Skin Infections...  
More than a bug bite!

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Scabies

- Female mite burrows into the skin, lays eggs, and produces secretions that cause allergic reactions.
- Larvae, or newly hatched mites, travel to the skin surface, lying in shallow pockets where they will develop into adult mites.
- Mite is scratched off the skin, it can live in bedding up to 24 hours.
- May be up to a month before a newly infested person will notice the itching, especially in people with good hygiene and who bathe regularly.
Scabies-Symptoms

- Itching, especially at night
- Little red bumps becoming crusty or scaly
- Warmer sites on the skin such as skin folds where clothing is tight. These areas include between the fingers, on the elbows or wrists, buttocks or belt line, around the nipples, and on the penis
- Bacterial infection may occur secondarily
Norwegian Crusted Scabies

- Symptoms are far more severe than usual. Large areas of the body, including hands and feet, may be scaly and crusted.
- Crusts hide thousands of live mites and their eggs.
- Treatment difficult because medications may not be able to penetrate the thickened skin.
- Occurs mostly among the elderly, in some AIDS patients, or immunosuppressed.
- Extremely infectious.
Scabies-Microscopic Diagnosis

- Scabies prep
- Biopsy
  - Scabid reaction
  - Nodular dermatitis with eosinophils
  - Scybula
Treatment

- Permethrin cream 5% applied to the skin from head-to-toe at bedtime, left on for 8 to 14 hours and washed off the next morning
  - Second treatment one week later may be recommended for infants with scabies of the palms and soles, or if new lesions appear after treatment
- Lindane lotion 1%, overnight treatment, left on for 8-12 hours
  - Effective after 1 to 2 doses
  - Avoid a second treatment within a 7-day period
  - Contraindicated in infants, small children, pregnant or nursing women, or people with seizures or other neurological diseases
Leprosy

- Appears in an Egyptian papyrus inscribed about 1552-1350 B.C.
- Indian writings dated at 600 B.C. describe a disease that most experts agree was leprosy.
- Does not appear in the records of ancient Greece until the army of Alexander the Great came back from India in 326 B.C.
- In Rome, the first mention coincides with the return of Pompey’s troops from Asia Minor in 62 B.C.
Leprosy In The Bible

- Words leprous or leprosy appear 54 times
- Bible equated this sickness with sin.
  - Uzziah, King of Judah, wanted to burn incense in the temple of Jehovah, a ceremony reserved for priests. The priests opposed him, and Uzziah became angry. God struck him with leprosy.
- Jesus healed the blind and deaf but cleansed the lepers, implying a moral stigma
- The Church ordered regulations against lepers at the Council of Ancyra in 314 A.D., defining them as unclean persons, bodily and morally
  - People classified as lepers included heretics
Leprosy-Pathophysiology

- Armauer Hansen discovered *M. leprae* in Norway in 1873
  - First bacillus to be associated with human disease
  - Not initially thought to be an infectious disease
- Animal reservoirs
  - 9-banded armadillos
  - Chimpanzees
  - Mangabey monkeys
Leprosy-Pathophysiology

- The areas most commonly affected by leprosy are cooler part of body
  - Superficial peripheral nerves, skin, mucous membranes of the upper respiratory tract, anterior chamber of the eyes, and testes
  - Tissue damage is caused by:
    - Degree to which cell-mediated immunity is expressed
    - Extent of bacillary spread and multiplication
    - Appearance of tissue-damaging immunologic complications (ie, lepra reactions)
    - Development of nerve damage and its sequelae.

- *M. leprae* is an obligate intracellular acid-fast bacillus with a unique ability to enter nerves
Leprosy—Worldwide Problem

- Approximately 6,000 patients with leprosy live in the United States
  - 95% of these patients acquired their disease in developing countries
  - 200-300 cases are reported each year esp states with large immigrant populations
- Worldwide prevalence of leprosy is reported to be 5.5 million cases
  - Majority of affected persons live in the tropics and subtropics
  - 80% of the cases are found in 5 countries: India, Myanmar, Indonesia, Brazil, and Nigeria
Leprosy—Clinical

- Anesthesia of a skin lesion or in the distribution of a peripheral nerve, thickened nerves, and typical skin lesions.
- Prodromal symptoms are generally slight but 90% of patients present with numbness first, sometimes years before the skin lesions appear.
- Neuropathy
  - Temperature is the first sensation lost
  - Next lost are light touch, pain, and finally deep pressure
  - Especially apparent in the hands and feet.
- Hypopigmented macule is often the first cutaneous lesion
- From this stage, most lesions evolve into the lepromatous, tuberculoid or borderline types
Indeterminate leprosy (IL)

- Early form causes one to a few hypopigmented, or sometimes erythematous, macules
- Sensory loss is unusual
- Most cases evolve from this state into one of the other forms, depending on the patient's immunity to the disease
  - Strong immunity may become cured of disease
  - Occasional persistence in this indeterminate form
  - Weaker immunity may progresses to one of the other forms
Tuberculoid leprosy (TT)

- Skin lesions are few in number
  - Usually one erythematous large plaque with well-defined borders that are elevated and slope down into an atrophic center
  - Lesions can become arciform or annular, and they can be found on the face, limbs or elsewhere, but spare intertriginous areas and the scalp
  - May involve a large asymmetric hypopigmented macule
- Both types of lesions are anesthetic and involve alopecia
- Neural involvement is common in TT and leads to tender, thickened nerves with subsequent loss of function
  - Great auricular nerve and superficial peroneal nerves are often prominent
- Spontaneous resolution can occur in a few years, leaving pigmentary disturbances or scars
- Progression can also occur, leading to borderline-type leprosy
- Rarely untreated patients develop lepromatous leprosy
Borderline tuberculoid leprosy (BT)

- Lesions in this form are similar to those in the tuberculoid form, but they are smaller and more numerous
  - Nerves are less enlarged, and less alopecia is present
- Disease can remain in this stage, convert back to the tuberculoid form, or progress
Borderline borderline leprosy (BB)

- Cutaneous lesions consist of numerous, red, irregularly shaped plaques that are less well defined than those in the tuberculoid type
  - Distribution may mimic those of the lepromatous type, but more asymmetric
  - Anesthesia is only moderate
  - Regional adenopathy may be present
- Disease may remain in this stage, improve or worsen
Borderline lepromatous leprosy (BL)

- Lesions are numerous and consist of macules, papules, plaques, and nodules
  - Annular punched-out-appearing lesions that look like inverted saucers are common
  - Anesthesia is often absent
- Disease may remain in this stage, improve, or regress
Lepromatous leprosy (LL)

- Early cutaneous lesions consist mainly of pale macules. Later, infiltrations are present, with numerous bacilli
  - Macular lesions are small, diffuse, and symmetric
  - Skin texture does not change, and little or no loss of sensation occurs
  - Nerves are not thickened, and sweating is normal
  - Lateral eyebrows are affected by alopecia (ie, madarosis), which spreads to the eyelashes and then the trunk. Scalp hair remains intact.
- Can be diffuse, nodules (called lepromas), or plaques
  - Diffuse type results in the appearance of a leonine facies
  - Neuritic lesions are symmetric and slow to develop
- Systemic
  - Eye involvement occurs, causing pain, photophobia, decreased visual acuity, glaucoma, and blindness
  - Testicular atrophy results in sterility and gynecomastia
  - Lymphadenopathy and hepatomegaly
  - Stridor and hoarseness are a result of laryngeal involvement
  - Nasal infiltration can cause a saddle-nose deformity
  - Aseptic necrosis and osteomyelitis can occur with repeated trauma after joint invasion
  - Brawny edema of the lower extremities is a late finding
- LL cannot convert back to the less severe borderline or tuberculoid types of disease
Leprosy Histopathology

- **TT**
  - Well-developed epithelioid granulomas are observed in the papillary dermis, often around neurovascular structures.
  - Granulomas are surrounded by lymphocytes, which extend into the epidermis. Langhans giant cells are common.
  - Dermal nerves are destroyed or swollen because of the granulomas.
  - Acid-fast bacilli are not observed.

- **LL**
  - Diffuse infiltrate of foamy macrophages is present in the dermis below a subepidermal zone of uninvolved papillary dermis.
  - Enormous number of acid-fast bacilli develop within the foamy macrophages, singly or in clumps called globi.
  - Lymphocytes are scant, and giant cells are typically absent.
  - Numerous bacilli invade the nerves, but these are fairly well preserved with little infiltrate.
  - Nodular, or dermatofibroma-like lesions in LL, referred to as histoid leprosy, result in a diffuse fascicular arrangement of spindled cells in the dermis admixed with foamy macrophages that contain numerous bacilli (Mycobacterium spindle cell tumor).
Leprosy Histopathology

- **BT form**
  - Well-developed epithelioid cell granulomas are apparent and diffuse
  - Bacilli are absent or rare, but they can be found in dermal nerves as well as in the arrector pilorum
  - Nerves are moderately swollen

- **BB form**
  - Diffuse epithelioid granulomas that lack giant cells are observed in the dermis below the subepidermal grenz zone
  - Nerves are slightly swollen, and acid-fast bacilli are present in moderate numbers
Leprosy Histopathology

- **BL form**
  - Smaller granulomas with some foamy changes and numerous lymphocytes are observed
  - Nerves often have an onion-skin appearance due to invasion of the perineurium
  - Few epithelioid cells may be observed

- **IL form**
  - Findings are nonspecific
  - Histiocytes and lymphocytes are scattered, with some concentration around dermal appendages and nerves
  - An acid-fast bacillus can be observed in a nerve bundle
  - Number of dermal mast cells may be increased
Mycobacterial spindle cell pseudotumor
Erythema nodosum leprosum
Syphilis

- The physician who knows syphilis knows medicine.

-----Sir William Osler
Syphilis in the United States

- 1940-100,000 cases (pre-antibiotic era)
- 1956-10,000 cases
- 1990-45,000 cases
  - AIDS
  - Intravenous (IV) drug and crack cocaine abuse
  - Prostitution
- 1995-16,500 cases
Three Stages

- **Primary syphilis** develops at the site of transmission
  - Incubation period of 10-90 days (mean 21-28 days)
  - Heals spontaneously in 3-7 weeks
- **Secondary syphilis**
  - About 4-10 weeks after the appearance of the primary lesion
  - Most common systemic manifestations include malaise, fever, myalgias, and arthralgias with a generalized body rash and lymphadenopathy
  - Symptomatic secondary syphilis usually resolves without treatment
- **Early latent syphilis**
  - Encompasses the first 1-2 years of the disease and is marked by occasional relapses of active secondary lesions
- **Late latent syphilis**
  - Asymptomatic and generally noninfectious
  - About one third of untreated patients develop tertiary syphilis
  - Latency period lasting years to decades and manifests as gummatous or cardiovascular syphilis or neurosyphilis
Syphilis Laboratory Evaluation

- Darkfield microscopy, immunofluorescent staining, or serologic testing is necessary for diagnosis of syphilis
  - Oral lesions should be avoided because of the difficulty in distinguishing *T. pallidum* morphologically from *Treponema macrodentium* and *Treponema microdentium*.
  - Positive darkfield examination is the only means of making an absolute diagnosis of syphilis.
- Negative darkfield examination does not rule out the diagnosis.
- Nontreponemal tests, VDRL and rapid plasma reagent (RPR), have sensitivities approaching 80% in patients with symptomatic primary syphilis and virtually 100% in patients with secondary syphilis.
  - Positive VDRL should be quantified and titers followed at regular intervals after treatment.
  - Most patients have nonreactive nontreponemal tests within several years after successful treatment for syphilis, but a significant number have persistently positive tests and are said to be serofast.
  - Specificities of the VDRL and RPR tests are only fair.
  - False-positive results may result after immunizations, in acute viral or bacterial infection, or during pregnancy.
- Patients with a reactive VDRL or RPR should have the result confirmed by specific treponemal testing. These tests include the fluorescent treponemal antibody absorption (FTA-ABS) and the microhemagglutination assay for *T. pallidum* (MHA-TP).
Secondary Syphilis Histopathology

- Psoriasiform dermatitis with superficial and deep mixed infiltrate with plasma cells
  - Plasma cells may be absent 10-15% of cases
- Epidermis may have collections of neutrophils, parakeratosis, and spongiosis
- Rarely granulomatous, neutrophilic dermatosis, or pseudolymphoma
Secondary Syphilis-Histopathology

- Warthin-Starry stains or other silver stains are usually positive for the organisms
- Silver stains may be negative in tertiary disease
Dermatophytosis

- Wet mount potassium hydroxide preparation (KOH prep)
  - Skin scrapings are placed on a slide and KOH is added with gentle heating
  - Stain such as lactophenol blue may be added and the slide is examined under the microscope
  - Dermatophytes often take weeks to culture
- Numerous histopathologic reaction patterns on skin biopsy
  - One classic pattern is the presence of neutrophils within the stratum corneum
  - Other common patterns include compact orthokeratosis and a layer of compact orthokeratosis underlying normal orthokeratosis (sandwich sign)
  - Dermatophyte infections of the hair are termed **endothrix** if it invades the hair shaft and **exothrix** if it remains on the surface
- Using a ultraviolet Wood's lamp, endothrix infections will not fluoresce as opposed to exothrix infections
Dermatophyte Histopathology


- Retrospective case-control study on 303 cases of spongiotic or psoriasiform dermatitides over a 35-month period
  - Hematoxylin and eosin (H&E) and PAS-D stains were utilized to identify intraepidermal neutrophils and fungi
  - Sensitivity and specificity for diagnosing dermatophyte infection based upon neutrophils within the stratum corneum were 62 and 59%, respectively
    - Positive and negative predictive values in our population were 4 and 98%, respectively

- CONCLUSION
  - Histologic feature of neutrophils within the stratum corneum is neither sensitive nor specific in the diagnosis of dermatophytosis
Leishmaniasis-Background

- Designs on pre-Columbian pottery and the existence of thousand-year-old skulls with evidence of leishmaniasis
- Restricted to tropical and temperate regions (natural habitat of the sandfly)
- Endemic in 88 countries (16 developed countries, 72 developing countries) on 5 continents of Africa, Asia, Europe, North America, and South America
- Widespread migration from rural to urban areas and movement of susceptible populations into endemic areas
- Co-infection with HIV has lead to the spread of leishmaniasis, typically a rural disease, into urban areas
- Although cutaneous leishmaniasis exists in many countries where \( L \) \textit{donovani} is prevalent, the 2 parasites are not present in the same regions
  - In India, visceral leishmaniasis is confined to the eastern parts, while cutaneous leishmaniasis is limited to the dry western parts
Sandfly

- Vector Sandflies (Phlebotomus species)
- Leishmania are intracellular parasites that infect the mononuclear phagocytes
**Clinical Variants**

- **Visceral**
  - *Leishmania donovani* causing visceral leishmaniasis (kala azar)
  - Worldwide but predominantly is encountered in India, South America, Central Asia, Middle East, and Africa

- **Cutaneous**
  - *Leishmania tropica* and *Leishmania brasiliensis*
  - *L. tropica* is seen mainly along the shores of the Mediterranean, through the Middle East, central Africa, and parts of India
  - Cutaneous leishmaniasis caused by *L. brasiliensis* is confined mainly to Central America and South America
Clinical Variants

- **Localized cutaneous leishmaniasis (LCL)**
  - Crusted papules or ulcers occur several weeks to months (and rarely years) after sandfly bite inoculation on exposed skin
  - Lesions may be associated with sporotrichotic spread and usually heal spontaneously

- **Diffuse cutaneous leishmaniasis (DCL)**
  - Analogous to lepromatous leprosy, individuals with DCL fail to mount a cell-mediated immune response to the *Leishmania* parasite
  - Develop multiple widespread cutaneous papules and nodules and are anergic to leishmanin skin testing

- **Recidivans cutaneous leishmaniasis (RCL)**
  - Uncommon clinical variant of leishmaniasis
  - Recurrence of lesions at the site of apparently healed disease years after the original infection
  - Occur on the face, and RCL presents as an enlarging papule, plaque, or coalescence of papules that heals with central scarring
  - May cause significant facial destruction similar to the lupus vulgaris variant of cutaneous tuberculosis
Clinical Variants

- Post-kala azar dermal leishmaniasis (PKADL)
  - Endemic to India and the Sudan
  - Develops months to years after the patient's recovery from visceral leishmaniasis
  - Range from hypopigmented macules to erythematous papules and from nodules to plaques, reflecting immune response of the individual

- Mucocutaneous leishmaniasis (MCL)
  - Predominantly a New World disease
  - May not manifest clinically until years after localized cutaneous disease apparently has healed
  - May migrate to the upper respiratory tract where relentless destruction of the oropharynx and nose ensues, may lead to death

- Visceral leishmaniasis (VL; kala azar)
  - *Leishmania* parasites localize to the reticuloendothelial system
  - Potentially fatal widespread systemic disease
Histopathology

- Parasitized macrophages widely disseminated
  - Spleen, liver, and bone marrow
  - Splenomegaly with vascular spaces dilated and engorged with blood, and the reticular cells of Billroth are increased markedly and packed with amastigote forms of the parasite
  - Liver Kupffer cells are increased in size and number and infected with amastigote forms of *Leishmania*
  - Bone marrow is hyperplastic with parasitized macrophages replacing the normal hemopoietic tissue
Histopathology-Skin

- **LCL**
  - Irregular acanthosis, with or without epidermal ulceration, and dense dermal infiltrate of mixed inflammatory cells, particularly plasma cells, lymphocytes, and histiocytes.
  - Early, organisms may be numerous and found readily within the cytoplasm of macrophages.
  - With time infiltrate is replaced by noncaseating granulomata in which few or no organisms can be seen.
  - Ulcerated lesions commonly may become infected secondarily.
  - Biopsy specimens from old (>6 mo), partially treated, or low-burden infections frequently are nondiagnostic.

- **DCL**
  - Individuals with poor cellular immunity to *Leishmania* parasites.
  - Dermis contains sheets of macrophages containing great numbers of amastigotes, with few lymphocytes or plasma cells.
Histiopathology Skin

- **PKADL**
  - Variable histology that is determined by the degree of host immunity and the parasite load
  - Granulomatous histology is seen with low numbers of organisms, while diffuse histiocytic or xanthomatous infiltrates may be seen with numerous organisms

- **RCL**
  - Usually is difficult to confirm because of the rarity of organisms and its histologic similarity to lupus vulgaris
Chromoblastomycosis

- Trauma to the skin with long interval, occasionally several years leading to small, raised, erythematous, asymptomatic papule
  - Splinters may be present
  - Lower extremities, especially the feet, hands, the arms, and the buttocks
- Over time leads to nodule or plaque
- Rarely lymphatic and hematogenous dissemination may occur,
- On the surface of both types of clinical variants, numerous black dots may be observed where the causative organisms are preferentially found. Hemopurulent material covering small ulcerations is commonly observed.
- Secondary infection with bacteria is common
Fungal Causes

- Four different genera:
  - *F pedrosoi*, *P verrucosa*, *C carrionii*, and *F compacta*
  - Different species of *Exophiala* have also been reported.
  - *C. carrionii* is the most common agent of chromoblastomycosis in that country
Histopathology

- Pseudoepitheliomatous hyperplasia of the epidermis with a diffuse, lymphomononuclear inflammatory infiltrate in the dermis
- Microabscesses, granulomas, granulomatous reactions
- Giant cells contain brown-colored, thick-walled fungal cells
  - Muriform fungal cells may be single, 2-celled, or multiple-celled
  - Copper pennies, Medlar bodies, sclerotic bodies
- Transepidermal elimination of the fungal cells is the histologic counterpart of the black dots clinically evident
Eczema Herpeticum

- Also known as Kaposi varicelliform eruption
- Caused by HSV-1
- Commonly develops in patients with atopic dermatitis, burns, or other inflammatory skin conditions
- Children are most commonly affected
Herpetic Whitlow

- Vesicular outbreaks on the hands and the digits, was most commonly due to infection with HSV-1
- Usually occurs in children who sucked their thumbs and, prior to the widespread use of gloves in health care workers
- Occurrence of herpes whitlow due to HSV-2 is increasingly recognized, probably due to digital-genital contact
During the acute phase, significant inflammation of the skin, dorsal root ganglia, and peripheral nerves is present.

Evidence for early denervation of skin tissue, hemorrhagic necrosis, and neuronal loss in dorsal root ganglia is present.

Inflammatory changes may persist for months and lead to scarring.
Congenital Cytomegalovirus Infection

- Presumed to be transplacental
  - May be transmitted perinatally, both by aspiration of cervicovaginal secretions in the birth canal and by breastfeeding
  - More than 50% of infants fed with breast milk that contains infectious virus become infected with CMV
- Infants who are not infected congenitally or perinatally with CMV are at high risk to acquire infection in day care centers
  - Prevalence of CMV infection in day care center attendants, particularly children younger than 2 years, approximates 80%
- May be transmitted via saliva, urine, and fomites
  - Children, in turn, may transmit infection to their parents
  - Major role in the epidemiology of many CMV infections in young parents
Clinical Variants

- Most common and important of all congenital infections
  - 30,000-40,000 infants are born with congenital CMV infection annually in the United States
  - Likelihood of congenital infection and the extent of disease in the newborn depend on maternal immune status
  - Average rate of transmission to the fetus is 40%
  - Most of these infants have clinical disease at birth
  - In the setting of recurrent maternal infection, risk of transmission to the fetus is lower, ranging from 0.5-1.5%
    - Most infants appear normal at birth thus may be classified as symptomatic or asymptomatic in nature
Clinical Variants

- Cytomegalic inclusion disease
  - Approximately 10% of congenitally infected infants have clinical evidence of disease at birth
  - Most severe form of congenital CMV infection
  - Almost always occurs in women who have primary CMV infection during pregnancy
  - Characterized by intrauterine growth retardation, hepatosplenomegaly, hematological abnormalities (particularly thrombocytopenia), and a variety of cutaneous manifestations, including petechiae and purpura (i.e., blueberry muffin baby)
- Most significant manifestations of CID involve CNS
  - Microcephaly, ventriculomegaly, cerebral atrophy, chorioretinitis, and sensorineural hearing loss are the most common neurological consequences of CID.
  - Intracerebral calcifications typically demonstrate a periventricular distribution
    - Predictive of cognitive and audiologic deficits in later life and predicts a poor neurodevelopmental prognosis.
  - Overall, 90% of infants who survive symptomatic CID have significant long-term neurological and neurodevelopmental sequelae
Clinical Variants

- Asymptomatic congenital CMV
  - Most infants with congenital CMV infection are born to women who have preexisting immunity to CMV
  - Clinically normal at birth but may have subtle growth retardation compared to uninfected infants and at risk for neurodevelopmental sequelae
  - Sensorineural hearing loss is major consequence
    - Approximately 15-20% of these infants will have unilateral or bilateral deafness
    - Routine newborn audiologic screening may not detect cases of CMV-associated hearing loss because this deficit may develop months or even years after delivery
Differential Diagnosis

- TORCH agents
- Congenital toxoplasmosis
  - Intracranial calcifications observed in congenital toxoplasmosis tend to be scattered diffusely throughout the brain and not in the classic periventricular distribution of CMV
- Other congenital infections to be considered include lymphocytic choriomeningitis virus (LCMV) infection, HSV infection, syphilis, enteroviral disease, HIV infection, and rubella