fast bacilli. The organism cannot be cultured.

- **Treatment**
  - **First line:** Dapsone + rifampin, add clofazimine for lepromatous leprosy.

13. CUTANEOUS ANTHRAX

- **General:** Most common form of anthrax (95%), caused by infection with the gram-positive, aerobic and sporulating bacterium, ***Bacillus anthracis.*** Transmitted by inhalation, ingestion or direct contact (eg, animal hides and

wool). Disease is caused by the production of **two toxins: edema toxin** and **lethal toxin.** Another form of anthrax is **pulmonary anthrax.** This presents with flu-like symptoms plus **pulmonary hemorrhage, shock** and **death.** The characteristic finding is a **widening mediastinum** on chest x-ray.

- **Clinical:** Begins with a purpuric macule or papule that evolves into a **"malignant pustule"** or vesicle surrounded by erythema. The vesicle ruptures and develops into the characteristic **ulcer** with **central "black eschar."** The ulcer in cutaneous anthrax is **painless** as opposed to the ulcer of a brown recluse spider bite.

- **Diagnosis**
  - **Best initial test:** Clinical + Gram stain of vesicle or ulcer exudate. If the patient has been treated with antibiotics, antibody serologies for *B. anthracis* are useful.
  - **Most accurate test:** Bacterial culture of infected tissue or exudate.

- **Treatment**
  - **First line:** Oral ciprofloxacin or doxycycline.
  - **Second line:** Clindamycin or penicillin V (if susceptible).

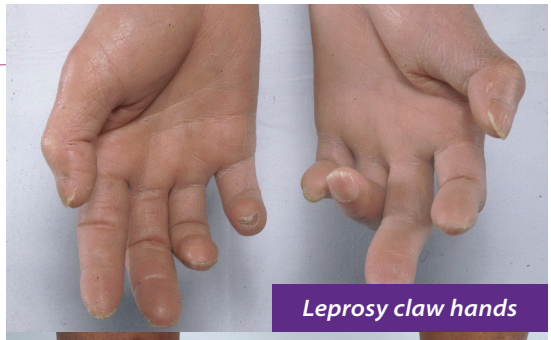
- **USMLE Pearls: Ecthyma Gangrenosum:** Cutaneous manifestation from septicemia caused by the aerobic gram-negative bacillus, ***Pseudomonas aeruginosa*.** Commonly occurs in hospitalized immunocompromised patients **(eg, neutropenic).** Begins with red-to-purple macules or pustules that evolve into short-lived, **hemorrhagic vesicles or bullae.** Once they rupture, they become **necrotic ulcers** with a **central "black eschar"** similar to cutaneous anthrax. *Treat* promptly with IV antipseudomonals antibiotics such as piperacillin/tazobactam, ceftazidime, ciprofloxacin or gentamycin. **Do not** confuse with **ecthyma,** which is a **deeper form of impetigo** caused by *S. pyogenes* and *S. aureus*. This presents with dark yellow-crusted ulcers extending into the dermis.

14. BACILLARY ANGIOMATOSIS

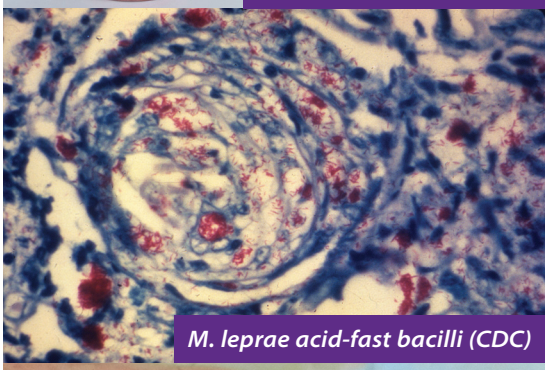
- **General:** Capillary proliferation in the skin and/or internal organs caused by the facultative intracellular gram-negative bacteria, ***Bartonella henselae*** and ***B. quintana*.** Commonly affects patients with **HIV infection** (CD4 < 200); it is classically transmitted by a **cat scratch or bite.** Extracutaneous manifestations may occur in the **liver** (bacillary peliosis hepatis) or **spleen** (bacillary peliosis splenis) and lead to liver dysfunction and pancytopenia, respectively. **Cat scratch disease** is another form of disease that presents in immunocompetent patients with **persistent regional lymphadenopathy** and occasionally systemic symptoms.

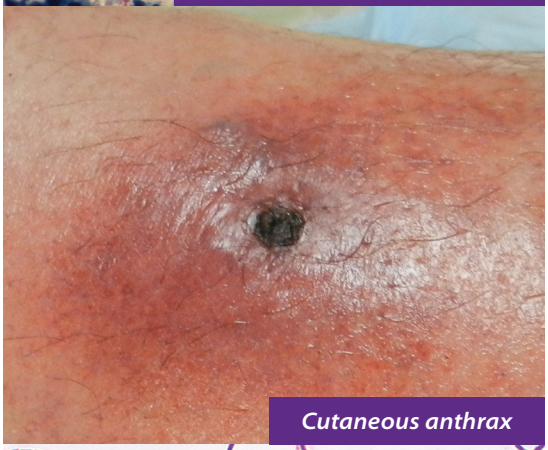
- **Clinical:** Single or multiple, **bright-red, beefy** papules and/or nodules, often with **satellite lesions.** Lesions vary greatly; they can be smooth, circumscribed, pedunculated, plaque-like or even ulcerated. Bacillary angiomatosis may be **confused** with pyogenic granuloma or Kaposi sarcoma.

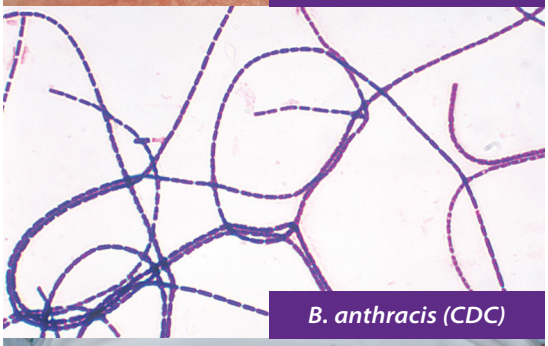
- **Diagnosis**
  - **Best initial test:** Clinical + *Bartonella* DNA detection via PCR of infected tissue. Consider testing for HIV if lesions are extensive and severe.
  - **Most accurate test:** Bacterial culture of infected tissue on specialized media (eg, chocolate agar).

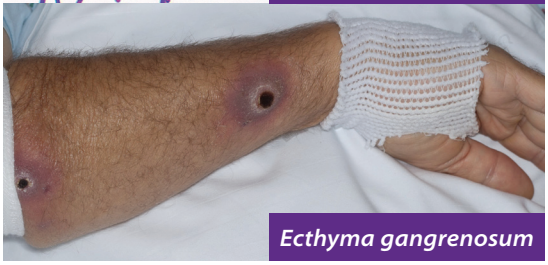

Leprosy claw hands

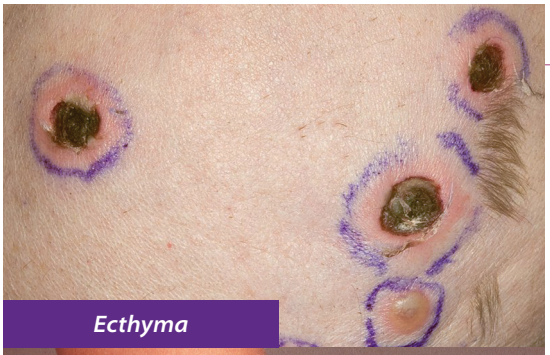

Leprosy deformed joints


M. leprae acid-fast bacilli (CDC)

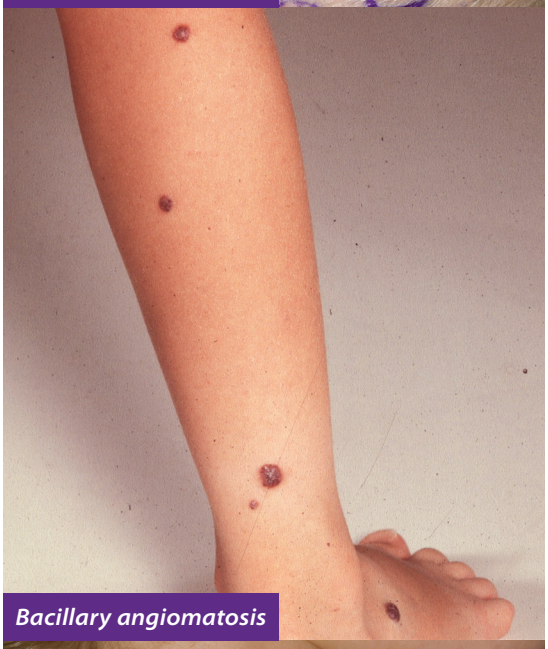

Cutaneous anthrax


B. anthracis (CDC)

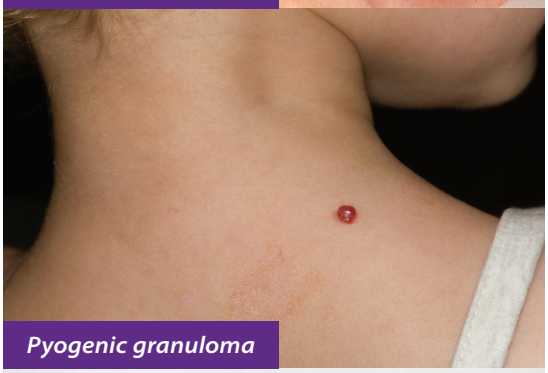

Ecthyma gangrenosum



Ecthyma



Bacillary angiomatosis



Pyogenic granuloma

Pyogenic granuloma

Pyogenic granuloma

- **Treatment**
  - **First line:** Oral erythromycin or doxycycline.
  - **Second line:** Oral azithromycin.

- **USMLE Pearls: Pyogenic Granuloma:** Benign, **vascular, beefy-red** papule that grows over days to weeks into a **painless, solitary,** polypoid red nodule with or without ulceration. Lesions usually range from 1 to 10 cm in diameter and **easily bleed when manipulated.** They are usually located in the **head and neck** area or the **fingers** but can occur almost anywhere. Associated with prior trauma, pregnancy or oral contraceptive pills use (estrogen stimulates angiogenesis).

Chapter 15

SELECTED FUNGAL INFECTIONS

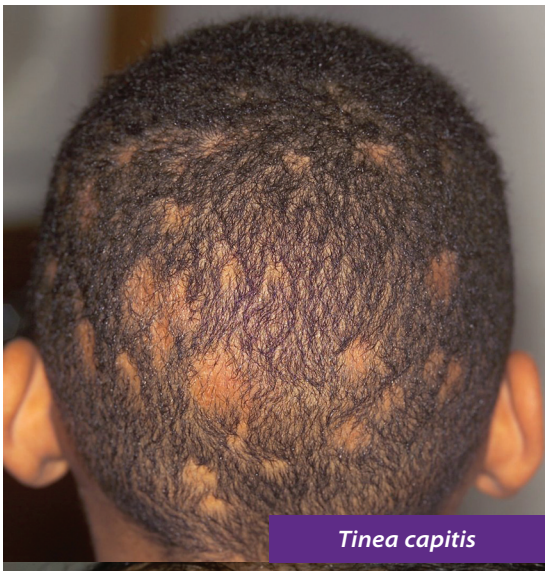
Table 15.1. Selected Fungal Infections Classification

Deep Mycoses		
Superficial Mycoses (Stratum corneum, hair and nails)	**Deep Mycoses** (Dermis and subcutaneous tissue +/- systemic infection)	
Dermatophytosis • Tinea capitis • Tinea corporis • Tinea cruris • Tinea pedis • Tinea unguium **Pityriasis (Tinea) Versicolor** **Candidiasis** • Intertrigo • Diaper dermatitis • Paronychia and onychomycosis • Oropharyngeal	**True Pathogens** Dimorphic fungi that exist as molds at **20°C** and as yeast or spherules at **37°C** (body temperature). Generally acquired via inhalation and cause pulmonary infection that can disseminate.	**Opportunistic Pathogens** Primarily affect immunocompromised hosts. Overall, mycoses are more severe and difficult to treat in immunosuppressed patients.
	• **Sporotrichosis** • **Blastomycosis** • **Histoplasmosis** • **Coccidiomycosis**	• **Mucormycosis** • **Aspergillosis** • **Cryptococcosis**

Superficial Mycoses

1. **DERMATOPHYTOSIS:** Superficial fungal infection of the *skin, hair and nails* most commonly caused by fungi in the genera ***Trichophyton*, *Microsporum*** and ***Epidermophyton*.** Dermatophytes are limited to the outermost cornified layer of the skin and rarely invade deeper. Transmission can be **anthropophilic** (human to human), **zoophilic** (animal to human) or **geophilic** (soil to human). **Tinea** in Latin means *"worm,"* but in medicine it is used to describe dermatophytes, generally followed by a word that identifies its ***location*:**

Tinea *capitis*	Dermatophytosis of the ***scalp***
Tinea *corporis*	Dermatophytosis of the ***body***
Tinea *cruris*	Dermatophytosis of the ***groin***
Tinea *pedis*	Dermatophytosis of the ***feet***
Tinea *manus*	Dermatophytosis of the ***hands***
Tinea *unguium*	Dermatophytosis of the ***nails***



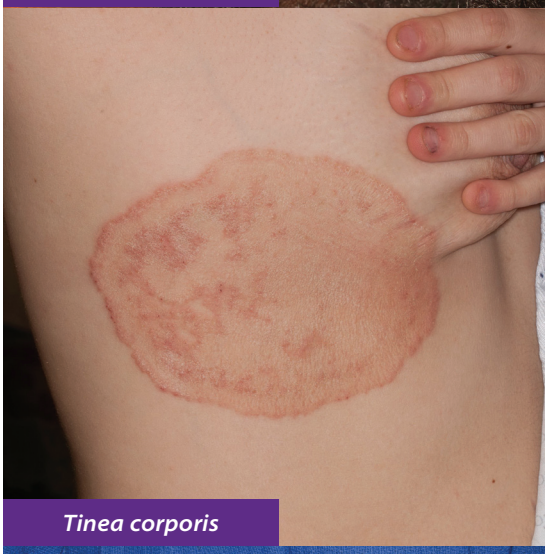
Tinea capitis

T. capitis (black dots)

- **Tinea Capitis**
  - **General:** Common superficial fungal infection of the *scalp,* most commonly caused by ***Trichophyton*** and ***Microsporum*** species. Usually affects school-age children and less commonly adults. Transmitted by direct contact with infected person, animal or fomite (eg, hairbrush, hat).


Tinea capitis


Kerion


Tinea corporis


Tinea corporis


Tinea cruris

- ***Trichophyton tonsurans*:** Most common pathogen causing tinea capitis; infects *within* the hair shaft **(endothrix pattern)** producing **"black dots"** on affected skin where the hair breaks off and patchy alopecia. Has a **negative Wood's lamp** examination (no fluorescence).
- ***Microsporum canis* and *M. audouinii*:** Affect the *outside* of the hair shaft **(ectothrix pattern)** producing **"gray patches"** on the scalp with small growing hairs. May have a **positive Wood's lamp** examination *(blue-green fluorescence).*

- **Clinical:** Characterized by discrete, scaly **circular patches of alopecia** often accompanied by inflammatory **papules and pustules** and **cervical lymphadenopathy.** Severe disease can present with exudative, pustular nodules and plaques known as **kerion.** This can lead to systemic illness and **scarring alopecia.**
- **Diagnosis**
  - **Best initial test:** Clinical + KOH prep of infected hair.
  - **Most accurate test:** Fungal culture of infected tissue. (**Note:** The majority of fungi in this chapter can be cultured on Sabouraud's agar medium).
- **Treatment**
  - **First line:** Oral terbinafine, itraconazole or griseofulvin (children).
  - **Second line:** Oral ketoconazole (more side effects).

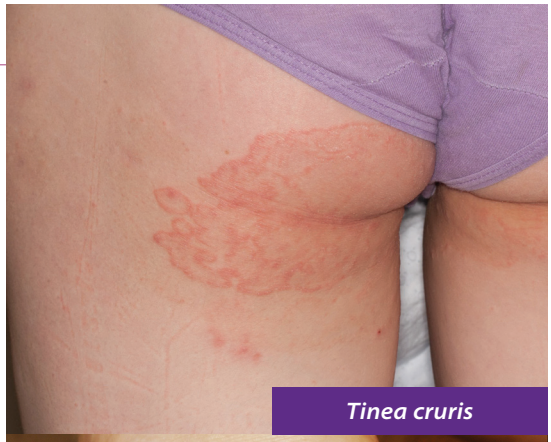
Tinea Corporis

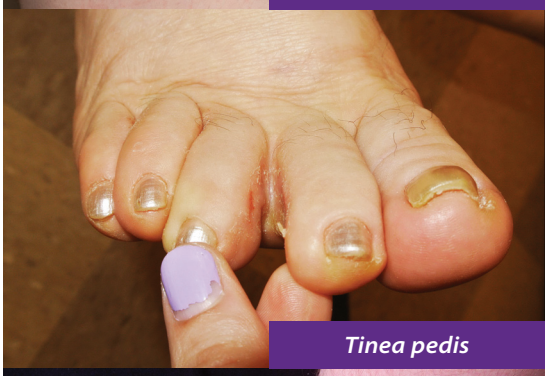
- **General:** Also known as **"ringworm,"** a common superficial fungal skin infection of the *body* most commonly caused by ***Trichophyton rubrum*.** Immunosuppression, occlusive wear and sweat favor fungal proliferation. Transmitted by direct contact with infected animal **(eg, cat or dog),** fomite or person, especially during **contact sports** such as wrestling **(tinea corporis gladiatorum).**
- **Clinical:** Characterized by an **erythematous, annular** patch or plaque with **raised** and **advancing borders.** The ring-shaped lesion may have **central clearing** and be accompanied by inflammatory papules and pustules. **Differential diagnosis** of annular lesions similar to tinea corporis include:
  - **Subacute cutaneous lupus erythematosus** (SCLE)
  - **Granuloma annulare**
  - **Nummular eczema**
  - **Erythema chronicum migrans** (Lyme disease)
  - **Erythema marginatum** (rheumatic fever)
  - **Necrolytic migratory erythema** (glucagonoma)
  - **Urticaria**
- **Diagnosis**
  - **Best initial test:** Clinical + KOH prep of scales from the leading edge of a plaque.
  - **Most accurate test:** Fungal culture of infected tissue.
- **Treatment**
  - **First line:** Topical terbinafine, ciclopirox or any of the azoles (eg, miconazole, clotrimazole, econazole or ketoconazole).
  - **Second line:** Oral terbinafine or azoles (eg, itraconazole) for recalcitrant or severe disease.
- **USMLE Pearls: Tinea Cruris (Jock Itch):** Male-predominant superficial fungal skin infection of the *groin area* presenting with **circum-**

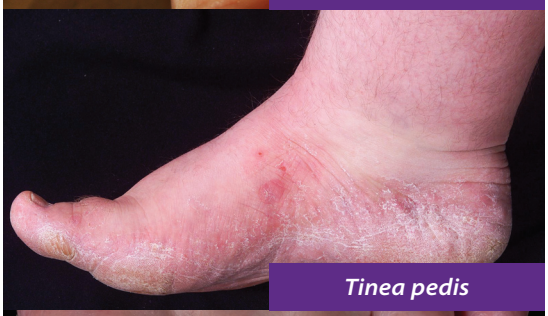
scribed, pruritic and **erythematous** plaques. Infection usually begins on the medial upper thighs and may spread to the perineum and buttocks, typically sparing the scrotum and penis. **Differential diagnosis** includes erythrasma and candidal intertrigo, which may involve the scrotum in men. *Diagnosis* and *treatment* of t. cruris is the same as tinea corporis (discussed above).

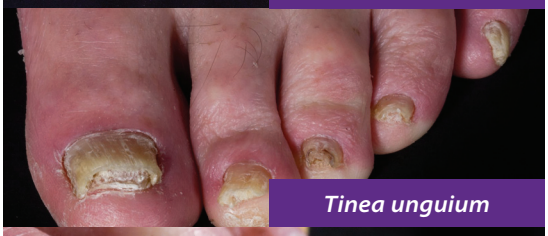
- **Tinea Pedis**
  - **General:** Commonly known as **athlete's foot,** a superficial fungal skin infection of the plantar aspect and interdigital webs of the *feet* most commonly caused by ***T. rubrum*** and ***T. mentagrophytes (interdigitale).*** Transmitted by direct contact with causative pathogens, especially when sharing shoes or walking barefoot (eg, locker rooms). Immunosuppression, occlusive wear and sweat favor fungal proliferation.
  - **Clinical:** Characterized by **scaling, erythematous** and **macerated** patches and plaques that usually start between the toes and spreads out to involve the feet. Patients may have **diffuse plantar scaling** on the soles and lateral feet in a **"moccasin"** distribution. Tinea pedis lesions may be the focus of entrance for bacterial infections (eg, cellulitis). Patients should be examined for co-existing tinea cruris, corporis and unguium.
  - **Diagnosis**
    - **Best initial test:** Clinical + KOH prep of skin scrapings from infected area.
    - **Most accurate test:** Fungal culture of infected tissue.
  - **Treatment**
    - **First line:** Topical terbinafine, ciclopirox or azoles (eg, ketoconazole).
    - **Second line:** Oral terbinafine, itraconazole or fluconazole for recalcitrant or severe disease.

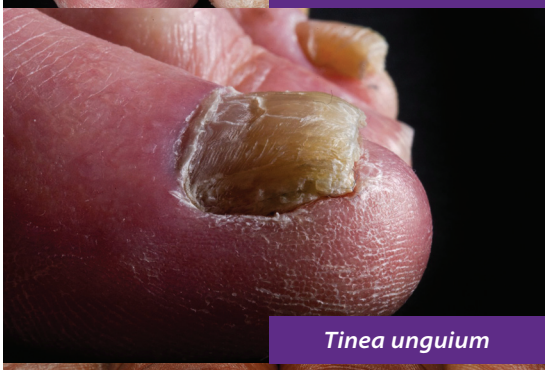
- **Tinea Unguium**
  - **General:** Also known as **dermatophytic onychomycosis,** a fungal infection of the *toenails* or *fingernails* most commonly caused by ***T. rubrum*.** Onychomycosis is difficult to treat, requiring prolonged therapy, often with recurrence.
  - **Clinical:** Characterized by **thickened** and **brittle nails** with a **yellow-to-brown discoloration.** With time, nails can loosen and fall off the nail bed **(onycholysis).** Onychomycosis may be confused with other pathologies involving the nails, such as psoriasis, lichen planus and subungual malignancies (eg, melanoma).
  - **Diagnosis**
    - **Best initial test:** Clinical + KOH prep of infected nail plate scrapings.
    - **Most accurate test:** Fungal culture or PAS stain of infected nail plate clippings.
  - **Treatment**
    - **First line:** Oral terbinafine or itraconazole (> 1.5 months for *fingernails* and > 3 months for *toenails*); monitor liver function tests (LFTs).
    - **Second line:** Oral griseofulvin or fluconazole (topical antifungal agents are generally ineffective for tinea unguium and t. capitis).


Tinea cruris

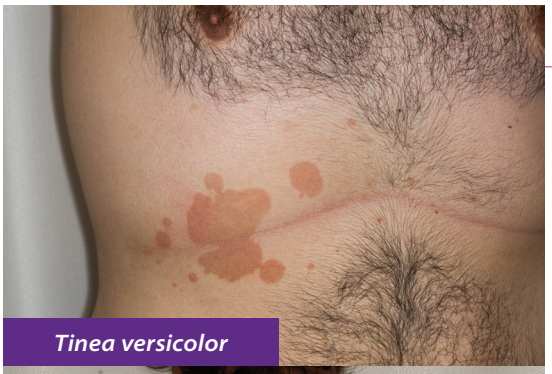

Tinea pedis

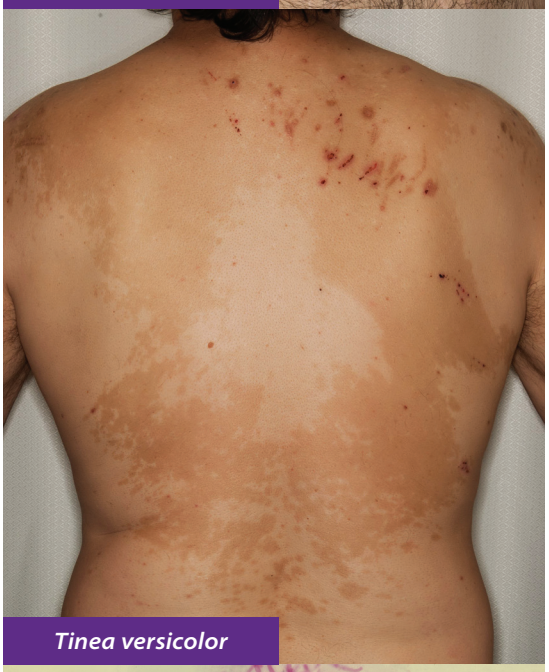

Tinea pedis

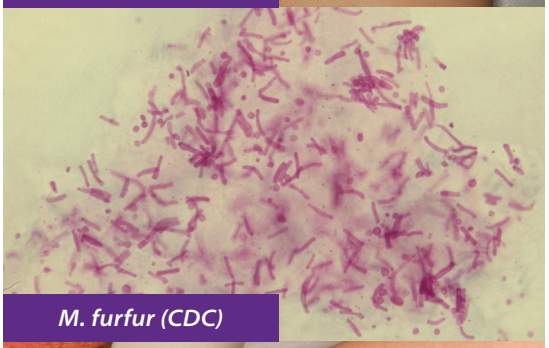

Tinea unguium

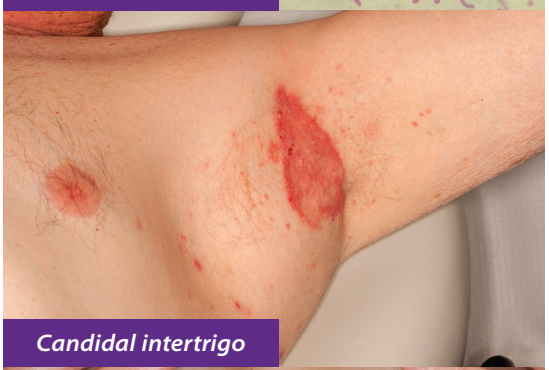

Tinea unguium

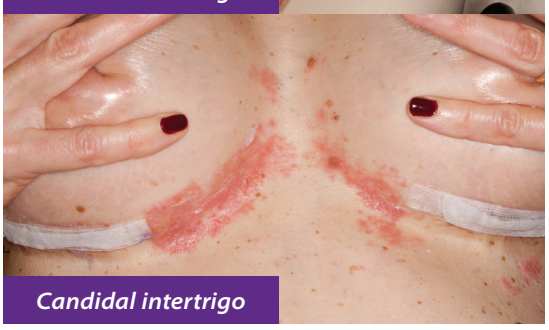

Tinea unguium


Tinea versicolor


Tinea versicolor


M. furfur (CDC)


Candidal intertrigo


Candidal intertrigo

2. TINEA VERSICOLOR

- **General:** Also known as **pityriasis versicolor,** common superficial fungal skin infection caused by ***Malassezia* sp.,** most commonly ***M. furfur*** and ***M. globosa*.** The yeast proliferates in moist and sebum-rich areas of the body. It is most common in tropical climates (high heat and humidity) and young adults with hyperhidrosis **(eg, athletes).**

- **Clinical:** Characterized by **scaly, hyper- or hypopigmented** macules and patches, hence the name "versicolor." Commonly located on the **upper chest, shoulders** and **back.** Lesions may clear during cold and dry winter months and reappear in the summer.
  - **Hyperpigmented type:** Fungus induces melanocytes to produce more melanin resulting in patches of **scaly, hyperpigmented skin** surrounded by normal skin.
  - **Hypopigmented type:** Fungus produces **azelaic acid** that *inhibits* tyrosinase enzyme in the melanin synthesis pathway. The affected skin **does not tan** on sun exposure resulting in **lighter spots** surrounded by tanned skin.

- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + KOH prep of infected skin showing **short hyphae** ("spaghetti") and **yeast** ("meatballs"). Wood's lamp examination accentuates skin color variation and can aid in diagnosis.

- **Treatment**
  - **First line:** Topical antifungal creams or shampoos (eg, zinc pyrithione, selenium sulfide, ketoconazole or ciclopirox).
  - **Second line:** Oral azoles (eg, itraconazole, fluconazole) for recalcitrant or severe disease.

3. CANDIDIASIS

- **General:** Superficial skin infection most commonly caused by the polymorphic fungus ***Candida albicans*.** *C. albicans* exists as **hyphae, pseudohyphae** and **budding yeast.** Candidiasis is associated with:
  - **Diabetes mellitus** (DM)
  - **Immunosuppression** (eg, neutropenia, dialysis, cancer, HIV)
  - **Prolonged antibiotic** or **corticosteroid use**
  - **Hot climates** and **moist areas**

- **Clinical:** Depends on the infection site.
  - **Candidal Intertrigo:** Characterized by a **red, glistening** and **macerated pruritic patches** affecting *intertriginous areas* (eg, inframammary, groin, axillae). Presence of **"satellite"** papules and pustules is typical. **Differential diagnosis** includes erythrasma (*C. minutissimum*). However, erythrasma:
    - **Lacks satellite lesions.**
    - Has *coral-red fluorescence* on Wood's lamp examination and **negative KOH prep.**
  - **Candidal Diaper Dermatitis:** Characterized by **beefy, erythematous, shiny** papules and plaques on the *diaper area.* The main clues are the **involvement of skin folds** and **"satellite" lesions.** Differential diagnosis for **pediatric diaper dermatitis** include:

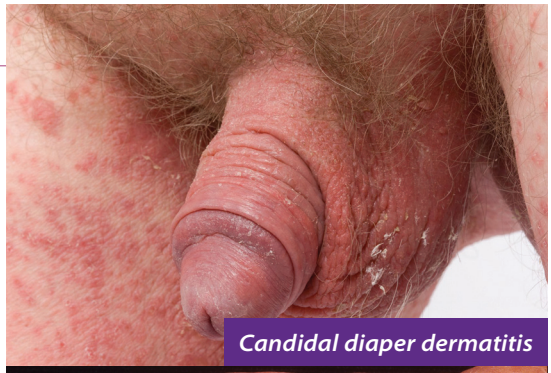
- **Irritant contact dermatitis:** Mainly caused by direct skin contact with *stool* and *urine* contained in the diaper, it typically **spares the skin folds.** Zinc barrier creams and frequent diaper change are helpful to prevent skin contact with irritant.
- **Seborrheic dermatitis:** Characterized by erythematous plaques with **greasy** and **yellow scaly crust involving the skin folds.** Other areas of the body are usually affected (eg, scalp, face, axillae).

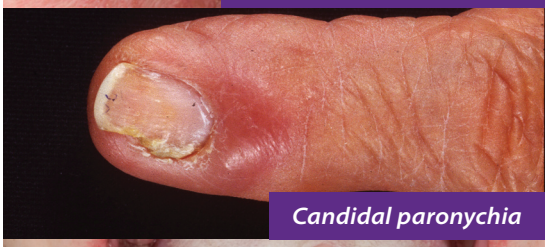
- **Candidal Paronychia and Onychomycosis:** Candida is the usual pathogen in cases of **chronic paronychial infection.** Paronychia is an inflammation of the *nailfold* presenting with **swelling, erythema** and **pain** on the skin around the nail with or without abscess formation. **Candidal onychomycosis** is generally associated with candidal paronychia and presents with **thickened, discolored** and **fragile cracked nails** that are clinically indistinguishable from tinea unguium.
- **Oropharyngeal Candidiasis (Thrush):** Characterized by a "cottage-cheese" **white pseudomembranous** or erythematous plaque on the tongue, gums and/or palate. Classically, lesions *bleed when scraped off* and may be painful. It may be the first sign of AIDS. A major differential diagnosis for thrush is:
  - **Oral leukoplakia:** White plaques that are commonly seen on the *lateral aspect* of the tongue and *cannot be scraped off.* Leukoplakia is strongly associated with *tobacco and alcohol* consumption. **Hairy leukoplakia** is a clinical variant caused by *EBV infection* and is primarily seen in HIV/AIDS patients. **Oral erythroplakia** is another clinical variant with *red oral lesions* instead of white. These oral lesions may be pre-malignant; consider biopsy to rule out SCC and monitor disease.

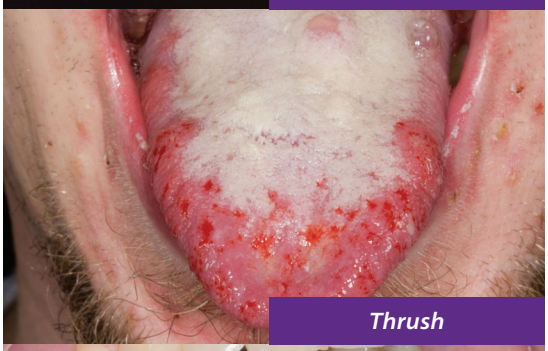
- **Diagnosis**
  - **Best initial test:** Clinical + KOH prep of infected tissue.
  - **Most accurate test:** Fungal culture of infected tissue.

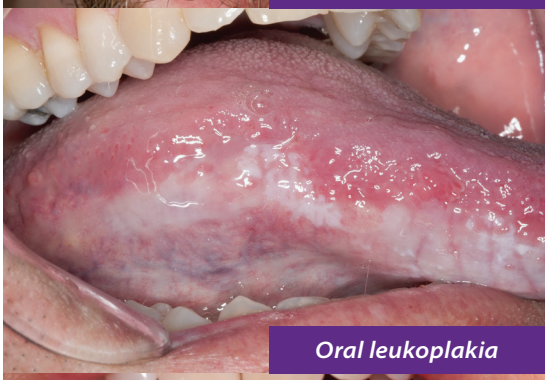
- **Treatment**
  - **Candidal intertrigo**
    - **First line:** Keep area dry + topical azoles (eg, clotrimazole) or nystatin.
    - **Second line:** Oral itraconazole or fluconazole for recalcitrant or severe disease.
  - **Candidal diaper dermatitis**
    - **First line:** Keep diaper area dry, gentle cleansing and air exposure + topical azoles (eg, miconazole) or nystatin.
    - **Second line:** Use of topical barrier ointment + low-potency topical steroids.
  - **Candidal paronychia and onychomycosis**
    - **First line:** For *paronychia*, keep hands dry and protected + topical azoles. Consider oral itraconazole or fluconazole for recalcitrant disease. For *onychomycosis*, use oral itraconazole or fluconazole.
  - **Oropharyngeal Candidiasis**
    - **First line:** Nystatin suspension or clotrimazole troches.
    - **Second line:** Oral itraconazole or fluconazole for recalcitrant or severe disease.

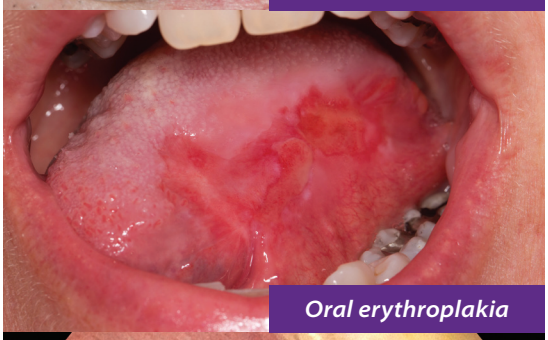
- **USMLE Pearls: Candidal Esophagitis:** Most common cause of esophagitis in **HIV patients.** Appears similar to oropharyngeal candidiasis but in the esophagus; lesions are often multiple. In HIV patients, this is diagnosed on a **"treat and response"** basis: if there is symptomatic

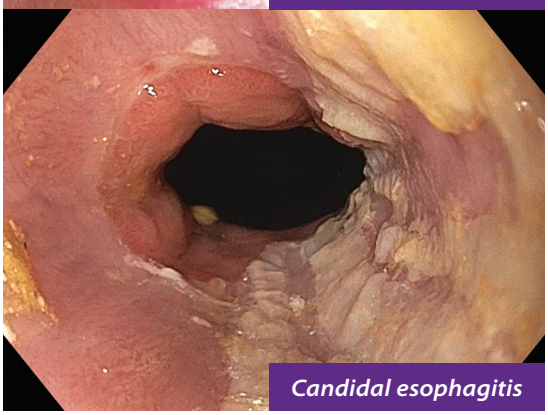

Candidal diaper dermatitis


Candidal paronychia

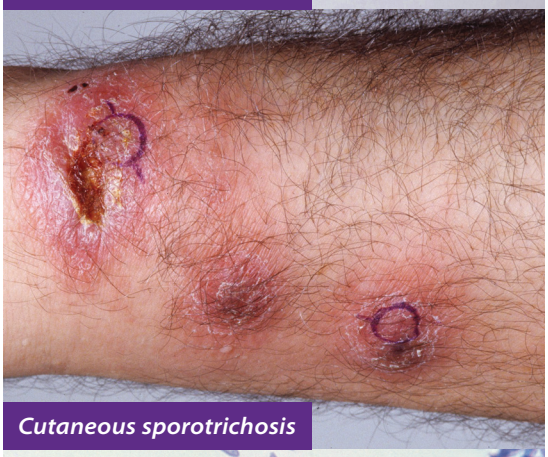

Thrush

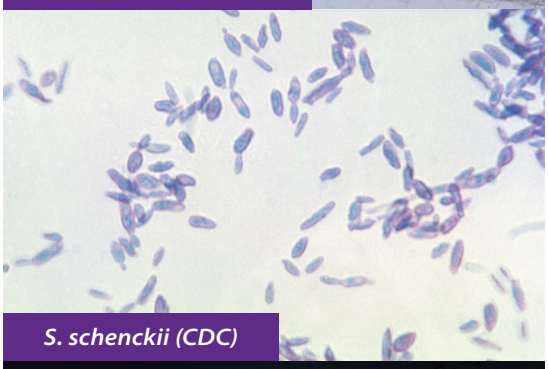

Oral leukoplakia

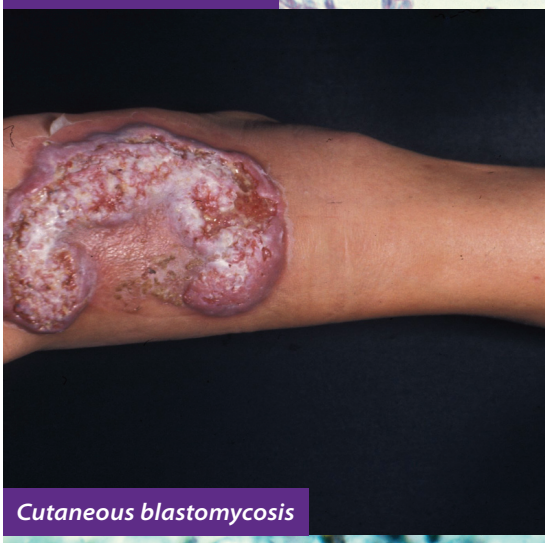

Oral erythroplakia

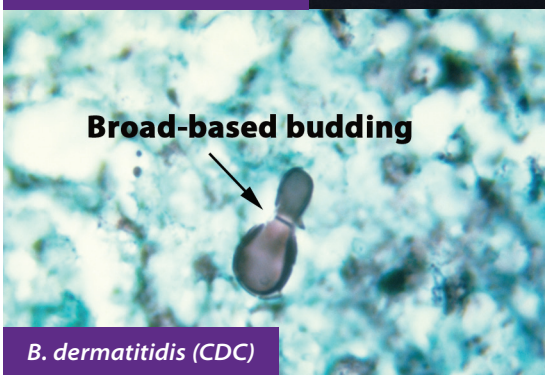

Candidal esophagitis


Cutaneous sporotrichosis


Cutaneous sporotrichosis


S. schenckii (CDC)


Cutaneous blastomycosis



B. dermatitidis (CDC)

improvement with **fluconazole therapy,** the diagnosis is confirmed. If the patient *does not* improve with fluconazole, the **next best step** is to do an **endoscopy** to rule out HSV or CMV esophagitis.

Deep Mycoses (True Pathogens)

4. SPOROTRICHOSIS

- **General:** Also known as **"rose gardener's" disease,** a subcutaneous fungal infection caused by cutaneous inoculation of the dimorphic fungus, ***Sporothrix schenckii*.** Sporotrichosis is characterized by a granulomatous inflammation mainly affecting **lymph nodes and skin.** The fungus resides in **soil and vegetation;** hence infection is more prevalent in people who work with plants and soil **(eg, gardeners).**

- **Clinical:** Usually begins with a small reddish papule or nodule a few weeks after a contaminated penetrating injury **(eg, rose thorn).** This is followed by development of **suppurating nodules** along the lymphatic drainage, starting from the initial node, known as **"sporotrichoid pattern."** Nodules can later evolve into necrotic ulcers. Severe sporotrichosis infection can be destructive and penetrate to bones, bursae, joints and tendons.

- **Diagnosis**
  - **Best initial test:** Clinical + skin biopsy showing cigar-shaped yeast using PAS or silver stain.
  - **Most accurate test:** Fungal culture of infected tissue.

- **Treatment**
  - **First line:** Oral itraconazole for 3 to 6 months for mild to moderate disease; IV amphotericin B for recalcitrant or severe disease.
  - **Second line:** Oral potassium iodide (KI) or terbinafine.

5. BLASTOMYCOSIS

- **General:** Cutaneous blastomycosis is a deep fungal infection caused by the dimorphic fungus, ***Blastomyces dermatitidis*.** Skin lesions are most commonly caused by cutaneous dissemination of the fungus from the lungs (primary infection site). The main reservoirs are **decaying wood, vegetation and soil.** The fungus is transmitted by inhalation of organisms. Blastomycosis is prevalent in **Midwestern US** (eg, Mississippi, Missouri, Minnesota, Wisconsin, Ohio).

- **Clinical:** Characterized by pulmonary symptoms with the addition of **skin involvement** and **osteolytic bone lesions.** Skin manifestations often begin as gray-to-purple **verrucous plaques** with or without ulceration accompanied by papules and pustule. Lesions heal from the center out and leave a **cribriform pattern** scarring.

- **Diagnosis**
  - **Best initial test:** Clinical + KOH prep or skin biopsy of infected tissue showing **broad-based budding** yeast with double-contoured walls.
  - **Most accurate test:** Fungal culture of infected tissue.

- **Treatment**
  - **First line:** Oral itraconazole for mild to moderate disease; IV amphotericin B for recalcitrant or severe disease.
  - **Second line:** Oral fluconazole or ketoconazole.

6. HISTOPLASMOSIS

- **General:** Also known as **Ohio Valley disease,** a fungal infection primarily of the lungs caused by the dimorphic fungus, ***Histoplasma capsulatum*.** Main reservoir is **soil,** especially containing bird and bat droppings. Infection is transmitted by inhalation of organism, particularly during **cave exploring,** exposure to **bird or bat droppings** and working on **soil excavation, chicken coops** or **dusty construction sites.** The yeast reproduces and lives within macrophages. Histoplasmosis is prevalent in **Midwestern US** (eg, Ohio, Mississippi, Indiana).

- **Clinical:** Characterized by pulmonary symptoms with **oral ulcers** and less commonly **hepatosplenomegaly** and **bone marrow** involvement leading to **pancytopenia.** Skin manifestations usually occur with disseminated disease and are nonspecific (vegetative or erythematous papules and nodules or ulcers).

- **Diagnosis**
  - **Best initial test:** Clinical + blood and urine *H. capsulatum* antigen detection (ELISA or PCR) or skin biopsy of infected tissue showing intracellular yeast in macrophages.
  - **Most accurate test:** Fungal culture of infected tissue (eg, skin, bone marrow, blood).

- **Treatment**
  - **First line:** Oral itraconazole for mild to moderate disease; IV amphotericin B for recalcitrant or severe disease.
  - **Second line:** Fluconazole, voriconazole or posaconazole.

7. COCCIDIOMYCOSIS

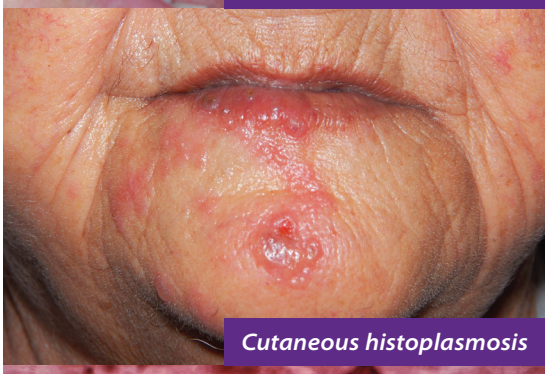
- **General:** Also known as **San Joaquin Valley fever,** fungal infection primarily of the lungs caused by the dimorphic fungus, ***Coccidioides immitis*.** The natural reservoir is **soil** and is transmitted by inhalation of dust, especially after **earthquakes** and **dust storms.** Prevalent in **southwestern US** (eg, California, Arizona) and northern Mexico.

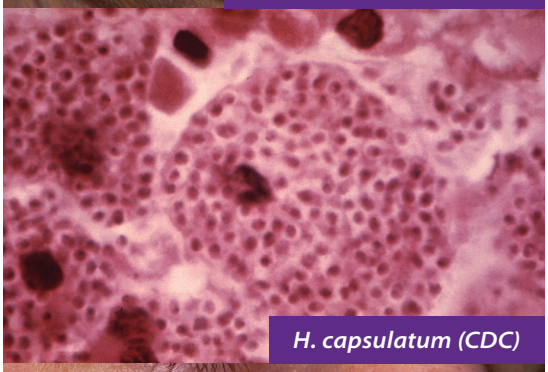
- **Clinical:** Characterized by pulmonary symptoms, **erythema nodosum** and **arthralgias.** Skin lesions from disseminated disease include nonspecific papules, pustules, plaques and/or abscesses with draining sinuses, most commonly located on the **face.**

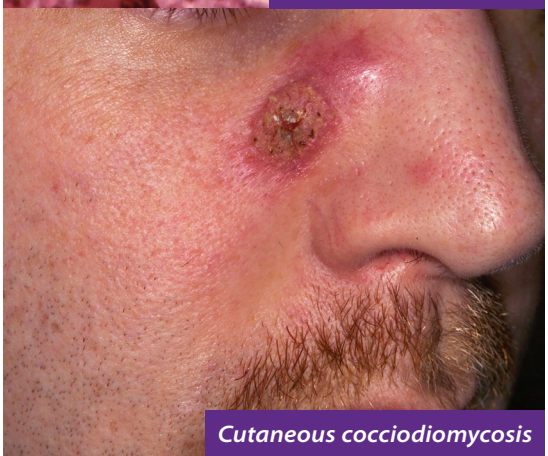
- **Diagnosis**
  - **Best initial test:** Clinical + skin biopsy showing spherules full of endospores.
  - **Most accurate test:** Fungal culture of infected tissue.

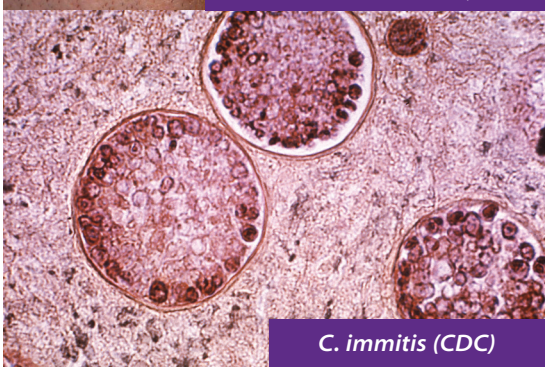
- **Treatment**
  - **First line:** Oral fluconazole or itraconazole for mild to moderate disease; IV amphotericin B for recalcitrant or severe disease.
  - **Second line:** Posaconazole, voriconazole or caspofungin.

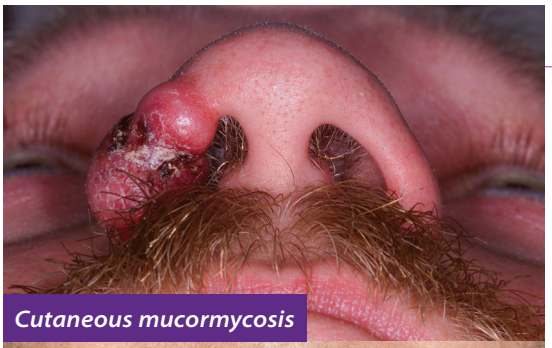

Histoplasmosis oral ulcers


Cutaneous histoplasmosis

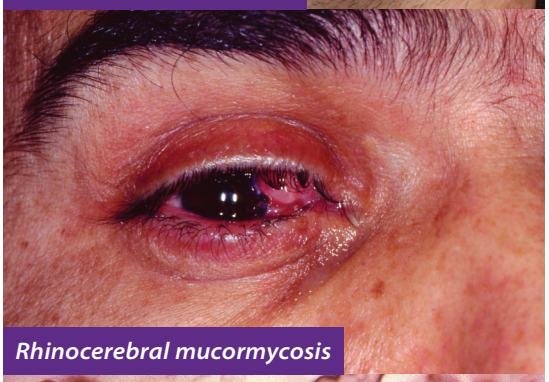

H. capsulatum (CDC)

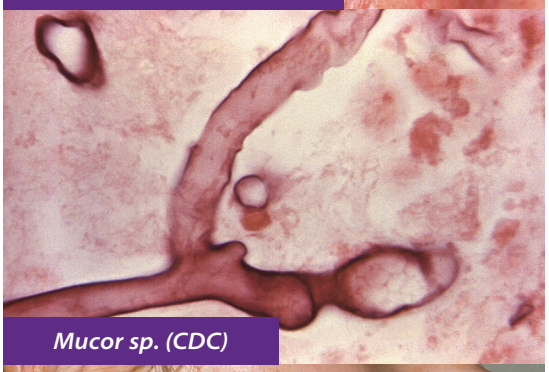

Cutaneous cocciodiomycosis


C. immitis (CDC)


Cutaneous mucormycosis


Cutaneous mucormycosis


Rhinocerebral mucormycosis


Mucor sp. (CDC)


Cutaneous cryptococcosis

Deep Mycoses (Opportunistic Pathogens)

8. MUCORMYCOSIS (ZYGOMYCOSIS)

- **General:** Severe angioinvasive fungal infection most commonly caused by species of the genera ***Rhizopus*** (most common), ***Absidia*** and ***Mucor.*** Mucormycosis is usually seen in **immunocompromised patients** (eg, leukemia, AIDS, transplant) and **diabetics or alcoholics with underlying ketoacidosis.** This fungal infection is difficult to treat and has high mortality.

- **Clinical:** Characterized by **severe sinusitis** that rapidly progress to **necrosis** and a **bloody nasal discharge.** As the infection evolves, the patient develops **facial erythema, edema and pain, retro-orbital headache, proptosis** and **diplopia.** Mucormycosis destructive ulcers can penetrate through the cribriform plate into the central nervous system (CNS).

- **Diagnosis**
  - **Best initial test:** Clinical + skin biopsy showing ribbon-like, *nonseptate, broad hyphae* with *irregular branching* in **right angles** (90°) and vascular invasion. Order a CT scan or MRI to evaluate extension of invasion and necrosis.
  - **Most accurate test:** Fungal culture of infected tissue.

- **Treatment**
  - **First line:** Correct underlying ketoacidosis + IV amphotericin B +/- surgical debridement.
  - **Second line:** IV posaconazole.

- **USMLE Pearls: Invasive Aspergillosis:** Deep fungal infection caused by the opportunistic angioinvasive fungi, ***Aspergillus fumigatus*** and ***A. flavus.*** Prevalent in immunocompromised patients, particularly those with **severe neutropenia** and **IV catheters.** Invasive aspergillosis may present with a severe **necrotizing sinusitis** similar to mucormycosis. The main *difference* is that on biopsy, ***Aspergillus*** has *thinner, septated hyphae* with *regular branching* in **acute angles** (45°). *Treat* with voriconazole +/- caspofungin.

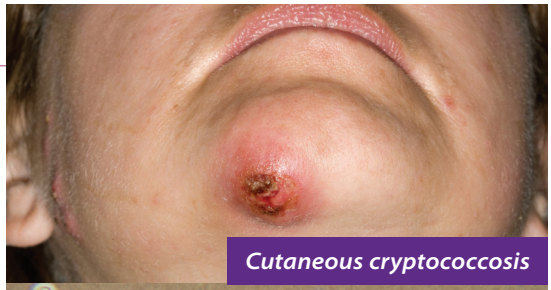
9. CRYPTOCOCCOSIS

- **General:** Invasive opportunistic fungal infection primarily of the lungs caused by the **encapsulated** dimorphic fungus, ***Cryptococcus neoformans.*** Transmission is by inhalation of yeast, especially when exposed to **pigeon droppings.** Extrapulmonary dissemination to the CNS, skin and bones usually occur in immunocompromised hosts, particularly those with **HIV/AIDS** and **organ transplantation.** It is the most common cause of **meningitis** in people with HIV.

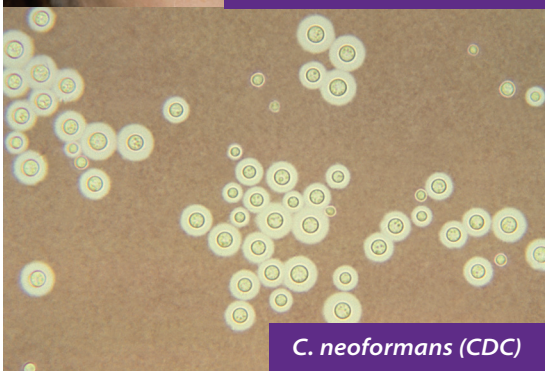
- **Clinical:** Skin manifestations are **nonspecific.** It may present with cellulitis, umbilicated papules **resembling molluscum contagiosum** and/or vegetating plaques, nodules, ulcers and abscesses with or without a draining sinus.

- **Diagnosis**
  - **Best initial test:** Clinical + cryptococcal antigen detection via ELISA or latex agglutination test. India ink staining of dermal scrapings, serum or CSF may demonstrate encapsulated yeast.
  - **Most accurate test:** Fungal culture of infected tissue.

- **Treatment**
  - **First line:** Oral fluconazole or itraconazole for mild to moderate disease not involving the CNS; for severe disease or CNS involvement, use IV amphotericin B + 5-flucytosine *followed by* maintenance therapy with fluconazole.
  - **Second line:** Voriconazole or posaconazole.



Cutaneous cryptococcosis



C. neoformans (CDC)

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Chapter 16

SELECTED PARASITIC AND ARTHROPOD INFESTATIONS

1. CUTANEOUS LARVA MIGRANS (CLM)

- **General:** Creeping skin eruption most commonly caused by the **accidental penetration** of the nematode, ***Ancylostoma braziliense*****,** also known as the **dog and cat hookworm.** Prevalent in **tropical areas** such as the Caribbean and southern US (eg, Florida). **Humans are "dead-end" hosts.** The life cycle of the nematode in humans is:
  - The **definitive host** (dog or cat) defecates on sand or soil → **Eggs** turn into **larvae** → Adult or children **walk barefoot** on sand or soil → Larvae **penetrate skin** and migrate through epidermis → Larvae generally **die in 2 to 8 weeks** as they are unable to pass beyond the epidermis.

- **Clinical:** Skin eruption with **multiple, advancing, serpiginous, red lines or tracks** ranging from 1 to 4 cm in length. The penetration and migration process of the nematode causes **intense pruritus.** Commonly affects the **hands, feet and buttocks.** The classical scenario is a patient with the eruption described above after walking barefoot on **soil, beach sand** or **sandboxes** (eg, gardeners, farmers, swimmers).

- **Diagnosis**
  - **Best initial test:** Clinical. Labs may show high IgE levels and peripheral eosinophilia.
  - **Most accurate test:** Skin biopsy from the leading edge of a track showing PAS-positive larva and many eosinophils.

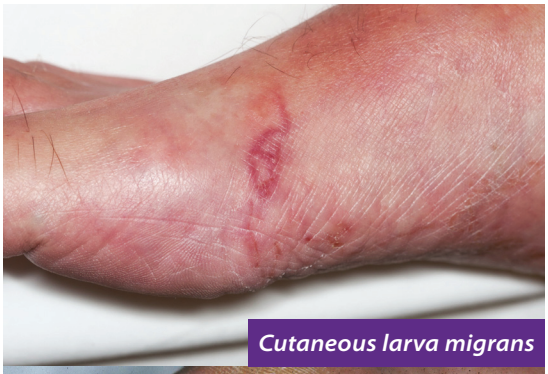
- **Treatment**
  - **First line:** Self-limited disease. For hastened resolution, use topical or oral thiabendazole.
  - **Second line:** Oral ivermectin or albendazole.

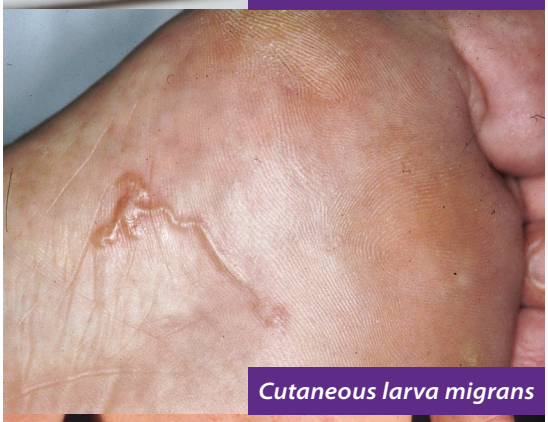
2. CUTANEOUS LEISHMANIASIS

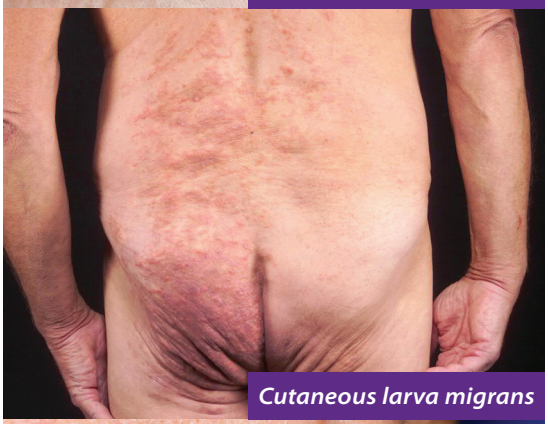
- **General:** Skin disease caused by different species of the intracellular parasitic protozoan, ***Leishmania*****.** Rare in the US, although some cases have been reported in **Texas;** it is more prevalent in the Middle East, Africa and South and Central America. The disease is mainly transmitted by the bite of a **female sandfly.** Prevent disease by using protective clothing and insect repellent.

- **Clinical:** It begins with a red papule or nodule and progresses over days to weeks to an **ulcer with raised borders** and a **central purulent crater or sinus.** Lesions on the extremities may have a *sporotrichoid spread* involving lymph nodes in a chainlike, linear pattern. The usual scenario is a **military official, soldier or immigrant** presenting with the lesion described after coming from an endemic area.

- **Diagnosis**
  - **Best initial and most accurate test:** Skin biopsy showing the parasite (amastigotes) using Giemsa staining or culturing on specialized medium such as Novy-MacNeal-Nicolle.


Cutaneous larva migrans

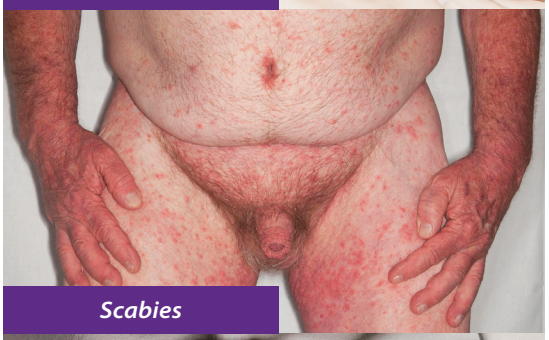

Cutaneous larva migrans

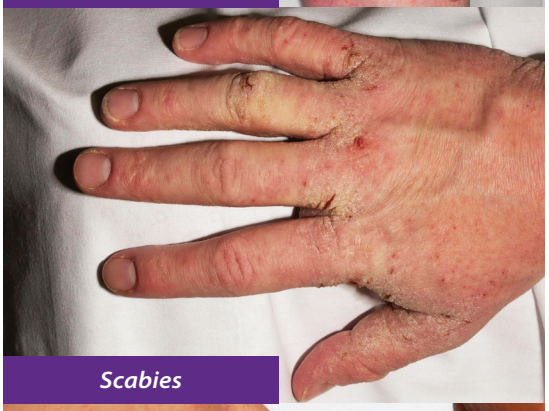

Cutaneous larva migrans

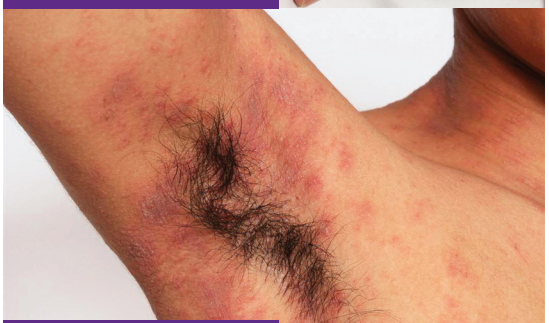

Cutaneous leishmaniasis


Cutaneous leishmaniasis


Scabies


Scabies


Scabies


Scabies


Pediculosis (lice)

- **Treatment**
  - **First line:** Intravenous pentavalent antimonials (eg, sodium stibogluconate, meglumine antimoniate) or oral miltefosine. Consider topical paromomycin for limited skin involvement.
  - **Second line:** IV liposomal amphotericin B or pentamidine.

3. SCABIES

- **General:** Common and *highly contagious* parasitic arthropod infestation caused by the human itch mite, ***Sarcoptes scabiei* var. *hominis*.** Adult female mites penetrate the stratum corneum and lay eggs at the end of intraepidermal tunnels known as **"burrows."** Mites cannot survive more than 2 to 3 days away from human skin. **Norwegian scabies,** a more severe variant with widespread and crusted lesions, can be seen in **immunocompromised patients** (eg, HIV). Scabies is associated with overcrowded areas, poor living conditions and shared clothing or bedding.

- **Clinical:** Characterized by **intensely pruritic,** small, crusted **red papules** with visible dark or elevated lines. These lines are **"burrows"** and are pathognomic for scabies infestation. A **hypersensitive skin reaction** to the mite may lead to nonspecific pruritic and **erythematous papules and plaques** that mimic any form of dermatitis ("the great imitator"). Infestation patterns are broadly divided into:
  - **Adults:** Typically *spares* the face, head, palms and soles and mainly affects: **interdigital webs, wrists, axillae, umbilicus, genitalia** and **nipples.**
  - **Children:** Mainly affects the **face, head, palms** and **soles.**

- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + mineral oil skin scrape showing scabies eggs, mites or fecal matter.

- **Treatment**
  - **First line:** Permethrin cream + place clothing and bedding in bags for 10 days *or* wash thoroughly in hot water and dry with high heat. Treat all close contacts. Children may return to school *24 hours after* first treatment. Pruritus may persist for weeks after treatment.
  - **Second line:** Topical lindane or oral ivermectin (lindane has more side effects than permethrin). Consider precipitated sulphur ointment for pregnant women and newborns.

4. PEDICULOSIS (LICE)

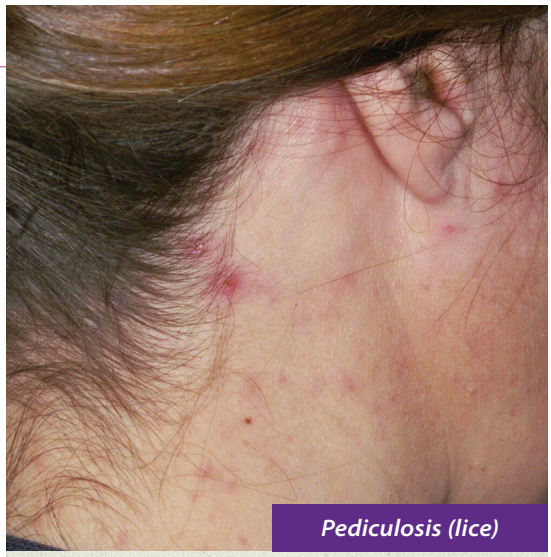
- **General:** Common *contagious* parasitic arthropod infestation caused by **human lice.** Lice feed from human blood and reproduce by laying eggs (nits) within hair shafts and clothing. Transmitted by **direct contact** with infested clothing and bedding, fomites (eg, combs) or person-to-person. Usually affect people living in **overcrowded areas** and **poor conditions.** The three main types of human lice are:
  - *Pediculus humanus capitis* **(scalp)**
  - *Pediculus humanus corporis* **(body)**
  - *Pthirus pubis* **(genital)**

- **Clinical:** The skin lesions are characterized by **erythematous and pruritic papules** with secondary **excoriations** and impetiginization. Commonly located on the scalp, axillae, groin, trunk and genitals. **Maculae cerulea** is a *blue-gray* discolored macule that may be produced by enzymes in lice saliva (pathognomonic for pubic lice). Pubic lice are considered a **sexually transmitted infection** and infestation in children should prompt a sexual abuse investigation.

- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + identification of a live louse or nit via *fine-tooth hair combing* or microscopic examination of particles. Live nits can be detected by Wood's lamp examination **(fluorescent white).**

- **Treatment**
  - **First line:** Two topical application of pediculicide one week apart: Malathion, permethrin, lindane or ivermectin.

- **USMLE Pearls: Pinworm *(Enterobius Vermicularis)*:** Parasitic infestation that also causes **intense pruritus,** especially in the **perianal area.** Most common parasitic helminth infestation. Classically presents with **perianal itching in school-aged children. Important clues:** pruritus worsens at night and the child has no anal skin lesions, as opposed to lice or scabies. *Diagnosis* is by placing cellophane tape on affected area and microscopically visualizing the eggs adhered to the tape **("Scotch tape" test).** *Treat* with oral albendazole, mebendazole or pyrantel pamoate + washing all clothing and bedding.



Pediculosis (lice)

Human lice

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Chapter 17

SELECTED VIRAL INFECTIONS

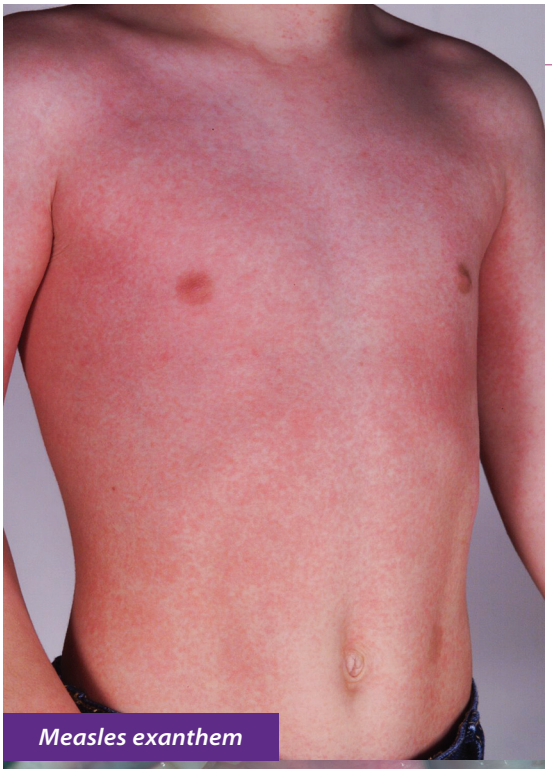
Table 17.1. Viral Infections Summary *(Refer to Appendix II for Viral Classification)*

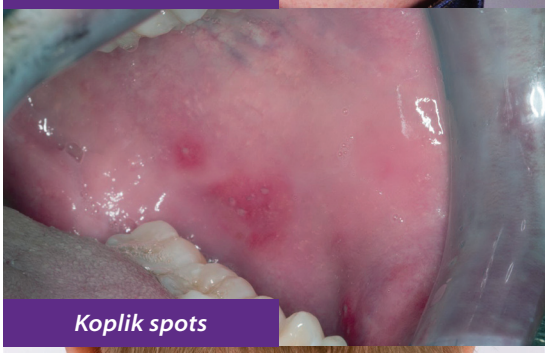
Disease and Pathogen	Associations	Complications	Exanthem Description	Unique Characteristics
Measles (Rubeola) • *Measles virus*	**Vitamin A deficiency** Immigrants (unvaccinated) Immunosuppression	**Giant cell pneumonia** **Superimposed infections** **Acute appendicitis** **Subacute sclerosing panencephalitis (SSPE)**	Erythematous **morbilliform eruption** that begins on the hairline and behind the ears and spreads downward, lasts **5 to 7 days**.	**Koplik spots** (appear first before rash)
Rubella (3-Day Measles) • *Rubella virus*	Immigrants (unvaccinated) **Pregnancy**	**Arthritis and arthralgias** **Congenital infection**	Milder than measles, lasts **1 to 3 days**. Erythematous **morbilliform eruption** that begins on the hairline and behind the ears and spreads downward.	**Postauricular and suboccipital lymphadenopathy** **Forchheimer sign**
Erythema Infectiosum • *Parvovirus B19*	**Hemoglobinopathies**	**Polyarthritis** **Hydrops fetalis** **Aplastic anemia**	Bright red erythema on the **cheeks** followed by **"lacy" reticulated rash** on the extremities and trunk that worsens with sun and heat exposure.	**"Slapped cheeks"**
Roseola Infantum • *HHV-6* • *HHV-7*	DRESS Chronic fatigue syndrome Immunosuppression	**Febrile seizures** Hepatitis Encephalitis	Mild non-itchy pink-to-red **morbilliform eruption** all over the body that **resolves in 1 to 3 days**.	**Sudden rash** after a period of high fever **"exanthem subitum"** **Nagayama spots**
HFMD and Herpangina • *Coxsackie virus*	School and nursery outbreaks	**Aseptic meningitis** **Dilated cardiomyopathy and pericarditis** **Type 1 diabetes mellitus**	Morbilliform rash on the **hands**, **feet** and **mouth** that starts as papules and vesicles and evolve into tiny ulcers. Involves **palms and soles**.	**Odynophagia** and **painful oral ulcers**
Varicella (Chicken Pox) • *Herpes-Zoster virus*	**Shingles** Immunosuppression	Pneumonia Encephalitis **Congenital infection**	**Itching**, **pain** and **paresthesias** followed by erythematous **papules**, **vesicles** and **crusted erosions** all over the body.	**Lesions at different stage of development**

1. MEASLES

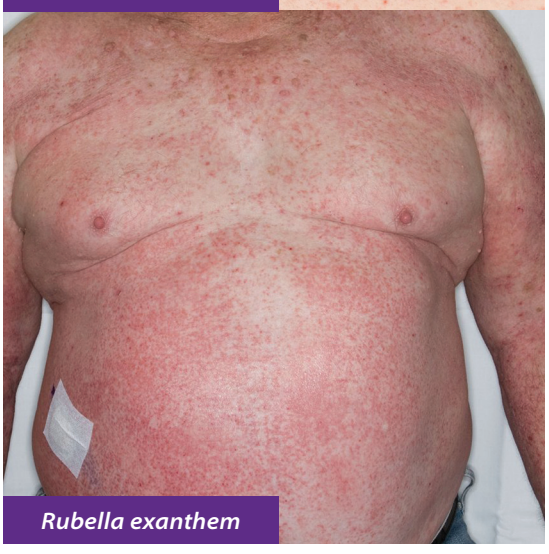
- **General:** Also known as **rubeola** or **"first disease."** Highly contagious childhood exanthem caused by the ss-RNA virus, ***Measles virus.*** Transmitted by respiratory droplets. The virus replicates in lymphoid tissue and destroys it. This leads to a *transient state of immunosuppression,* which is followed by viral dissemination to other organs (eg, skin, respiratory tract). Vaccination has greatly reduced the incidence in the US and cases are mainly limited to unimmunized individuals (eg, immigrants). Associated with **vitamin A deficiency** and **pregnancy.** Important measles complications include:

Measles conjunctivitis


Measles exanthem


Koplik spots


Rubella exanthem


Rubella exanthem

- **Giant cell pneumonia** (Warthin-Finkeldey)
- **Myocarditis**
- **Acute appendicitis** from lymphoid hyperplasia.
- **Superimposed infections**: Occur secondary to transient viral immunosuppression (leukopenia). The most common infections are bacterial pneumonia, diarrhea, otitis media, croup and hepatitis.
- **Subacute sclerosing panencephalitis (SSPE):** Severe degenerative brain disease that occurs *years after* initial infection and presents with behavioral and intellectual deterioration and seizures (most feared outcome).

- **Clinical:** Begins with a prodrome of fever, anorexia, malaise and **C**ough, **C**oryza and **C**onjunctivitis **(the "three Cs"). Koplik spots,** small *blue-white* macules surrounded by erythema in the oral mucosa, appear first, followed 2 to 4 days later by the classic measles exanthem; an **erythematous morbilliform eruption** beginning on the hairline and behind the ears and spreading to the trunk and extremities over 24 to 48 hours. The exanthem last for **5 to 7 days** and resolves cephalocaudally leaving hyperpigmented "copper-colored" patches. The virus is **contagious 5 days before and after** the appearance of the exanthem. During this time period, exposed individuals need postexposure prophylaxis (PEP).

- **Diagnosis**
  - **Best initial test:** Clinical + *Measles virus* IgM and IgG antibodies *or* DNA detection via PCR.
  - **Most accurate test:** Viral culture from infected tissue.

- **Treatment**
  - **First line:** Vitamin A + rest, fluids and acetaminophen. Antibiotics for superimposed infections (eg, pneumonia).
  - **Second line:** Ribavirin.

- **Postexposure prophylaxis (PEP):** MMR vaccine **within 3 days** for everyone except *immunocompromised, pregnant* or *infant* patients. For these patients with contraindications to live vaccinations, use human immunoglobulin **within 6 days** of known exposure.

2. RUBELLA

- **General:** Also known as **German measles** or **"third disease."** Childhood viral exanthem caused by the ss-RNA virus, ***Rubella virus.*** Mainly affects the **skin, lymph nodes** and **joints.** Rubella infection is milder and more benign than measles infection; the prodrome and rash are less prominent and only lasts 3 days **("3-day measles").** The most serious complication of rubella is congenital infection causing:
  - **Intrauterine growth restriction** (IUGR)
  - **Patent ductus arteriosus** (PDA) and **pulmonary artery stenosis**
  - **Cataracts** and **microphthalmia**
  - **Sensorineural hearing loss** and **encephalitis**
  - **Hepatosplenomegaly** and **thrombocytopenia**
  - **"Blueberry muffin" baby:** Caused by extramedullary hematopoiesis, presents with widespread blue-to-purple marks on the skin. CMV and toxoplasmosis can also lead to blueberry muffin baby.

- **Clinical:** Commonly affect **unimmunized individuals** such as immigrants. Exanthem may develop after MMR live vaccination. The presentation is very **similar to measles** (rubeola) including the flu-like prodrome with **c**ough, **c**oryza and **c**onjunctivitis followed by the **cephalocaudal morbilliform skin eruption.** The *three main differences* are:
  - Rubella has petechial red spots in the **soft palate** known as **Forchheimer sign** (compare Koplik spots, which are usually inside the cheek and vary in color).
  - Rubella is usually accompanied by tender **postauricular, posterior cervical** and **suboccipital lymphadenopathy** (very important).
  - Rubella in adults may present with **arthralgias** and **arthritis.**

- **Diagnosis**
  - **Best initial test:** Clinical + *Rubella virus* IgM and IgG antibodies *or* DNA detection via PCR.
  - **Most accurate test:** Viral culture from infected tissue.

- **Treatment**
  - **First line:** Supportive with rest, fluids and acetaminophen.

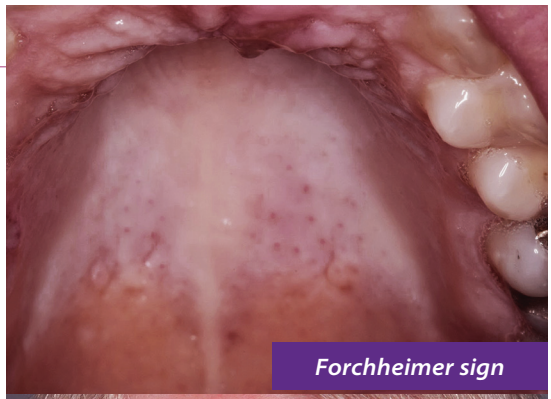
3. ERYTHEMA INFECTIOSUM

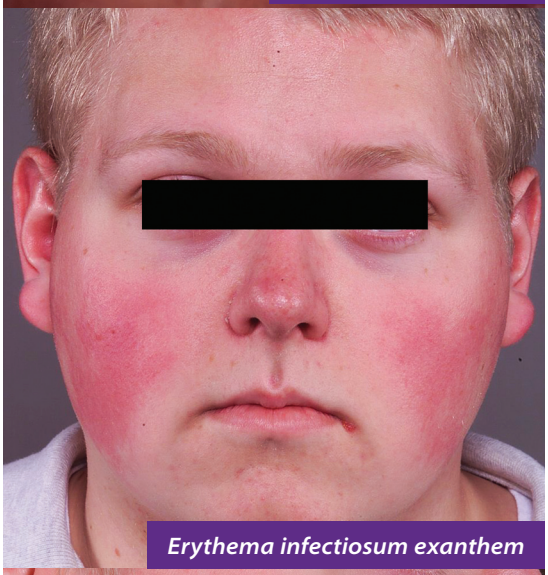
- **General:** Also known as **"fifth disease,"** viral exanthem caused by the only ss-DNA virus, ***Parvovirus B19.*** The virus induces formation of immunocomplexes that deposit in **skin** and **joints** causing **rash** and **arthritis,** respectively. Damage is mediated by complement activation and not the virus itself. Transmitted transplacentally and by respiratory droplets. The virus is infectious *before* the prodrome of symptoms *until* the skin rash develops. Parvovirus is directly cytotoxic to RBCs and may lead to:
  - **Hydrops fetalis:** Profound fetal anemia leading to heart failure and severe edema in the heart, lungs and abdomen (high mortality).
  - **Aplastic anemia:** Generally affect patients with underlying hemoglobinopathies (eg, sickle cell disease, spherocytosis, thalassemia).

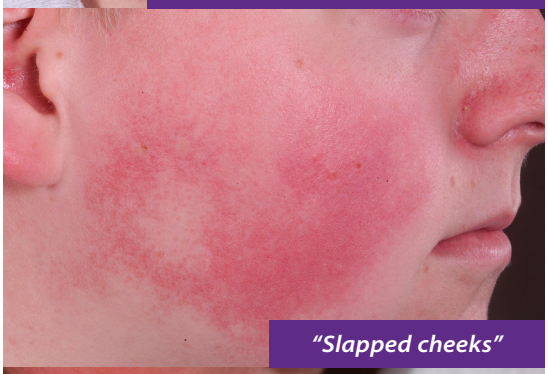
- **Clinical:** Affects primarily young children, begins with 2 to 3 days of flu-like illness with headache, fever, sore throat and coryza. A symptom-free period for one week is followed by the skin eruption. The characteristic rash is a diffuse, macular, **bright-red erythema on the cheeks.** It spares the nasal, perioral and periorbital areas, producing a **"slapped cheeks"** appearance. Four days later, a collection of erythematous macules and papules extends to the **trunk and extremities,** which often produces a **"lacy"** or **reticulate configuration.** The skin eruption **worsens with sun and heat** exposure. In adults, the skin eruption may not have the classic "slapped cheeks" appearance. Up to 80% of adult women may present with **polyarticular symmetric arthritis** of small joints (eg, hands, fingers, toes). Children with the rash are *not* infectious and can attend school without posing any risk to close contacts.

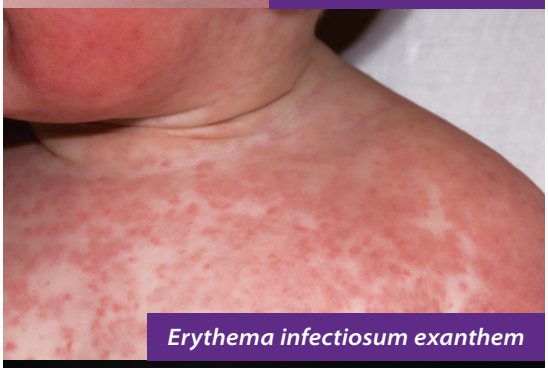
- **Diagnosis**
  - **Best initial test:** Clinical + *Parvovirus B19* IgM and IgG antibodies.
  - **Most accurate test:** *Parvovirus B19* DNA detection via PCR.

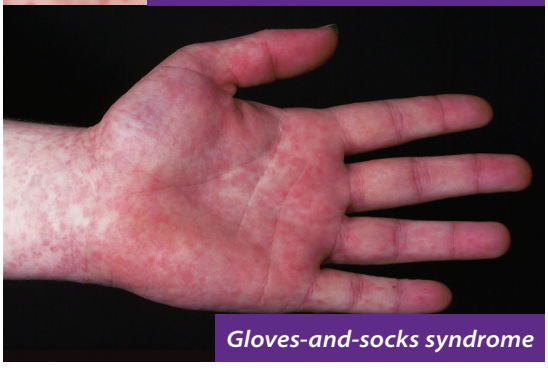
- **Treatment**
  - **First line:** Supportive with rest, fluids and NSAIDS for arthritis.
  - **Second line:** IVIG for aplastic anemia and hydrops fetalis.

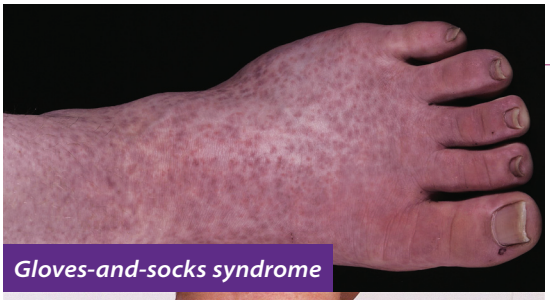

Forchheimer sign

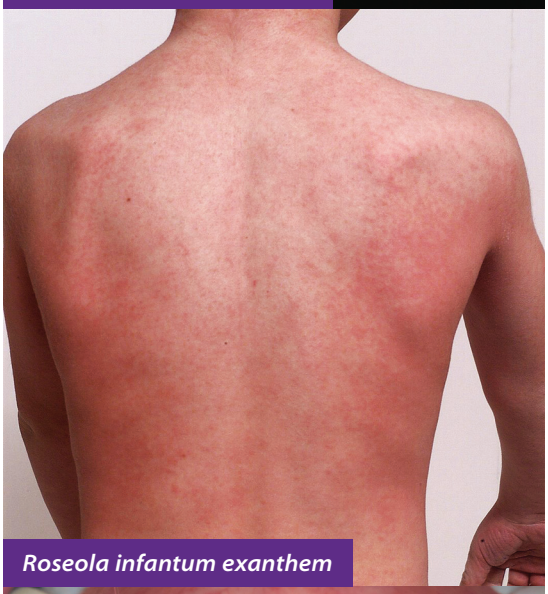

Erythema infectiosum exanthem

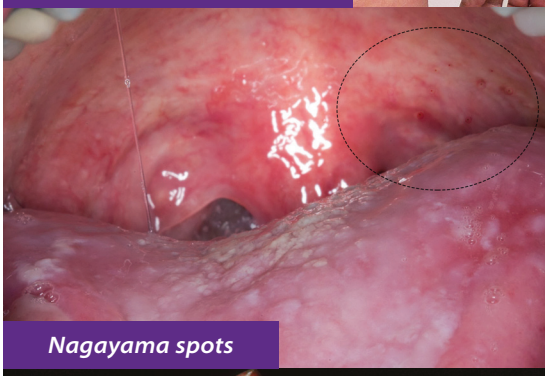

"Slapped cheeks"

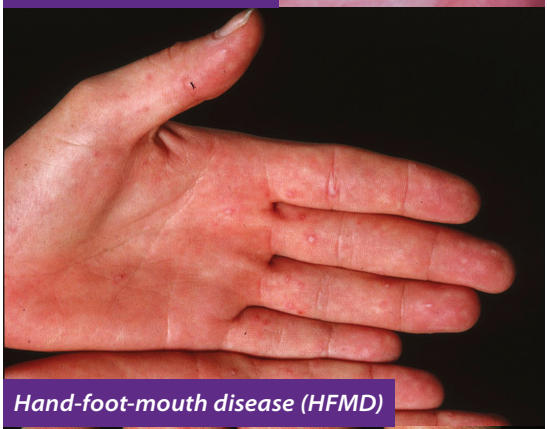

Erythema infectiosum exanthem

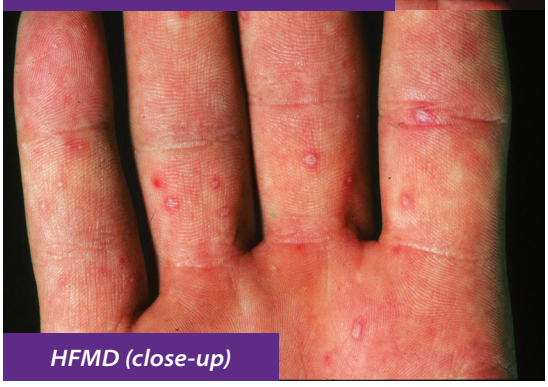

Gloves-and-socks syndrome


Gloves-and-socks syndrome


Roseola infantum exanthem


Nagayama spots


Hand-foot-mouth disease (HFMD)


HFMD (close-up)

- **USMLE Pearls: Papular-Purpuric Gloves and Socks Syndrome:** Typically caused by *Parvovirus B19*. Primarily affects teenagers and young adults. Patients experience **swelling, pruritus** and **erythema of hands and feet** with demarcation of the rash at the wrists and ankles. Lesions become **purpuric** over several days. The rash typically resolves after 5 weeks.

4. ROSEOLA INFANTUM

- **General:** Also known as **exanthem subitum or "sixth disease."** Childhood viral exanthem caused by the ds-DNA viruses, ***Human herpesvirus-6*** (HHV-6) and HHV-7. After the initial infection, HHV-6 remains latent in leukocytes and monocytes indefinitely. In immunocompromised patients (eg, HIV, transplant), the virus can reactivate and present with severe **encephalitis** and **hepatitis.** HHV-6 is also associated with **chronic fatigue syndrome** and **DRESS** (discussed in chapter 8).

- **Clinical:** Begins with flu-like symptoms and **abrupt onset of high fevers** that spontaneously resolve in 3 to 5 days. When the **fever subsides,** the child develops a non-itchy, pink-to-red **morbilliform rash** all over the body known as **"exanthem subitum."** The enanthem is characterized by small erythematous papules on the uvula and soft palate **(Nagayama spots).** The skin eruption is self-limited and lasts 1 to 3 days. Children often develop **seizures** during the febrile period.

- **Diagnosis**
  - **Best initial test:** Clinical + HHV-6 and HHV-7 IgM and IgG antibodies *or* DNA detection via PCR.
  - **Most accurate test:** Viral culture from infected tissue.

- **Treatment**
  - **First line:** Supportive with rest, fluids and acetaminophen.
  - **Second line:** Consider antiviral prophylaxis with ganciclovir for immunocompromised and transplant patients.

5. COXSACKIE VIRUS

- **General:** Viral infection of the skin and internal organs caused by the ss-RNA virus, ***Coxsackie virus.*** Highly infectious virus transmitted by **fecal-oral route** and respiratory droplets. Associated with **nursery** and **school outbreaks.** Hand-washing and disinfecting surfaces and fomites prevent transmission. Coxsackie virus mainly affect:
  - **Brain:** Encephalopathy and aseptic meningitis.
  - **Pancreas:** Leads to type 1 diabetes mellitus.
  - **Heart:** Pericarditis and dilated cardiomyopathy.

- **Clinical:** Skin manifestations are mainly divided into **hand-foot-mouth disease** (HFMD) and **herpangina.** Additionally, coxsackie virus may affect patients with eczema in a similar manner to eczema herpeticum **("eczema coxsackium").**
  - **Hand-foot-mouth disease (HFMD):** Begins with a prodrome of sore throat, odynophagia, fever, anorexia and lymphadenopathy. This is followed by a pink-to-red **morbilliform eruption** mainly located on the **hands, feet and mouth.** The papules evolve into **tiny gray vesicles**

that rupture to form 1 to 5 mm crusted ulcers on an erythematous base. Oral ulcers are usually located on the gingiva, tongue or inside the cheeks.
  - **Herpangina:** Similar to HFMD with *2 main differences*: Herpangina **lacks the cutaneous eruption** and the **oral ulcers are located more posteriorly** on the soft palate, uvula, tonsils and throat.

- **Diagnosis**
  - **Best initial test:** Clinical + *Coxsackie virus* IgM and IgG antibodies.
  - **Most accurate test:** Viral culture or PCR from an infected vesicle or ulcer.

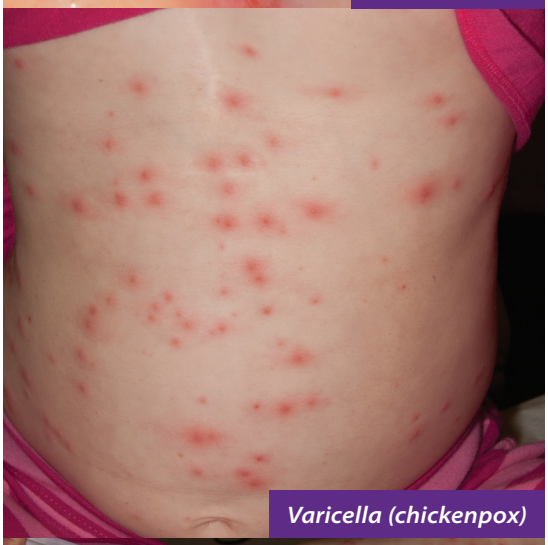
- **Treatment**
  - **First line:** Supportive with rest, fluids and acetaminophen.

6. VARICELLA-ZOSTER VIRUS (VZV)

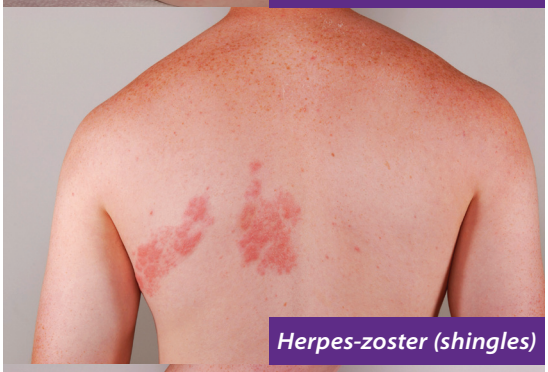
- **General:** Common viral exanthem caused by the ds-DNA virus, ***Varicella-zoster virus*****,** also known as ***Human herpesvirus-3*** **(HHV-3).** After primary infection, the virus remains latent in the sensory neurons of **dorsal root ganglia.** Transmitted by direct contact with vesicles, respiratory droplets or transplacentally. The virus is **contagious 2 days before** the prodrome of symptoms **until all lesions have crusted.** Cover lesions or isolate patient during this period. **VZV live vaccine** prevents infection and is recommended for adults over 60 and children 12 months and older. Important complications of varicella infection include:
  - **Pneumonia**
  - **Encephalitis** and **cerebellar ataxia**
  - **Secondary skin infections** (eg, impetiginization)
  - **Congenital varicella syndrome:** Maternal VZV infection early in pregnancy **(< 20 weeks),** neonate presents with microphthalmia, cataracts, deafness, hypoplastic limbs with contractures and cutaneous scars.
  - **Neonatal varicella:** Maternal varicella infection *5 days before* or *2 days after* delivery (30% mortality).

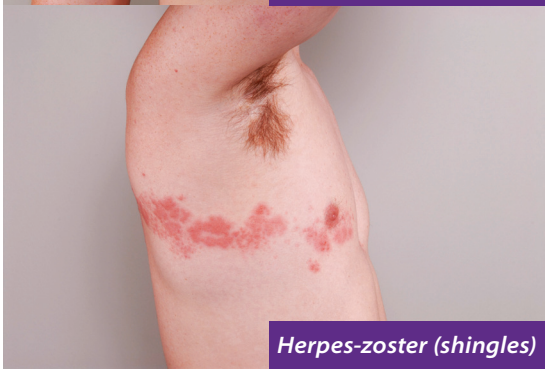
- **Clinical:** Skin manifestations are divided into **varicella** (chickenpox) and **herpes-zoster** (shingles).
  - **Varicella (Chickenpox):** This is the **primary infection,** begins with a prodrome of flu-like illness and diffuse itching, pain and paresthesias. One or 2 days later, a pruritic, **vesicular eruption** overlying erythematous macules **("dewdrop on a rose petal")** involves the trunk and spreads to the face and extremities. In several days, the vesicles rupture and form tiny crusted erosions. The classic finding is **lesions at different stages of development:** *papules*, *vesicles* and *crusted erosions*. Varicella in adults is more severe than in children.
  - **Herpes-Zoster (Shingles):** Caused by **reactivation** of VZV during periods of immunosuppression. Begins with focal pain and paresthesias followed by the development of painful red papules and vesicles in a **unilateral dermatomal distribution.** In immunocompromised patients (eg, HIV), the eruption can be severe and involve multiple dermatomes and cross midline. It may involve the geniculate ganglion and present with CN-VII palsy and vesicles on the face, mouth and auditory ear canal **(Ramsay-Hunt syndrome).** The **Hutchinson sign** is zoster on the tip of the nose and it is a sign of ocular involvement (dendritic ulcers).

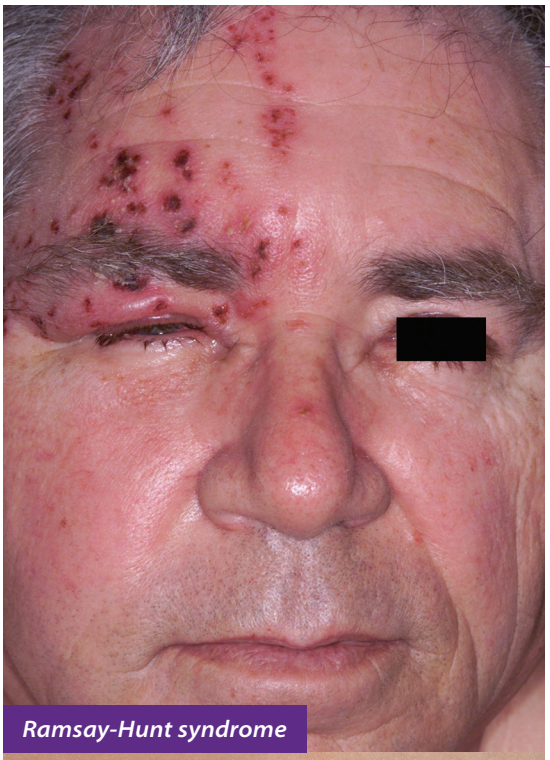

Herpangina

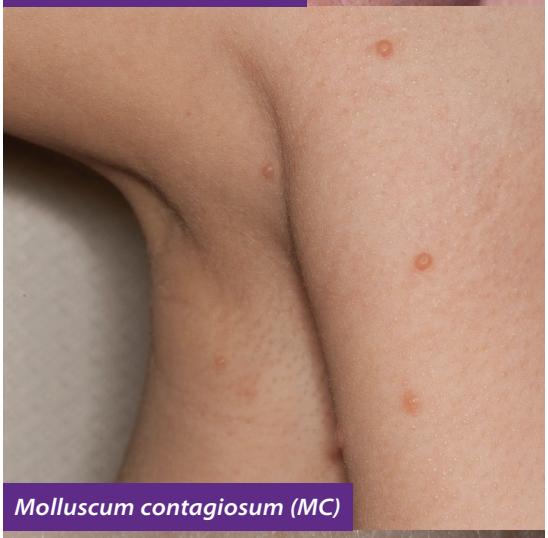

Varicella (chickenpox)

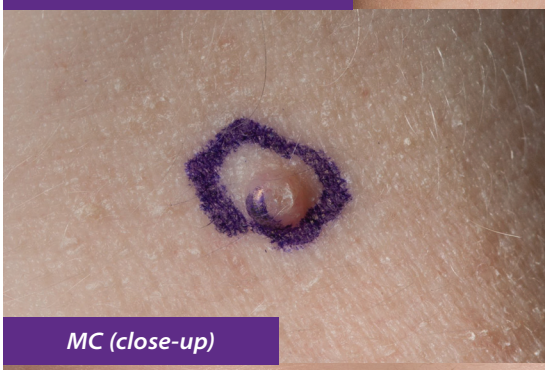

Varicella (chickenpox)


Herpes-zoster (shingles)


Herpes-zoster (shingles)


Ramsay-Hunt syndrome


Molluscum contagiosum (MC)


MC (close-up)


Irritated MC

- **Diagnosis**
  - **Best initial test:** Clinical + Tzanck smear *or Varicella-Zoster virus* IgM and IgG antibodies *or* DNA detection via PCR.
  - **Most accurate test:** Viral culture from infected vesicle fluid.

- **Treatment**
  - **Varicella (Chickenpox)**
    - **First line:** Symptomatic with antihistamines and acetaminophen. To avoid Reye syndrome, do not use aspirin in children.
    - **Second line:** Acyclovir for immunocompromised patients and varicella-zoster immune globulin (VariZIG) for infants.
  - **Herpes-Zoster (Shingles)**
    - **First line:** Acyclovir, famciclovir or valacyclovir (decreases incidence of post-herpetic neuralgia) and IV acyclovir for immunocompromised patients.
    - **Second line:** Gabapentin, pregabalin or TCA drugs may be used to treat post-herpetic neuralgia.

- **Postexposure prophylaxis (PEP):** Nonimmune adults and children should receive live attenuated varicella vaccine (Varivax) **within 5 days** of known exposure. If there are contraindications to live vaccination (eg, immunocompromised, allergy, pregnancy), use varicella-zoster immune globulin (VariZIG) or IVIG **within 10 days.**

7. MOLLUSCUM CONTAGIOSUM (MC)

- **General:** Viral infection of epidermal cells caused by the ds-DNA virus, ***Molluscum contagiosum virus*** (MCV). Transmitted by direct contact or self-inoculation (scratching). Common in **children, immunocompromised patients** and individuals who practice **contact sports** (eg, wrestling). It can be sexually transmitted. Consider sexual abuse in children with genital molluscum contagiosum.

- **Clinical:** Characterized by **smooth, dome-shaped, flesh-colored pearly papules** with **central umbilication** ranging from 2 to 6 mm in diameter. Papules are filled with keratin material that contains the infectious **molluscum bodies.** They are generally asymptomatic but may become irritated secondary to trauma. Commonly located on the trunk, limbs and anogenital area; the palms and soles are spared. **Do not confuse** with *common warts*, which have an irregular verrucous surface, lack central umbilication and commonly appear on palms and soles.

- **Diagnosis**
  - **Best initial test:** Clinical. Consider HIV testing for adults with multiple molluscum contagiosum lesions of sudden onset.
  - **Most accurate test:** Skin biopsy with Wright-Giemsa staining showing *Henderson-Patterson* (molluscum) bodies.

- **Treatment**
  - **First line:** Observation. Most patients experience spontaneous remission in 6 to 9 months.
  - **Second line:** Cryotherapy, curettage or cantharidin for cosmetics or persistent lesions.

8. HUMAN PAPILLOMA VIRUS (HPV)

- **General:** Neoplasm of the skin and mucosae caused by infection with the ds-DNA virus, ***Human papillomavirus.*** Transmitted by self-inoculation or direct contact (eg, sex, sharing clothing, birth process, fomites). The main skin lesion is the **verruca,** which is caused by hundreds of HPV types. The *common wart* is generally caused by **HPV type 1, 2 and 4** and the *flat wart* by **HPV type 3 and 10.**

- **Clinical:** Very common in children, *common warts* are characterized by a **flesh-colored outgrowth** with a **rough** and **irregular verrucous surface. Black dots** on the surface represent thrombosed capillaries. The *flat wart* is usually **less elevated** and **smoother** in texture. Both obliterate the normal skin lines. Most commonly located on the **hands and fingers** but can occur anywhere. Children can acquire **laryngeal papillomas** during birth process and present with **respiratory distress and cyanosis.** Most common cause of perianal warts in children < 3 years old is vertical (perinatal) transmission, *not* child abuse.

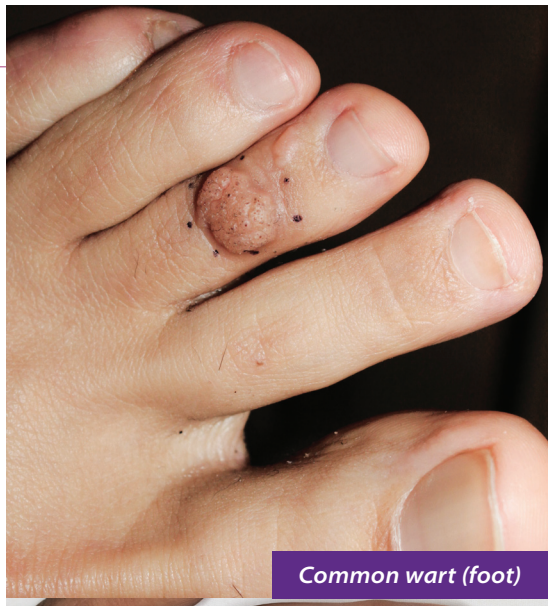
- **Diagnosis**
  - **Best initial test:** Clinical. Consider HPV typing and DNA detection via PCR.
  - **Most accurate test:** Skin biopsy showing the classic HPV viral cytopathic changes (koilocytes).

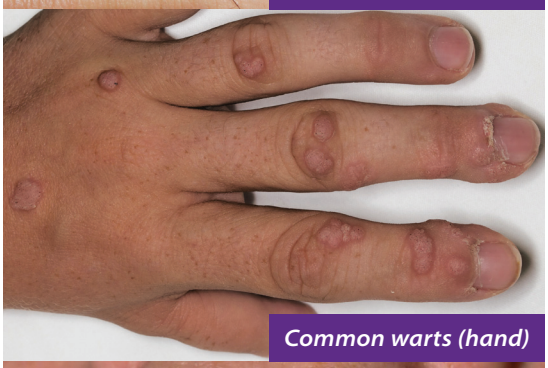
- **Treatment**
  - **First line:** Observation. Approximately 90% of patients experience spontaneous remission in 6 to 24 months.
  - **Second line:** Cryotherapy, podophyllin, imiquimod, salicylic acid, laser or excision for cosmetics or persistent lesions.

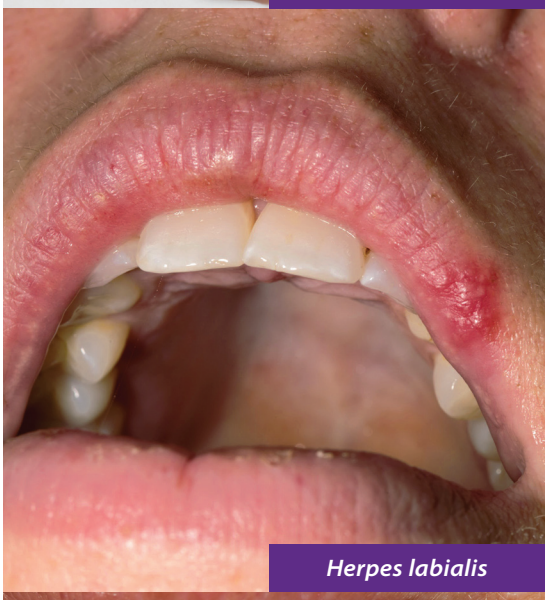
9. HERPES SIMPLEX

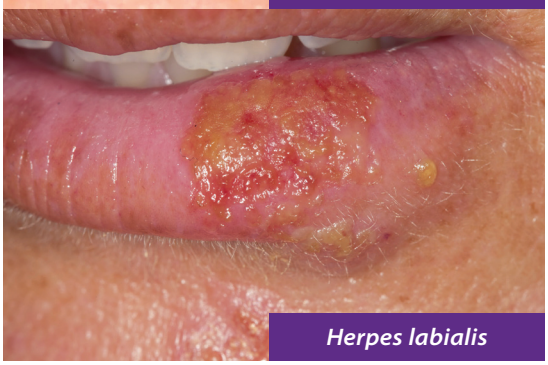
- **General:** Common, chronic, recurrent viral infection caused by the ds-DNA herpes viruses, ***Herpes simplex virus-1*** (HSV-1) and less commonly ***Herpes simplex virus-2*** (HSV-2). After primary infection, the virus remains **latent in sensory neuronal cells** (eg, trigeminal ganglia). HSV-1 has a predilection for orofacial skin but can occur anywhere. Transmitted by direct contact with infected vesicles and saliva. Herpes simplex infections are mainly asymptomatic and > 75% of the population has antibodies to HSV. Reactivation of latent virus occurs more frequently among immunocompromised patients (eg, HIV) or after specific stimuli (eg, menses, fever, stressful events, sun exposure, trauma). Common organs affected by HSV are:
  - **Eyes:** Uveitis and herpetic keratitis (dendritic ulcers).
  - **Brain:** Meningitis and **temporal encephalitis** (bloody CSF tap, high mortality).
  - **GI tract and liver:** Esophagitis and hepatitis.

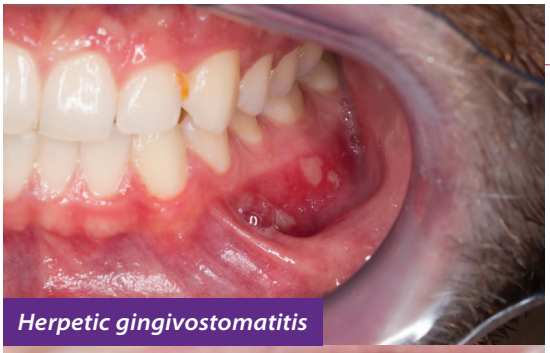
- **Clinical**
  - **Herpes labialis:** Most common HSV-1 presentation, characterized by a **severe and prolonged primary infection,** followed by milder and shorter reactivation episodes. Primary HSV infection in children presents with *acute herpetic gingivostomatitis.* This begins with severe flu-like symptoms and **localized oral/perioral itching, burning and**

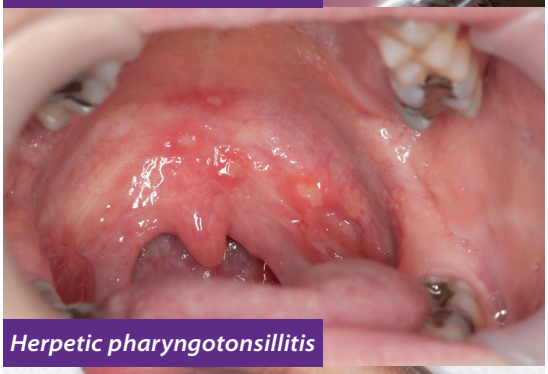

Common wart (foot)


Common warts (hand)

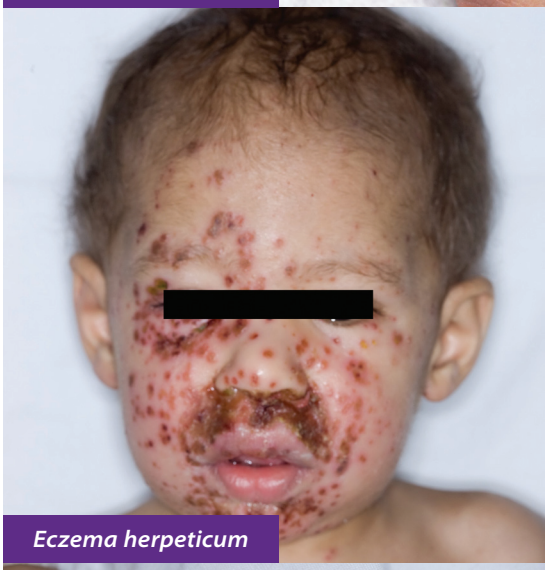

Herpes labialis

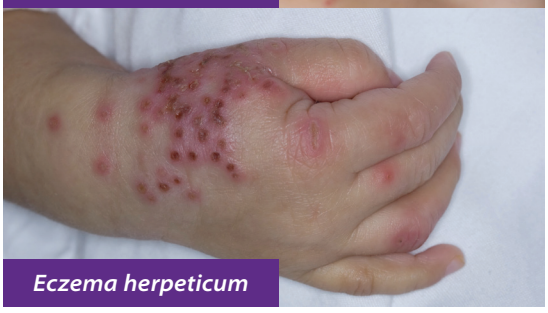

Herpes labialis


Herpetic gingivostomatitis


Herpetic pharyngotonsillitis


Herpetic whitlow


Eczema herpeticum


Eczema herpeticum

tingling. Two to three days later, **small, grouped, whitish vesicles** appear on the oral mucosae, tongue, gums, lips and/or perioral skin. The vesicles rupture to form painful, **yellow-crusted ulcers.** In adults, primary HSV causes *acute herpetic pharyngotonsillitis,* which is similar to herpetic gingivostomatitis except vesicles and ulcers are located in the pharynx and tonsils. **Primary HSV** typically last 2 to 3 weeks and may be accompanied by generalized lymphadenopathy. **Reactivation episodes** are milder without systemic symptoms, ulcers are mainly restricted to the lips and episodes last 1 to 2 weeks.

- **Herpetic whitlow:** Herpes infection of **hands or fingers** presenting with throbbing pain, swelling and herpetic vesicles. It commonly occurs in oral healthcare workers such as **dentists, oral surgeons** and **dental assistants.**
  - Do not confuse with a **felon,** which is a closed-space bacterial infection of the fingertip most commonly caused by ***S. aureus.*** A minor cut or a wood splinter injury on the fingertip is the usual initiating factor. It is characterized by edema, tension, redness and pus in the **distal pulp of the fingertip.** *Treat* with incision and drainage + dicloxacillin.
- **Eczema herpeticum (Kaposi varicelliform eruption):** *Disseminated* herpes infection that occurs more commonly in infants and children with **history of eczema** (eg, atopic dermatitis). Begins with pruritic, **erythematous-based clustered vesicles** that evolve into tiny, painful erosions with hemorrhagic crust. Commonly affect areas with preexisting atopic dermatitis or other eczematous lesions. The classic scenario is a close contact (eg, family member) that has or recently had clinically active herpes simplex and days later the child developed eczema herpeticum. It is a **medical emergency.** *Treat* immediately with acyclovir.
- **Herpes gladiatorum:** Most commonly presents with painful, erythematous-based clustered vesicles and papules on the trunk, arms, face or neck in a person who practices **contact sports,** classically **wrestling.** The rash may be accompanied by flu-like symptoms and lymphadenopathy.

- **Diagnosis**
  - **Best initial test:** Clinical + Tzanck smear showing *multinucleated giant cells* with Cowdry A bodies *or* HSV DNA detection via PCR of infected tissue.
  - **Most accurate test:** HSV viral culture from infected vesicle fluid or ulcer tissue.

- **Treatment**
  - **First line:** Oral acyclovir, famciclovir or valacyclovir. Daily acyclovir reduces reactivation episodes. IV acyclovir for immunocompromised patients or herpes simplex encephalitis.
  - **Second line:** Topical penciclovir or acyclovir (may shorten duration by 1 day). Foscarnet for resistant cases.

10. EBOLA

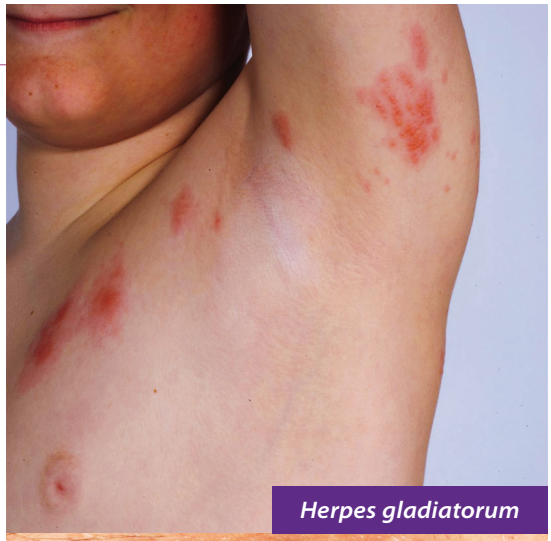
- **General:** Rare viral **hemorrhagic fever syndrome** caused by the ss-RNA virus, ***Ebola virus.*** Ebola induces widespread **intravascular coagulation,** leading to organ ischemia and tissue damage. In the last phases, it **injures the lining of vessels,** causing **blood leakage** into different organs. The

virus is endemic in **West Africa;** the natural reservoir is thought to be primates and bats. Transmitted by exposure to **infected body fluids** (eg, urine, saliva, blood, feces). In the US, cases are mainly limited to direct contact with immigrants, aid workers and tourists coming from an endemic area and people who handle **burial preparations** or infected wild animal meat **(bush meat).**

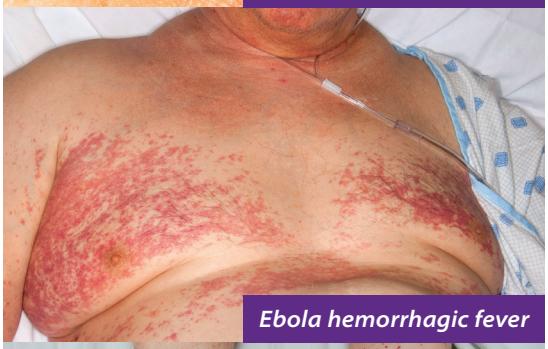
- **Clinical:** Begins with nonspecific flu-like symptoms, followed by an asymptomatic **pinpoint to maculopapular eruption** beginning in the trunk and centripetally spreading to the extremities. The final stage is characterized by the hemorrhagic fever syndrome. The main manifestations are:
  - **Skin:** Bleeding from venipuncture or surgical sites and widespread petechiae, purpura and ecchymoses.
  - **Eyes and nose:** Conjunctivitis and epistaxis.
  - **Liver and GI:** Severe hepatitis, abdominal pain, diarrhea, nausea and vomiting, dysphagia and GI bleeding.
  - **Kidney:** Oliguria or anuria and hematuria.
  - **Brain:** Encephalitis, confusion and seizures.

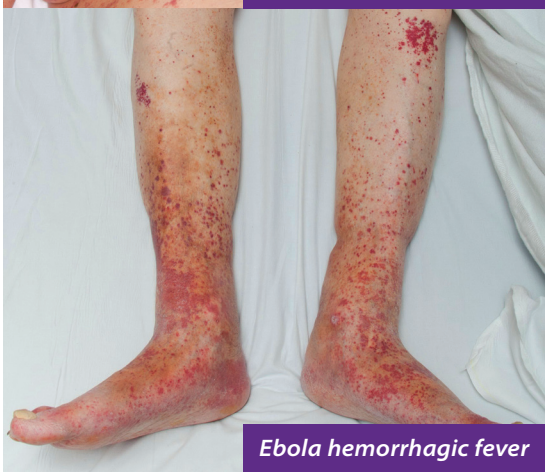
- **Diagnosis**
  - **Best initial test:** *Ebola virus* antigen detection via ELISA or PCR from infected tissue. IgM and IgG antibodies may be helpful later in disease course. Laboratories may show thrombocytopenia, leukopenia, prolonged PT/PTT and elevated AST, ALT, bilirubin, BUN and Cr.
  - **Most accurate test:** Viral culture from infected tissue.

- **Treatment**
  - **First line:** Quarantine + supportive with IV fluids, electrolytes, clotting factors, oxygen and nutrition. There is no FDA-approved treatment.
  - **Second line:** Interferon, TKM Ebola antiviral (small interfering RNAs) and special immunoglobulins or monoclonal antibodies (ZMapp) preparations (all are experimental drugs and nonproven).


Herpes gladiatorum


Ebola hemorrhagic fever


Ebola hemorrhagic fever


Ebola hemorrhagic fever

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Chapter 18

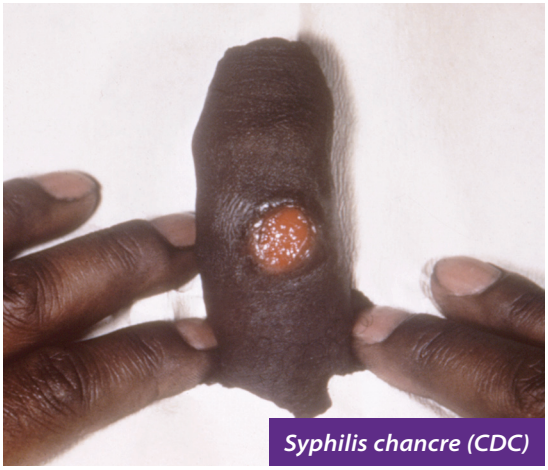
SEXUALLY TRANSMITTED INFECTIONS (STIs)

Table 18.1. Genital Ulcer Adenopathy Syndromes Summary

Disease and Pathogen	Painful or Painless Ulcer	Ulcer Description	Lymphadenopathy (LAD) Description	Suppurative or Nonsuppurative LAD	Associations and Characteristics	Ulcer Course
Syphilis • *Treponema pallidum*	**Painless**	Usually **single** ulcer with **clean base** (nonpurulent) and **firm, raised edges**.	**Painless**, bilateral LAD.	**Nonsuppurative**	**Aortitis, gummas and neurosyphilis** **Condyloma lata** **Maculopapular rash**	Heals without treatment
Lymphogranuloma Venereum (LGV) • *Chlamydia trachomatis L1-L3*	**Painless**	Usually **single shallow** ulcer that **heals rapidly**, often unnoticed.	**Painful**, ***unilateral* or *bilateral*** LAD, develops days to weeks ***after*** ulcer.	**Suppurative**	**Proctocolitis** **Genital elephantiasis**	Heals without treatment
Granuloma Inguinale (Donovanosis) • *Klebsiella granulomatis* • *Formerly known as Calymmatobacterium granulomatis*	**Painless**	Single or multiple **"beefy-red"** ulcers with **rolled-up edges** that bleed easily.	LAD is usually **absent**, may develop **pseudobuboes**.	**Not applicable**	**Immigrants from Australia, the Caribbean and New Guinea**	Need antibiotics to heal
Genital Herpes • *HSV-2 (most common)* • *HSV-1*	**Painful**	Multiple, itchy **yellow-crusted** ulcers preceded by **grouped vesicles**.	**Painful**, ***bilateral* regional** LAD, often with flu-like symptoms.	**Nonsuppurative**	**Recurrent episodes (reactivation)**	Heals without treatment
Chancroid • *Haemophilus ducreyi*	**Extremely painful**	Usually multiple ulcers with **"ragged" edges** and base with **yellow-gray purulent exudate**.	**Painful**, unilateral LAD.	**Suppurative**	**Sex workers**	Need antibiotics to heal

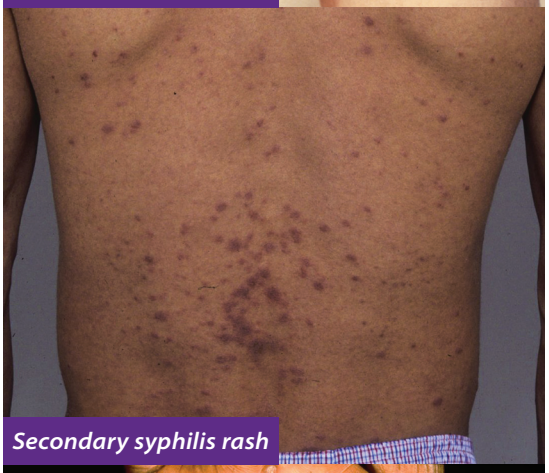
1. SYPHILIS

- **General:** Sexually transmitted infection caused by the gram-negative spirochete ***Treponema pallidum*.** Following infiltration, the organism travels to the lymphatics and internal organs. In **blood vessels,** *T. pallidum* causes **inflammation of the tunica intima** leading to occlusion of the vessel lumen **(obliterating endarteritis).** Transmission is primarily sexual or maternal-fetal. It is more common in men and associated with men who have sex with men **(MSM).** Syphilis has been called **"the great imitator"** owing to its wide variety of clinical presentations.

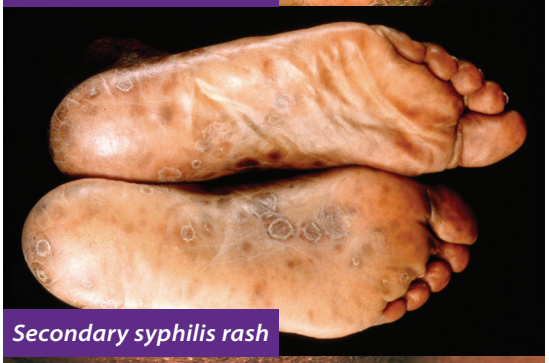


Syphilis chancre (CDC)


Syphilis LAD (CDC)


Secondary syphilis rash


Secondary syphilis rash


Secondary syphilis rash


Condyloma lata (CDC)

- **Clinical:** Divided into 4 stages *(primary*, *secondary*, *latent* and *tertiary syphilis)*.
  - **Primary syphilis:** Occurs within 90 *days* of sexual contact. The patient develops a **firm, painless papule** that evolves into an ulcer known as a **chancre.** The ulcer is **painless** with **raised, firm edges** and a **clean (nonpurulent) base,** commonly on the genital area. This is followed by **painless, bilateral, nonsuppurative** inguinal and pelvic lymphadenopathy (LAD). Chancres heal spontaneously in 1 to 2 months without treatment.
  - **Secondary syphilis:** Occurs *weeks to months* after primary infection; characterized by **systemic spread** of *T. pallidum* spirochetes. A non-pruritic, **"copper-colored" maculopapular eruption** may develop on the **trunk, palms and soles.** The rash is accompanied by flu-like symptoms, generalized lymphadenopathy and **patchy alopecia.** Highly infectious, gray-to-flesh-colored, **flat-topped** papules and plaques known as **condyloma lata** develop on the anogenital area and other skin folds. **Mucous patches** are the oropharyngeal equivalent and present as circumscribed, **silvery erosions.**
  - **Latent stage:** Important to distinguish for treatment purposes.
    - **Early latent stage:** Defined as *less than 1 year* from initial infection. In this stage, the patient is generally **infectious** and completely *asymptomatic*. Serologic tests for syphilis are positive.
    - **Late latent stage:** Defined as *more than 1 year* after initial infection or disease of **unknown duration.** In this stage, the patient is generally ***not* infectious** and is *asymptomatic*. Serologic tests for syphilis are positive.
  - **Tertiary syphilis:** Occurs *1 or more years* after initial infection. The main features of this stage are:
    - **Cardiovascular syphilis:** Obliterating endarteritis of the aorta vasa vasorum causes **aortitis** and **aortic aneurysms.** Dilation and weakening of the aorta may result in **regurgitation.**
    - **Gummatous syphilis:** Presents with granulomatous nodules and ulcers involving any organ; **bone involvement** leads to intense dull pain that is often worse at night.
    - **Neurosyphilis:** Meningitis, uveitis, hearing loss, seizures and dementia. **Spinal cord disease** presents with sensory and gait changes **(tabes dorsalis),** bladder dysfunction, shooting pains and Charcot joints.

- **Diagnosis**
  - **Best initial test:** VDRL or RPR (nontreponemal tests) followed by confirmatory FTA-ABS or MHA-TP (treponemal tests).
  - **Most accurate test:** Microscopic examination of *any* infected tissue using *T. pallidum* special stains *OR* detection of *T. pallidum* spirochetes by dark field microscopy of **chancre** or **condyloma latum** (used less often).

- **Treatment**
  - **Primary, secondary and early latent syphilis:** Single intramuscular (IM) dose of benzathine penicillin G (2.4 million units). Doxycycline, erythromycin or ceftriaxone are used as second-line agents or for penicillin allergic patients.
  - **Late latent or tertiary (gummatous or cardiovascular) syphilis:** Three IM doses of benzathine penicillin G (2.4 million units) administered weekly.

- **Neurosyphilis:** IV penicillin G (3 to 4 million units every 4 hours) for 10 to 14 days. For penicillin allergic patients, consider *penicillin desensitization* rather than second line therapy.

- **USMLE Pearls: Penicillin G** is standard of care for treatment of **pregnant patients** with syphilis infection. If the patient is **allergic,** conduct *penicillin desensitization* (gradual challenge with penicillin until toleration). The patient needs to be **off beta-blocker** medications and **epinephrine** must be available for possible anaphylaxis.

- **USMLE Pearls: Jarisch-Herxheimer reaction:** May occur within hours **following treatment initiation** of syphilis and other spirochetal infections. Patients develop **fever, myalgias, hypotension** and **rash** due to release of proteins from dead spirochetes. *Treatment* is symptomatic with antipyretics; there is **no pretreatment** to prevent the reaction.

2. LYMPHOGRANULOMA VENEREUM (LGV)

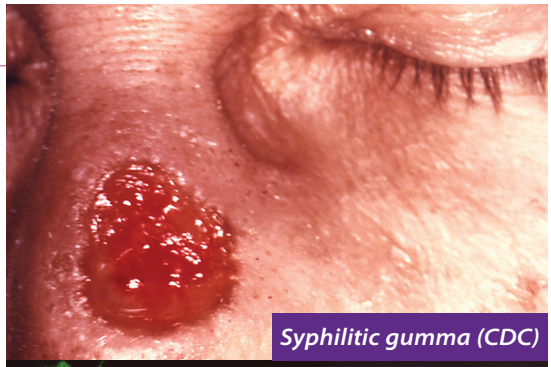
- **General:** Sexually transmitted infection caused by the obligate intracellular bacterium, ***Chlamydia trachomatis L1-L3*.** Rarely diagnosed in the US. Cases are mainly limited to **immigrants** from developing countries (eg, Africa, Asia, the Caribbean, South America). Following entry via disrupted skin or mucosa, the organism **invades the lymphatic system** of the anogenital area and replicates within monocytes and macrophages. Outbreaks have been reported in men who have sex with men **(MSM).**

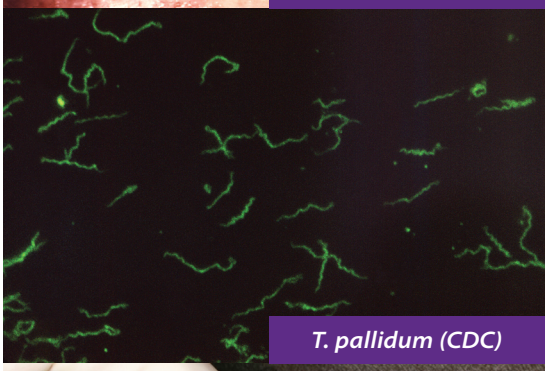
- **Clinical:** Divided into *three stages*.
  - **First stage:** Begins with a small papule that develops into a **painless shallow ulcer.** The ulcer heals quickly *without* treatment and frequently goes unnoticed.
  - **Second stage:** Occurs days to weeks after the first stage. Begins with flu-like symptoms and **rapid, painful, unilateral** or **bilateral** enlargement of inguinal lymph nodes. The lymph nodes often merge and rupture leading to severe *suppurative lymphadenopathy* known as **buboes.**
  - **Third stage:** Rare stage typically occurring among untreated patients characterized by inflammation of the rectum and colon **(proctocolitis).** Patients can have **bloody diarrhea, tenesmus** and **rectal pain,** leading to confusion with inflammatory bowel disease (IBD). Further progression may lead to permanent **lymphatic obstruction** resulting in **genital elephantiasis.**

- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + *C. trachomatis* DNA detection via nucleic acid amplification test (NAAT) or PCR of infected tissue. Serologic testing for *C. trachomatis L1-L3* is also helpful.

- **Treatment**
  - **First line:** Doxycycline. Also treat partners.
  - **Second line:** Erythromycin **(first line in pregnancy).**

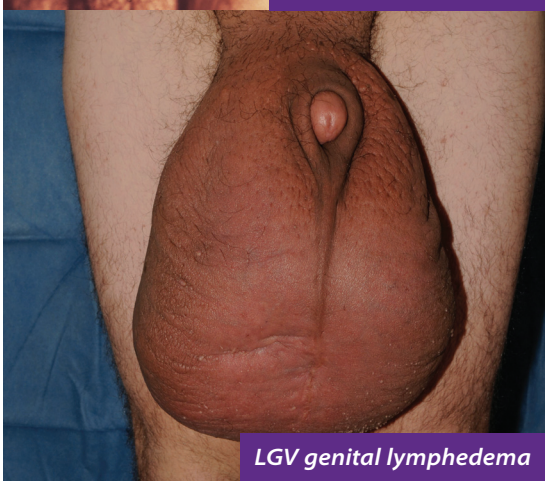
- **USMLE Pearls: *C. trachomatis D-K*:** Commonly known as chlamydia, it is the *most common* bacterial STI in the US. Affected males experience **epididymitis, prostatitis and urethritis,** while females experience

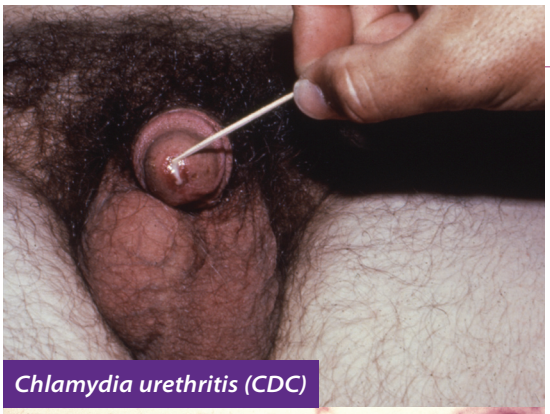

Syphilitic gumma (CDC)

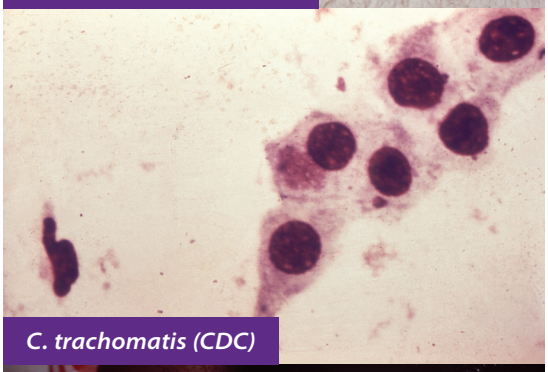

T. pallidum (CDC)

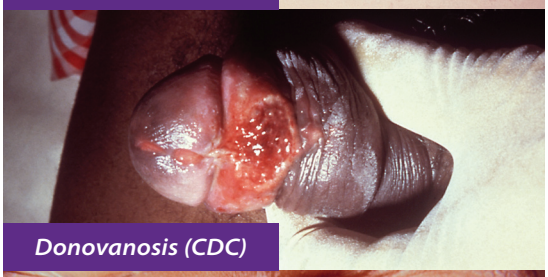

LGV ulcer

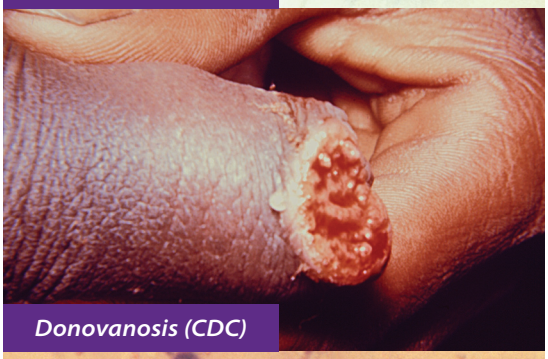

LGV buboes (CDC)

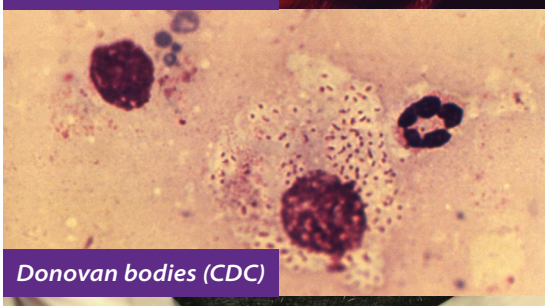

LGV genital lymphedema


Chlamydia urethritis (CDC)


C. trachomatis (CDC)


Donovanosis (CDC)


Donovanosis (CDC)


Donovan bodies (CDC)


Genital herpes vesicles

cervicitis, pelvic inflammatory disease (PID) and urethritis. ***Neisseria gonorrhoeae*** (commonly known as gonorrhea) is the second most common bacterial STI in the US and presents similarly. Dissemination of gonorrhea may lead to **dermatitis-arthritis-tenosynovitis syndrome,** featuring a **maculopapular rash** involving **palms and soles,** along with **migratory polyarthralgia** and **tenosynovitis.** *Diagnosis* of either infection is made via NAAT of urine or vaginal samples. **Doxycycline** is first-line treatment for chlamydia, while **ceftriaxone** is used for gonorrhea. Diagnosis of one infection necessitates treatment for the other as well, given common coinfection.

- **USMLE Pearls:** ***C. trachomatis A-C*****:** Different serotype that is not sexually transmitted. It is characterized by **trachoma** formation, a serious form of **conjunctivitis** that leads to permanent blindness. This infection is endemic in Africa and the **leading infectious cause of blindness** worldwide.

3. GRANULOMA INGUINALE (DONOVANOSIS)

- **General:** Sexually transmitted infection caused by the gram-negative intracellular bacterium, ***Klebsiella granulomatis*** (formerly known as *Calymmatobacterium granulomatis*). It is mainly transmitted by sexual contact and is prevalent in tropical areas such as **Australia, the Caribbean** and **New Guinea.**

- **Clinical:** Initially, a red, papulonodular lesion on the genital area evolves into a **suppurative** and **expanding painless ulcer** with **rolled-up borders.** The ulcer is **"beefy-red"** from granulation tissue and **bleeds easily** when manipulated. If left untreated, the ulcer can invade and destroy surrounding tissue. Inguinal lymphadenopathy is usually *absent* unless the ulcer is secondarily infected with bacteria. However, **subcutaneous nodules** outside lymph nodes that resemble buboes may develop **(pseudobuboes).**

- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + Wright or Giemsa stained tissue showing rod-shaped organisms inside macrophages (Donovan bodies).

- **Treatment**
  - **First line:** Azithromycin or doxycycline.
  - **Second line:** Ciprofloxacin, trimethoprim-sulfamethoxazole or erythromycin **(first line in pregnancy).**

4. GENITAL HERPES

- **General:** Sexually transmitted infection caused by ***Herpes simplex virus-2*** **(HSV-2)** and less commonly by ***Herpes simplex virus-1*** **(HSV-1).** Genital herpes is characterized by a **severe** and **prolonged primary infection,** followed by **milder** and **shorter recurrent episodes.** After primary infection, the virus remains latent in the **sacral ganglia** until reactivation. Reactivation of latent virus occurs more frequently among immunocompromised patients (eg, HIV) or after specific stimuli (eg, menses, fever, stressful events, sun exposure, trauma).

- **Clinical:** Primary infection begins with flu-like symptoms and **localized genital pain, itching** and **burning.** Two to three days later, **grouped, erythematous, short-lived vesicles** appear, developing into yellow-crusted ulcers that spontaneously heal in several weeks. This episode may be accompanied by **painful, bilateral, nonsuppurative** inguinal lymphadenopathy (LAD). Recurrent episodes are generally shorter without systemic symptoms.

- **Diagnosis**
  - **Best initial test:** Clinical + Tzanck smear of clinical lesion (ulcer base) showing multinucleated giant cells. HSV DNA detection via PCR of infected tissue is also helpful.
  - **Most accurate test:** Viral culture of vesicle fluid or ulcer tissue.

- **Treatment**
  - **First line:** Oral acyclovir, famciclovir or valacyclovir. Daily antivirals reduce reactivation episodes.
  - **Second line:** Topical penciclovir or acyclovir (may shorten duration by 1 day). Foscarnet is used for resistant cases.

5. CHANCROID

- **General:** Sexually transmitted infection caused by the gram-negative facultative anaerobic bacterium, ***Haemophilus ducreyi*.** Rarely diagnosed in the US. Cases are mainly limited to **immigrants** from developing countries **(Africa, Asia** and **the Caribbean).** Chancroid is more common among **sex workers** and **men.** Presence of genital ulceration consistent with chancroid may increase risk of HIV acquisition.

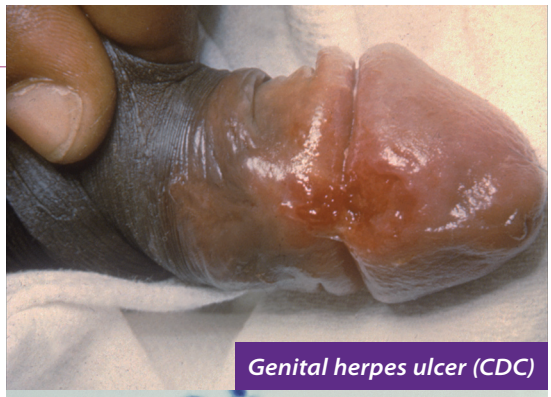
- **Clinical:** Usually presents with multiple erythematous papules or pustules that evolve into **extremely painful** excavated ulcers. Ulcer **edges are soft, "ragged"** and well-demarcated; the base has **friable granulation tissue** with a **yellow-gray purulent exudate.** It is often accompanied by **painful, unilateral** and **suppurative** inguinal lymphadenopathy (LAD).

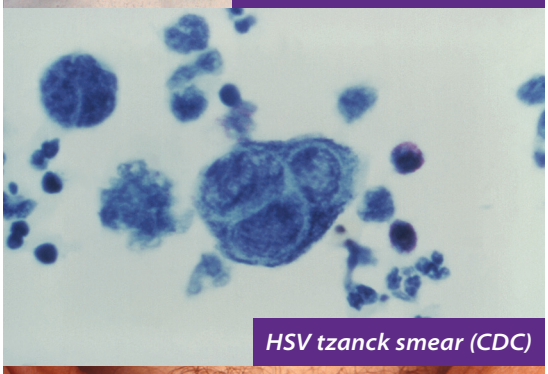
- **Diagnosis**
  - **Best initial test:** Clinical + Gram stain of ulcer exudate showing *H. ducreyi* bacteria arranged in a *"railroad track"* or *"school-of-fish"* pattern.
  - **Most accurate test:** Bacterial culture of infected tissue on specialized media that contains factor X.

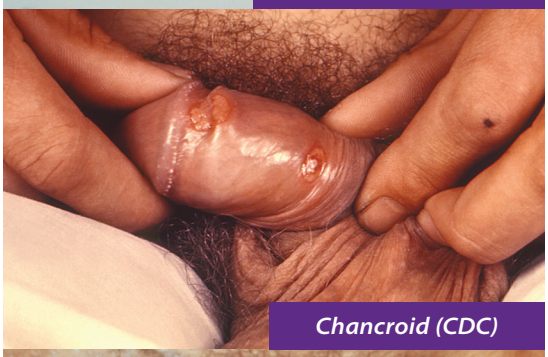
- **Treatment**
  - **First line:** Azithromycin, ceftriaxone (preferred in pregnancy), erythromycin or ciprofloxacin (contraindicated in pregnancy).

6. CONDYLOMA ACUMINATA

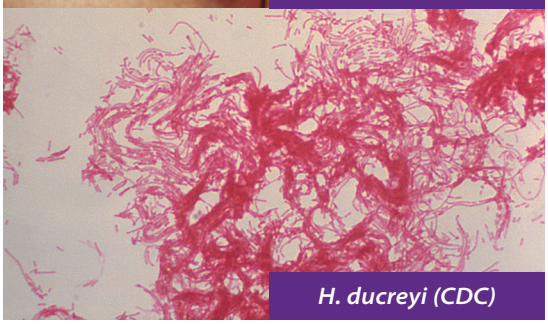
- **General:** Also known as **anogenital warts,** a sexually transmitted infection caused by the ds-DNA virus, ***Human papillomavirus*** (HPV). The virus predominantly infects epidermal cells of the **anogenital area.** HPV proteins **E6 and E7** bind and inhibit tumor suppressor genes **p53 and RB,** respectively. The result is dysregulation of the cell cycle, leading to


Genital herpes ulcer (CDC)


HSV tzanck smear (CDC)


Chancroid (CDC)


Chancroid LAD (CDC)


H. ducreyi (CDC)


Condyloma acuminata


Condyloma acuminata


Condyloma (close-up)


Pearly penile papules *

precancerous and cancerous lesions. Neoplastic potential mainly depends on the **HPV type: 6 and 11** (low risk) or **16 and 18** (high risk). Immunocompromised patients are at higher risk of malignant transformation. Condyloma acuminata is associated with **multiple sexual partners, early age of coitus** and **HIV.** Screening via Pap smear has tremendously reduced cervical cancer incidence by early detection of high-risk HPV infection. Vaccines **(eg, Gardasil)** have been developed against **HPV types 6, 11, 16 and 18;** they are recommended for administration to males and females aged 9 to 26.

- **Clinical:** Characterized by single or multiple, **irregular, cauliflower** or **plaque-like** eruption involving the anogenital area. Lesions are flesh colored-to-brown and range in size from one to several centimeters. Avoid confusion with **condyloma lata,** which are smoother, **"flat-topped"** papules seen in secondary syphilis. Consider sexual abuse in children with anogenital warts.

- **Diagnosis**
  - **Best initial test:** Clinical. Consider HPV typing via PCR of infected tissue to distinguish low-risk from high-risk HPV lesions.
  - **Most accurate test:** Skin biopsy showing the classic HPV cytopathic changes (koilocytes).

- **Treatment**
  - **First line:** Imiquimod or podophyllotoxin (patient applied); cryotherapy, laser, excision or trichloroacetic acid (physician applied).

- **USMLE Pearls: Pearly penile papules:** Benign fibrous outgrowths of the **glans penis,** characterized by rows of circumferentially arranged, **smooth, shiny, flesh-colored papillomas** ranging from **1 to 2 mm** in diameter. Similar findings **(vestibular papillomatosis)** may occur on the vaginal labia of females. Pearly penile papules affect about 30% of males and may be confused with condyloma acuminata. **No treatment is required** and patients should be **reassured** these are a benign variant of normal.

Chapter 19

SELECTED SKIN DISORDERS

Section 1: Pediatric Skin Disorders

1. ERYTHEMA TOXICUM NEONATORUM

- **General:** Benign self-limiting immune-mediated eruption affecting approximately **50%** of full-term neonates. Most cases begin **24 to 48 hours after delivery** and **spontaneously resolve** in 1 to 2 weeks without permanent sequelae. The rash is often confused with infectious exanthems; however, erythema toxicum *lacks* systemic findings.

- **Clinical:** Neonates are **healthy** and **lack any systemic symptoms** such as fever, lethargy, irritability or neck stiffness. The skin eruption is characterized by erythematous macules often with a central papule or pustule. Mainly affects **hair-bearing areas (follicular distribution)** and *spares* mucosae, palms and soles. The number of lesions varies from a few to full body involvement.

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical. Labs showing peripheral eosinophilia and Wright's staining of intralesional content revealing eosinophils supports the diagnosis.

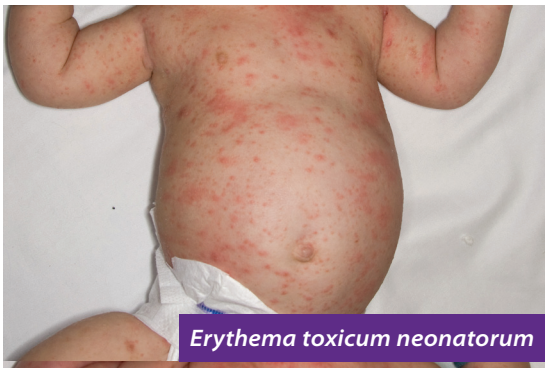
- **Treatment**
  - **First line:** Reassurance.

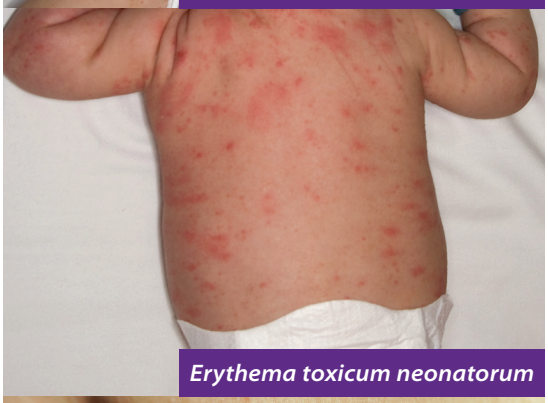
2. MILIARIA

- **General:** Commonly known as **heat rash.** Occurs frequently in neonates, but can occur in adults as well. **Blockage of eccrine sweat ducts** results in leakage of sweat into epidermis or dermis. Prevalent in areas of high heat and humidity. Miliaria is **exacerbated by skin occlusion** (eg, tight clothing, medicine patches, bandages, dressings). Usually peaks in the first week of life and is self-limiting.

- **Clinical**
  - **Miliaria crystallina:** May be present **at birth.** Sweat duct obstruction occurs *superficially* in the stratum corneum. Clinically presents with asymptomatic **1 to 2 mm clear vesicles** that rupture easily when manipulated. Vesicles may coalesce and appear as a thin superficial white layer. There is **no surrounding erythema or systemic symptoms.**
  - **Miliaria rubra:** Usually seen **after the first week of life.** Level of obstruction is *deeper* in the epidermis. Presents with **stinging** and extremely **pruritic erythematous papules and vesicles.** Lesions are *nonfollicular* in distribution, as opposed to erythema toxicum neonatorum.

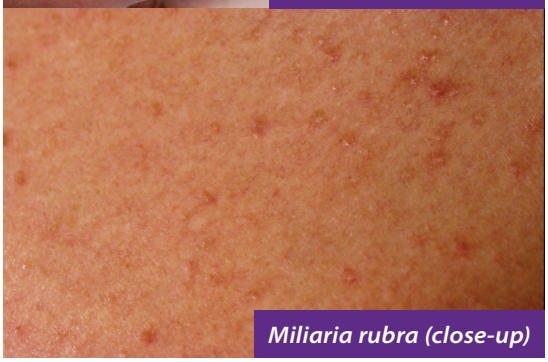
- **Diagnosis**
  - **Best initial test:** Clinical.

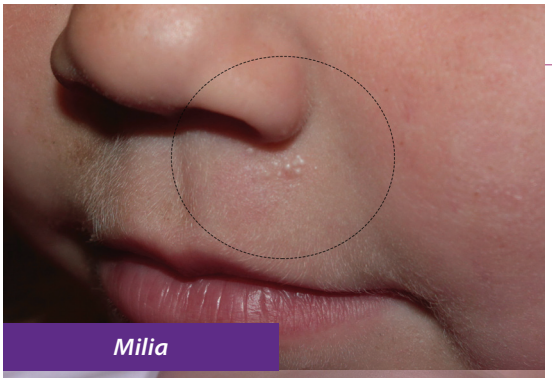

Erythema toxicum neonatorum


Erythema toxicum neonatorum

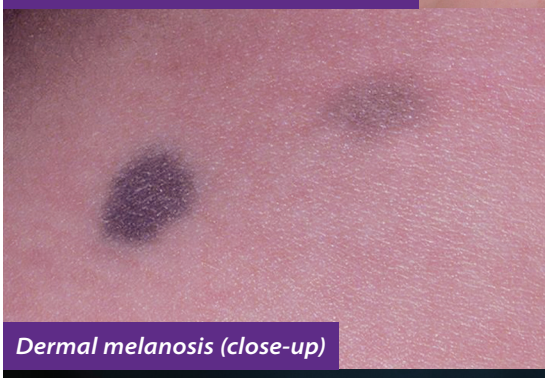

Miliaria crystallina

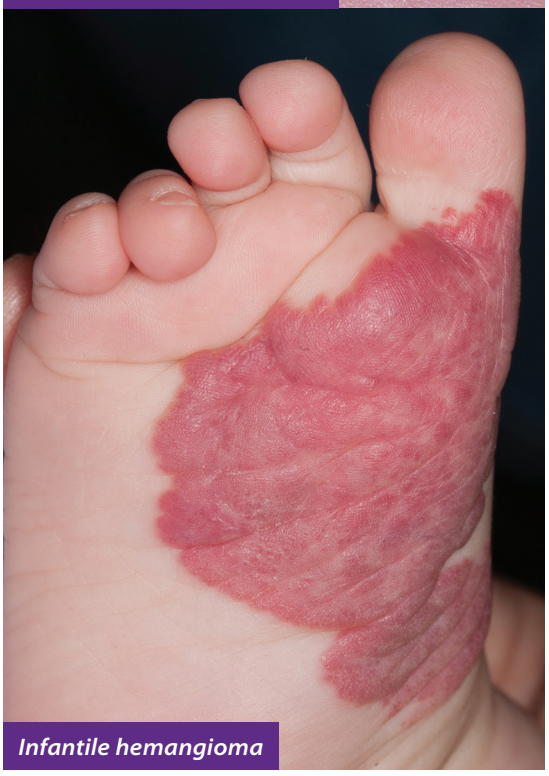

Miliaria rubra


Miliaria rubra (close-up)


Milia


Dermal melanosis (Mongolian spot)


Dermal melanosis (close-up)


Infantile hemangioma

- **Most accurate test:** Skin biopsy showing subcorneal vesicles with little surrounding inflammation **(miliaria crystallina)** or intraepidermal vesicles with an inflammatory infiltrate in the dermis **(miliaria rubra).**

- **Treatment**
  - **First line:** Control heat and humidity and limit physical activity.

- **USMLE Pearls: Milia:** Different from miliaria. Milia are keratin-filled cysts that commonly affect infants but can occur at any age. Milia occur in hair-bearing areas secondary to damage to the follicular pilosebaceous units. Clinically, they appear as **pearly white dome-shaped superficial cysts** that measure approximately **1 to 2 mm** in diameter. Most often found on the face, but can occur anywhere. *Diagnosis* is clinical. *Treatment* is reassurance.

3. DERMAL MELANOSIS (MONGOLIAN SPOT)

- **General:** Formerly known as **Mongolian spot,** this is a congenital melanosis due to **entrapment of melanocytes** in the dermis during neural crest migration. Extensive Mongolian spots are rarely associated with inborn errors of metabolism and spinal meningeal tumors.

- **Clinical:** Usually presents **at birth** or during the **first week of life.** Asymptomatic **blue-to-gray macular pigmentation** commonly located on the **sacrococcygeal area** but can occur almost anywhere. Lesions can be single or multiple and vary in pigmentation. Mongolian spots look similar to bruises and are often **confused with child abuse.**

- **Diagnosis**
  - **Best initial test:** Clinical.
  - **Most accurate test:** Skin biopsy showing melanocytes entrapped in the reticular dermis.

- **Treatment**
  - **First line:** Reassurance. Most regress spontaneously in 1 to 4 years.
  - **Second line:** Laser therapy.

4. INFANTILE HEMANGIOMA

- **General:** Benign vascular tumor; the *most common* neoplasm of infancy. Infantile hemangiomas typically have an **early stage of proliferation** (within first 5 months of age) followed by **spontaneous involution over multiple years.** Peak growth is in the first year of life and most involute by age 9. Lesions can be cutaneous and/or visceral and may cause several complications, depending on the location. The main complications are:
  - **High-output cardiac failure** (large liver hemangiomas)
  - **Ulceration** (outsourced blood supply)
  - **Airway obstruction** (laryngeal, pharyngeal or nasal hemangiomas)
  - **Visual defects** (periorbital hemangiomas)
  - **PHACE syndrome: P**osterior fossa malformations, **H**emangiomas, **A**rterial anomalies, **C**oarctation of the aorta and **E**ye abnormalities. Associated with large infantile hemangiomas of the face.

- **Clinical:** Hemangiomas vary in color; *superficial hemangiomas* are **bright red** while *deeper hemangiomas* may have a **purple-to-blue hue.** Morphologies may be **plaque-like, nodular or macular;** size and shape varies greatly. Most commonly located in the head and neck area or trunk but can occur anywhere.

- **Diagnosis**
  - **Best initial test:** Clinical. MRI or U/S imaging may be used to delineate the extent of the tumor.
  - **Most accurate test:** Skin biopsy showing masses of endothelial cells with thin vascular spaces. **GLUT1** staining may help differentiate infantile hemangiomas from other vascular tumors.

- **Treatment**
  - **First line:** Reassurance and close observation for uncomplicated infantile hemangiomas.
  - **Second line:** Propranolol, steroids or laser therapy for infantile hemangiomas that cause physical or functional impairment or ulcerate.

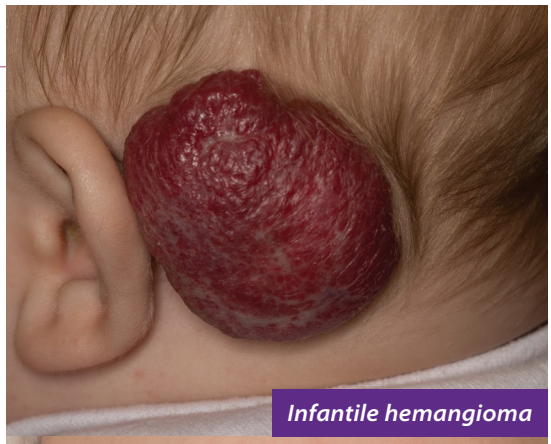
- **USMLE Pearls:** The terms **"strawberry" or "capillary" hemangiomas** are used for *superficial infantile hemangiomas*. The term **"cavernous" hemangioma** is used for *deep infantile hemangiomas*. Both of these lesions are types of infantile hemangiomas and may spontaneously regress with time. The terms **"cherry" or "senile" hemangiomas** are used for angiomas that occur in elderly individuals. Although the clinical appearance is similar, these lesions are different from infantile hemangiomas. Cherry hemangiomas **spontaneously appear** with aging and **do not involute** with time.

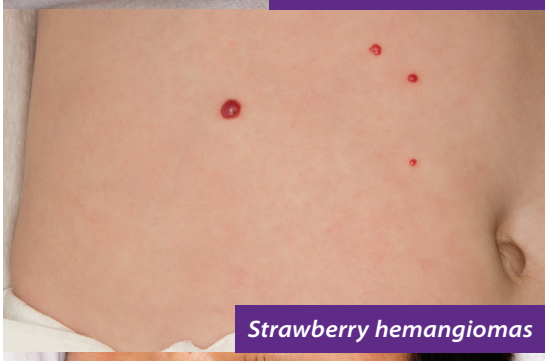
5. KAWASAKI DISEASE

- **General:** Also known as **mucocutaneous lymph node syndrome,** a small-to-medium-size **vasculitis** of unknown origin mainly affecting children. It has a predilection for the **coronary arteries** and is a common cause of acquired heart disease in children. Necrosis of the vessels tunica media separates the internal and external elastic laminae leading to **vascular aneurysms.** Kawasaki disease is prevalent in **Asian** children, especially from **Japan** and Taiwan.

- **Clinical:** Begins with 1 to 2 weeks of flu-like symptoms, **acute high fever,** uveitis, **bilateral conjunctivitis, erythema and edema on hands, feet** and perianal, **strawberry tongue with lip fissures** and **cervical lymphadenopathy** (> 1.5 cm in diameter). The skin manifestation is a nonspecific maculopapular, erythematous or target-like eruption on any part of the body. In the next 4 to 6 weeks, the fever subsides and the child develops **desquamation of hands and feet** and transverse grooves on the nails **(Beau lines).** During this period, the child is at risk for **coronary aneurysms, myocardial infarctions** and sudden death. This stage is followed by resolution of clinical and laboratory findings; however, the child may still be at risk for cardiac manifestations.

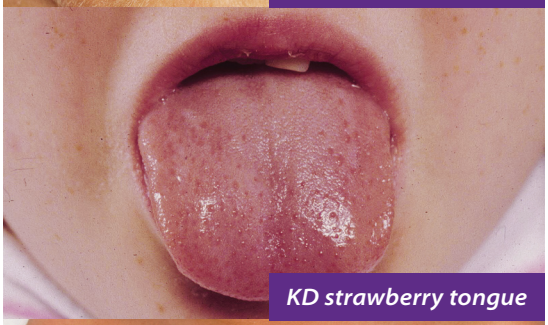
- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + labs showing elevated ESR and CRP, leukocytosis and thrombocytosis (> 500,000/uL). Perform **baseline echocardiography** (must repeat in 2 weeks and in 6 to 8 weeks). Rule out other causes of childhood exanthems (eg, scarlet fever, SSSS, measles).

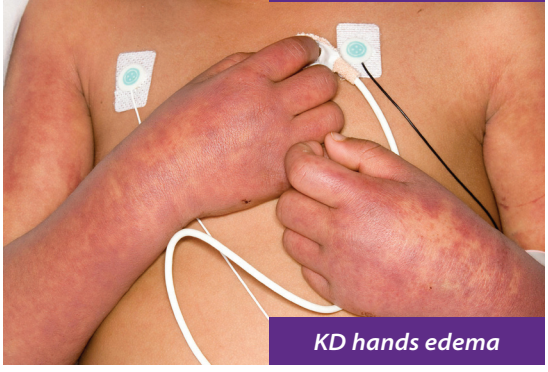

Infantile hemangioma

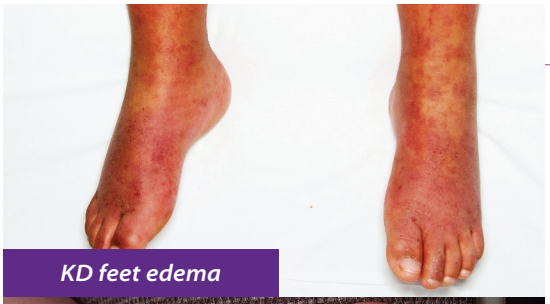

Strawberry hemangiomas


Kawasaki disease (KD)

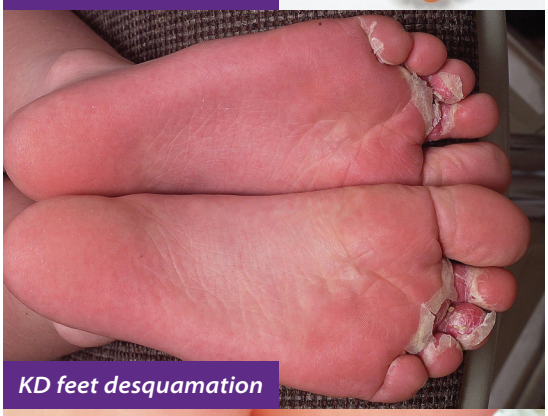

KD lip fissures


KD strawberry tongue

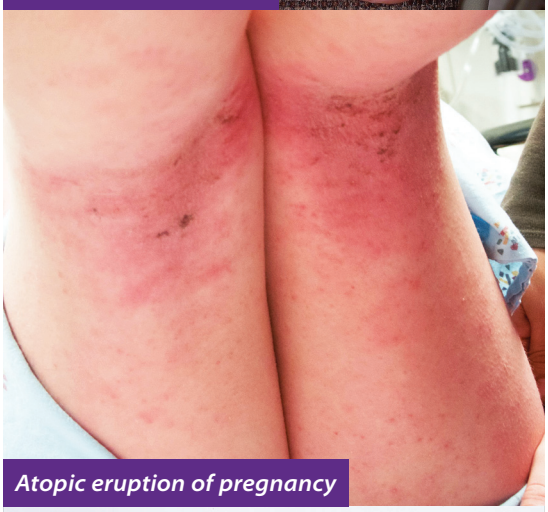

KD hands edema



KD feet edema



KD feet desquamation



Atopic eruption of pregnancy

Atopic eruption of pregnancy

Polymorphic eruption of pregnancy (PEP)

- **Treatment**
  - **First line:** Aspirin + IVIG.
  - **Second line:** Steroids or infliximab for refractory cases (controversial).

- **USMLE Pearls:** When using aspirin, yearly influenza vaccination is necessary to prevent Reye syndrome. When using IVIG, delay **live vaccinations** for > 10 months after last IVIG dose. **Live vaccines:** MMR, varicella, zoster, oral polio (Sabin), rotavirus, yellow fever, oral typhoid (salmonella), BCG, influenza (intranasal) and smallpox.

Section 2: Pregnancy-Specific Skin Disorders

1. ATOPIC ERUPTION OF PREGNANCY (AEP)

- **General:** Most common pregnancy dermatosis (may be as high as 1 in 5 women). Benign **pruritic eruption** in pregnant females with **personal or family history of atopy** (eg, asthma, eczema, rhinitis). Pathogenesis is unknown but there seems to be a genetic predisposition. Commonly **recurs in subsequent pregnancies** and newborns are predisposed to atopic disorders later in life.

- **Clinical:** Usually appears in **first or second trimester** and may last throughout pregnancy. Presents with extremely **pruritic eczematous lesions** or **erythematous papules and plaques.** Pruritus is **worst at night** and interferes with sleeping. Most commonly affects the neck, breasts and creases of the wrist, elbows and knees. Preexisting atopic dermatitis lesions are exacerbated.

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical. Labs may show high IgE levels and peripheral eosinophilia. Obtain serum bile acid levels to exclude intrahepatic cholestasis of pregnancy (may be detrimental to developing fetus).

- **Treatment**
  - **First line:** Emollients + topical steroids and oral antihistamines.
  - **Second line:** Phototherapy for severe cases.

2. POLYMORPHIC ERUPTION OF PREGNANCY (PEP)

- **General:** Formerly known as **P**ruritic **U**rticarial **P**apules and **P**laques of **P**regnancy **(PUPPP).** Second most common pregnancy dermatosis. Benign eruption that usually occurs in the **third trimester of first pregnancy.** Pathogenesis is unknown and the eruption **does not recur in subsequent pregnancies.** PEP is self-limited and resolves in 4 to 6 weeks independent of delivery.

- **Clinical:** Intensely **pruritic erythematous papules overlying** prominent **striae distensae.** Small vesicles may accompany the papules. Commonly located in the abdomen, buttocks and thighs and usually **spares the periumbilical area,** face, palms and soles. When vesicles are present, PEP

may be *confused* with pemphigoid gestationis, a rare pregnancy-related blistering dermatosis. The *main differences* between these two skin disorders are that **PEP:**

- **Spares** the periumbilical area.
- **Does not** form bullae.
- **Does not** recur in subsequent pregnancies.

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical. Consider a skin biopsy for routine histology and DIF to differentiate PEP from pemphigoid gestationis.

- **Treatment**
  - **First line:** Topical steroids and oral antihistamines.
  - **Second line:** Systemic steroids for severe cases.

3. PEMPHIGOID GESTATIONIS

- **General:** Formerly known as **herpes gestationis;** has no association or relation to herpes infection. Pregnancy-related autoimmune bullous dermatosis with **IgG antibodies** against hemi-desmosomal protein **BP180** (same antibody as seen in bullous pemphigoid). Pemphigoid gestationis tends to **recur in subsequent pregnancy** or with OCP use.

- **Clinical:** Begins late in **second or third trimester** of pregnancy. Primary lesions are **erythematous papules and plaques** that progress to **tense vesicles and bullae.** Mainly affects the **abdomen** and **involves the periumbilical area.** Face, palms and soles are usually spared. Lesions are extremely pruritic and often affect patient functionality. The eruption tends to **resolve upon delivery** of the baby. Pemphigoid gestationis involves the **periumbilical area,** have **bullae formation** and **recur** in subsequent pregnancies (unlike PEP).

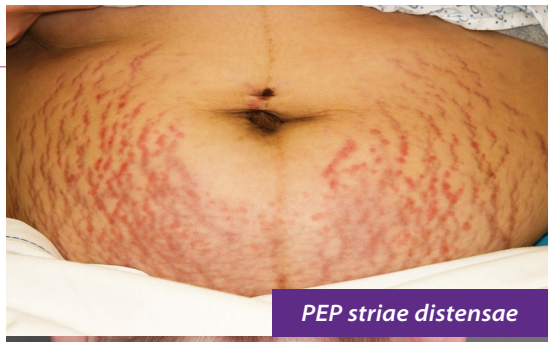
- **Diagnosis**
  - **Best initial and most accurate tests:** Clinical + skin biopsy showing subepidermal blisters with eosinophils and **DIF** showing a linear band of C3 at the DEJ. Serum IgG antibodies against BP180 are helpful when positive.

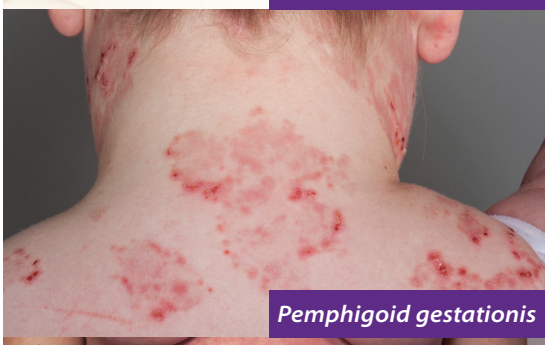
- **Treatment**
  - **First line:** Antihistamines and potent topical steroids for limited disease. Systemic corticosteroids for extensive skin involvement.
  - **Second line:** Plasmapheresis for recalcitrant or severe cases.

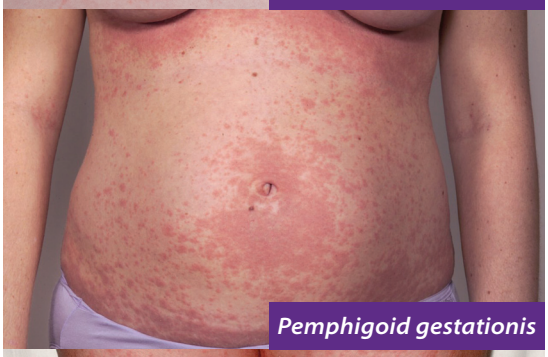
Section 3: Geriatric Skin Disorders

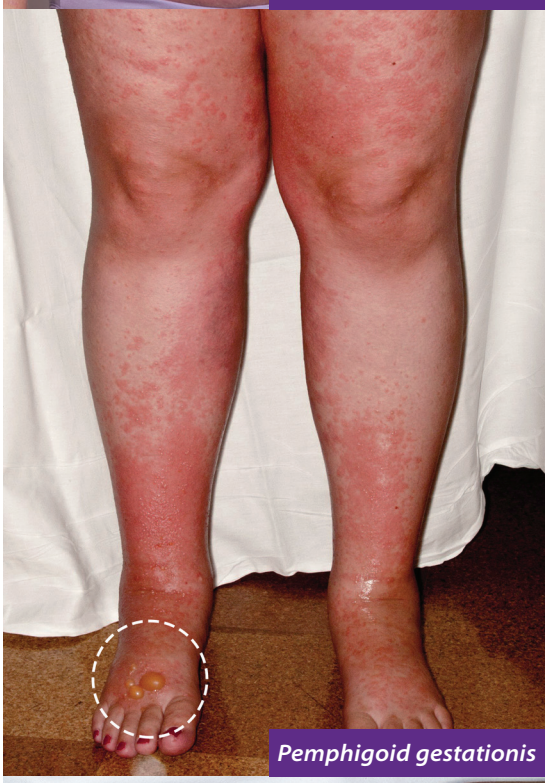
1. XEROSIS (ASTEATOSIS)

- **General:** As a normal process of **skin aging,** there is thinning of the epidermis, dermis and subcutaneous fat with *decreased* number of hair follicles and sweat glands. Xerosis **(dry skin)** may occur in the elderly due to **cutaneous loss of skin lipids** leading to excessive transepidermal

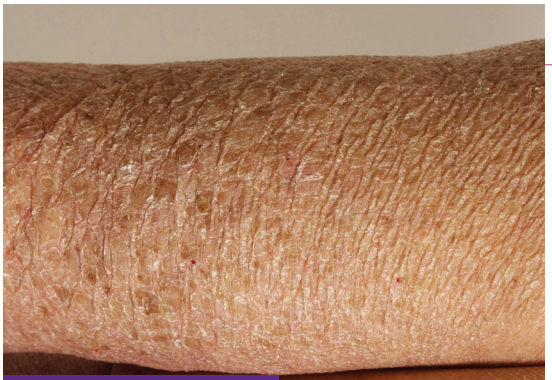

PEP striae distensae


Pemphigoid gestationis

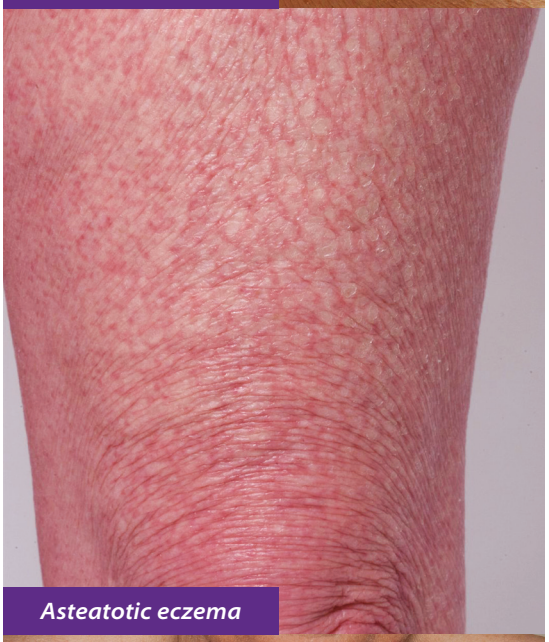

Pemphigoid gestationis


Pemphigoid gestationis

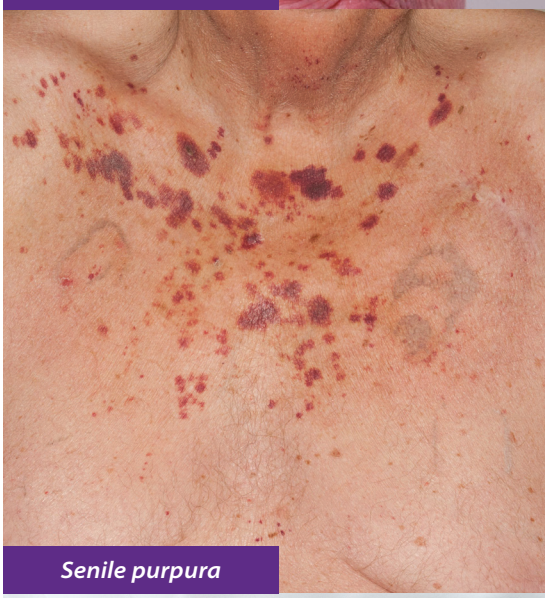

Xerosis



Xerosis



Asteatotic eczema



Senile purpura

Senile purpura

water loss (dehydrated skin). This is the **most common cause of pruritus** in the elderly. Common exacerbating factors are:
- **Cold weather** (eg, winter months, air conditioner).
- **Excessive bathing,** swimming and hydrotherapy.
- **Hypothyroidism** and excessive weight loss.
- Frequent contact with soaps, detergents and solvents.

- **Clinical:** Characterized by **cracked and polygonally fissured, scaly** and **pruritic skin.** The skin has a "crazy pavement" pattern and **accentuated skin markings.** Most commonly affects the lower legs but can occur anywhere.

- **Diagnosis**
  - **Best initial and most accurate test:** Clinical.

- **Treatment**
  - **First line:** Petrolatum-based emollients + lifestyle modifications (eg, limit baths, avoid cold).
  - **Second line:** Oral antihistamines or short-term topical steroids for pruritus.

- **USMLE Pearls: Asteatotic (xerotic) eczema:** Also known as **"eczema craquelé."** Dehydrated keratinocytes lose cellular volume and stretch the skin, creating fissures. When fissures rupture, they disrupt the skin integrity and lead to dermatitis. Clinically presents as **scaly erythematous and swollen, dry skin.** Excoriations and erosions secondary to intense scratching are commonly seen. *Diagnosis* is clinical. *Treatment* is with emollients + topical steroids.

2. SENILE PURPURA

- **General:** Also known as **solar purpura.** Elderly individuals normally lose collagen and elastic tissue as they age. Elastic tissue is also permanently damaged by extensive sunlight exposure (solar elastosis). **Perivascular loss of elastic tissue** results in **weak vessels** that are susceptible to **dermal blood leakage** after mild trauma.

- **Clinical:** Characterized by asymptomatic **petechiae, purpuric macules** and/or **ecchymotic** lesions in an elderly patient. Lesions are induced by any cause of **minor trauma.** Most commonly affect the **extensor surface** of the forearms, legs and hands. Lesions spontaneously resolve in 1 to 3 weeks and may leave a **brown area of hyperpigmentation.**

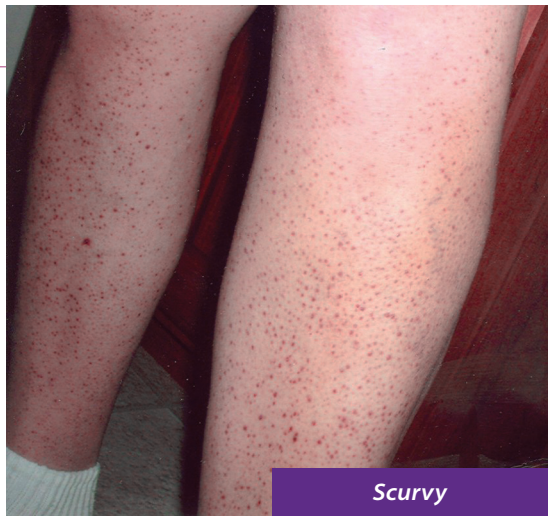
- **Diagnosis**
  - **Best initial test:** Clinical. Consider checking PT, PTT and platelet count to rule out underlying bleeding disorders.
  - **Most accurate test:** Skin biopsy showing thinned epidermis with extravasated RBCs and solar elastosis in dermis.

- **Treatment**
  - **First line:** Reassurance and avoidance of trauma.

- **USMLE Pearls: Scurvy:** Due to **vitamin C (ascorbic acid) deficiency.** Vitamin C is required for the triple helix collagen formation process. Defective collagen leads to weak vessels that are prone to bleeding.

Elderly patients who follow the **tea-and-toast diet** are prone to develop scurvy. The usual scenario is an elderly patient that lives alone or has recently lost his/her significant other. *Treatment* is with fruit and vegetables rich in vitamin C or with ascorbic acid supplements. The most common manifestations of scurvy are:

- **Bleeding gums** after minor trauma (eg, brushing teeth).
- **Perifollicular hemorrhage** with **corkscrew hairs.**
- **Intraarticular bleeding** (hemarthrosis) presenting with joint pain.
- **Poor wound healing** and **loss of teeth.**
- **Iron deficiency** (GI absorption requires vitamin C).



Scurvy

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Appendix I

BACTERIAL CLASSIFICATION

BACTERIAS

COCCI

Gram (+) Catalase (+)	Gram (+) Catalase (–)	Gram (–)
Staphylococcus sp. • S. aureus (Coagulase +) • S. epidermidis • S. saprophyticus	**Streptococcus sp.** • S. pneumoniae • S. viridans • S. pyogenes • S. agalactiae • E. faecalis • S. bovis	**Neisseria sp.** • N. meningitidis • N. gonorrhoeae **Moraxella sp.** **Eikenella sp.** **Kingella sp.** **Veillonella sp.**

GRAM (+) RODS

Spore Forming

Aerobic		Anaerobic	
Motile	**Non-Motile**	**Motile**	**Non-Motile**
Bacillus cereus	Bacillus anthracis	Clostridium tetani Clostridium botulinum Clostridium difficile	Clostridium perfringens

Non-Spore Forming

Aerobic		Anaerobic
Motile	**Non-Motile**	**Non-Motile**
Listeria monocytogenes	Corynebacterium diphtheriae Nocardia asteroides (acid-fast)	Actinomyces israelii Propionibacterium acnes

GRAM (–) RODS

Aerobic	Facultative Anaerobic		Anaerobic
Pseudomonas aeruginosa (oxidase +) Bordet*ella* pertussis Francis*ella* tularensis Legion*ella* pneumophila Bruc*ella* sp. • B. abortus • B. suis • B. melitensis Barton*ella* sp. • B. quintana • B. henselae Burkholderia cepacia	Vibrio sp. • V. cholerae • V. parahaemolyticus • V. vulnificus Haemophilus influenzae	Helicobacter pylori Campylobacter jejuni Gardnerella vaginalis Pasteurella multocida Brucella melitensis	Bacteroides fragilis Prevotella melaninogenica Fusobacterium sp.
	Enterobacteriacea		
	Lactose Fermenting	Non-Lactose Fermenting	
	Escherichia coli Klebsiella pneumonia	Shigella sp. Salmonella sp. Yersinia sp. • Y. pestis • Y. enterocolitica Proteus mirabilis	

Appendix I. Bacterial Classification *(continued)*

MISCELLANEOUS			
Spirochetes	**Acid-Fast**	**Intracellular**	**No Cell Wall**
Treponema pallidum **Borrelia sp.** • B. burgdorferi • B. recurrentis **Leptospira sp.**	**Mycobacterium sp.** • M. tuberculosis • M. avium-complex • M. leprae • M. marinum	**Chlamydiaceae** • C. psittaci • C. trachomatis • C. pneumoniae **Rickettsia sp.** **Coxiella burnetii** **Ehrlichia sp.**	**Mycoplasmas** • M. pneumoniae • U. urealyticum

Appendix II

VIRAL CLASSIFICATION

RNA VIRUSES

Double-Stranded	Single-Stranded				
Naked	Positive-Sense			Negative-Sense	Ambi- and Negative-Sense
	Enveloped		Naked	Enveloped	Enveloped
Icosahedral	Icosahedral	Helical	Icosahedral	Helical	Helical
Reovirus • Rotavirus • Colorado Tick Fever Virus	**Retrovirus** • HIV • HTLV 1 & 2 **Togavirus** • Rubella Virus • Chikungunya Virus • Western Equine Encephalitis • Eastern Equine Encephalitis **Flavivirus** • Hepatitis C Virus • Dengue Virus • Zika Virus • Yellow Fever Virus • West Nile Virus • St. Louis Encephalitis	**Coronavirus** • Coronaviruses • SARS-CoV • MERS-CoV	**Picornavirus** • Hepatitis A Virus • Coxsackie A & B • Rhinoviruses • Echoviruses • Enteroviruses • Polio Virus **Calicivirus** • Norwalk Virus **Hepevirus** • Hepatitis E Virus	**Orthomyxovirus** • Influenza A & B **Paramyxovirus** • Measles Virus • Mumps Virus • RSV • Parainfluenza Virus • Metapneumovirus **Rhabdovirus** • Rabies Virus • Vesicular Stomatitis **Filovirus** • Marburg Virus • Ebola Virus	**Arenavirus** • Lassa Fever Virus • Lymphocytic Choriomeningitis Virus **Bunyavirus** • California Encephalitis • La Crosse Virus • Hantavirus

DNA VIRUSES

Single-Stranded	Double-Stranded				
Naked	Enveloped			Naked	
Icosahedral	Icosahedral		Complex	Icosahedral	
	Linear	Circular		Linear	Circular
Parvovirus • Parvovirus B-19	**Herpesvirus** • Herpes Simplex Virus • Epstein-Barr Virus • Varicella-Zoster Virus • Cytomegalovirus • Human Herpesvirus-6 • Human Herpesvirus-7 • Human Herpesvirus-8	**Hepadnavirus** • Hepatitis B Virus	**Poxvirus** • Molluscum Contagiosum Virus • Variola Virus • Vaccinia Virus	**Adenovirus** • Adenoviruses	**Papillomavirus** • Human Papillomaviruses **Polyomavirus** • JC Virus • BK Virus

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IMAGE ACKNOWLEDGMENTS

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CHAPTER 5: CUTANEOUS MANIFESTATIONS OF INTERNAL DISEASES

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- **Image 5.20. Chronic pellagra:** Centers for Disease Control and Prevention (CDC), Public Health Image Library (PHIL). *Image*: Hands displaying alcoholic pellagra. *Attribution*: CDC.

CHAPTER 7: DISORDERS OF THE HAIR

- **Image 7.12. Menkes kinky hair syndrome:** *Image*: Menkes Kinky Hair Disease. *License*: CC-BY-SA 3.0 US. *Attribution:* Datta AK, Ghosh T, Nayak K, Ghosh M. *Source*: A case report. Cases J. 1, 1, 158. 2008. doi:10.1186/1757-1626-1-158. PMID 18801184.

CHAPTER 9: ECZEMA (DERMATITIS)

- **Image 9.2. Subacute eczema histology:** *Image*: Micrograph of mild spongiotic dermatitis-Very high mag. *License:* CC-BY-SA 3.0 US. *Attribution*: Nephron. *Source*: Own work.
- **Image 9.3. Chronic eczema histology:** *Image*: Micrograph of lichen simplex chronicus-High mag. *License:* CC-BY-SA 3.0 US. *Attribution*: Nephron. *Source*: Own work.

CHAPTER 12: MELANOCYTIC SKIN DISORDERS

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CHAPTER 13: PREMALIGNANT AND MALIGNANT SKIN DISORDERS

- **Image 13.31. Sezary cell:** *Image*: Pleomorphic abnormal T cells with convoluted nucleus seen in mycosis fungoides (leukemic phase). *License*: CC-BY-SA 3.0 US. *Attribution*: Paulo Henrique Orlandi Mourao. *Source*: Own work.

CHAPTER 14: SELECTED BACTERIAL INFECTIONS

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CHAPTER 15: SELECTED FUNGAL INFECTIONS

- **Image 15.16. *M. furfur*:** Centers for Disease Control and Prevention (CDC), Public Health Image Library (PHIL). *Image*: Fungus *Malassezia furfur. Attribution*: Dr. Lucille K. Georg.
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- **Image 15.38. *Mucor* sp.:** Centers for Disease Control and Prevention (CDC), Public Health Image Library (PHIL). *Image*: Patient ill with mucormycosis. *Attribution*: Dr. Lucille K. Georg.
- **Image 15.41. *C. neoformans*:** Centers for Disease Control and Prevention (CDC), Public Health Image Library (PHIL). *Image*: *Cryptococcus neoformans* using a light India ink staining preparation. *Attribution*: Dr. Leanor Haley

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- **Image 18.2. Syphilis LAD:** Centers for Disease Control and Prevention (CDC), Public Health Image Library (PHIL). *Image*: Syphilitic chancre accompanied by enlargement of the bilateral inguinal lymph nodes. *Attribution*: Susan Lindsley.
- **Image 18.6. Condyloma lata:** Centers for Disease Control and Prevention (CDC), Public Health Image Library (PHIL). *Image*: Secondary syphilitic lesions of vagina. *Attribution*: J. Pledger.
- **Image 18.7. Syphilitic gumma:** Centers for Disease Control and Prevention (CDC), Public Health Image Library (PHIL). *Image*: Gumma of nose due to tertiary syphilis. *Attribution*: J. Pledger.
- **Image 18.8. *T. pallidum*:** Centers for Disease Control and Prevention (CDC), Public Health Image Library (PHIL). *Image*: Numerous *Treponema pallidum* spirochetes by using the indirect fluorescent antibody (FA) staining. *Attribution*: Russell.
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- **Image 18.21. Chancroid LAD:** Centers for Disease Control and Prevention (CDC), Public Health Image Library (PHIL). *Image*: Inguinal bubo along with a penile ulceration due to a chancroid infection. *Attribution*: Renelle Woodall.
- **Image 18.22. H. ducreyi:** Centers for Disease Control and Prevention (CDC), Public Health Image Library (PHIL). *Image*: Numerous Gram-negative, *Haemophilus ducreyi* bacteria in a bacterial culture. *Attribution*: Dr. Mike Miller.
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