PSORIASIS
Epidemiology

• Over 8 million Americans currently have psoriasis

• Psoriasis often starts between 15 and 25, but can develop at any age

• About 30% of psoriasis patients develop psoriatic arthritis, which affects the joints, tendons and ligaments

• Psoriasis has several inflammatory comorbidities such as diabetes, heart disease, and depression¹
Plaque psoriasis

Plaque psoriasis is the most common form of the disease and appears as raised, red patches covered with a silvery white buildup of dead skin cells. Most often show up on the scalp, knees, elbows and lower back. Often itchy and painful, and they can crack and bleed.
GUTTATE

Guttate psoriasis is a form of psoriasis that appears as small, dot-like lesions.

This is the second-most common type of psoriasis, after plaque psoriasis.

Frequent in childhood or young adulthood.

Most often preceded by a strep infection 3 weeks prior.

About 10 percent of people who get psoriasis develop guttate psoriasis.
20%-30% of patients with psoriasis have inverse (intertriginous) involvement affecting inframammary, axillary, inguinal, intergluteal, or other skin folds.

Inverse psoriasis shows up as pink to red well demarcated lesions.

Comorbidities such as obesity, diabetes mellitus, and/or hypertension often occur in patients with inverse psoriasis.
Pustular Psoriasis

White to yellowish pustules surrounded by red skin.

The pus consists of white blood cells. It is not an infection, nor is it contagious.

Pustular psoriasis can occur on any part of the body, but occurs most often on the hands or feet.

Very common with heavy smokers.
Erythrodermic psoriasis

Severe form of psoriasis with widespread redness over 75% of the body.

May be associated with severe itching and pain.

Occasionally, desquamation in sheets.

It is rare, occurring in 1-2% of Psoriatics.

Unstable cases require cyclosporine or infliximab as first-line therapy.
Key Inflammatory Mediators

**Keratinocytes and inflammatory dendritic cells and T cells are responsible for psoriatic skin.**

**TH1 and TH17 (T-helper cells 1 and 17) responses are triggered by interleukins 12 (IL-12) and IL-23 producing activated dendritic cells.**

The activated Dendritic Cells are pivotal for keratinocyte activation and production of inflammatory molecules including Tumor Necrosis Factor Alpha (TNF-α).
ANCIENT THERAPIES
Paulus Aegineta discussed the use of a liquid pitch for the treatment of leprosy and "psora" in 700 AD in book 4 of his medical encyclopaedia.
The Goeckerman regimen, first published in 1925 for the treatment of generalized psoriasis, consists of exposure to ultraviolet B (UVB) light and application of crude coal tar for 4 hours under Saran wrap occlusion.

In a published study conducted at UCSF, 100% of patients on Goeckerman therapy achieved 75% reduction of psoriasis by 3 months.

Concern for Skin cancer with UV and the multiple carcinogens in Tar was refuted by two 25-year follow-up studies at the Mayo Clinic showing no significant increase in cancer incidences in psoriasis and eczema patients treated with Goeckerman compared to the general population.
Goeckerman Therapy

Goeckerman therapy is still in use today at Mayo Clinic and UCSF. It remains as an extremely effective option, while providing a long duration of remission.
THERAPIES

LATE 20TH CENTURY
**Systemic Steroids**

Pros:

- Rapid acting, inexpensive.

Cons:

- Cannot be administered orally in this subgroup. Short duration, potential to cause a rebound of disease with Generalized Pustular Psoriasis upon withdrawal.
- Injection site atrophy.
- Steroid side effects that worsen comorbidities: Diabetes, HTN, etc.
ACITRETIN

Pros: Oral or topical administration. Relatively safe for healthy male and postmenopausal patients.

First line for Generalized Pustular Psoriasis

Cons: CANNOT be used in women of childbearing potential. (Up to 5 years of teratogenicity in oral form)

Slow to act. (Months)

Systemic side effects: Liver toxicity, hair thinning, dry skin.
Methotrexate

- Pros: INEXPENSIVE, easily administered oral or IM weekly dosing
- Cons:
  - Vomiting, nausea, loss of appetite, mouth sores, redness and swelling inside the mouth, and fatigue are common side effects.
- Serious Side effects
- Fetal Toxicity
- Pneumonitis (potentially fatal)
- Liver toxicity and eventual fatty liver changes
- Renal damage
**Pros:** fast acting weeks to months. Great for acute flares.

**Cons:** Not generally safe during pregnancy.

Requires extensive lab monitoring every 2wks x 3-4 mos.

May cause Hypertension and severe renal damage.

Significantly increased risk for malignancy.
Immune Modulators

The role of Immune Modulation is being explored in medicine.

Today's modern therapies are targeting the immune responses that are directly and indirectly involved in the psoriatic cascade.

These are medications that can be delivered orally as small molecule Phosphodiesterase Inhibitors or parenterally as large molecule proteins as in the more recent Biologic Therapies.

These medications often have a more narrow side effect profile and have shown increased efficacy over the traditional therapies of 15 years ago.
Known Immune response in Psoriasis
Comorbid Conditions
Depression

- Should be considered the #1 Comorbidity of Psoriasis.

- In the recent study by Roger Ho MD, at New York University School of Medicine/Langone Medical Center, 16.5% of Psoriasis patients showed signs of major depression.

- Psoriasis Patients had twice the odds of major depression after controlling for variables,! (OR, 2.09 [95% CI, 1.41-3.11], P<.001)
Diabetes

IL23R and IL23A has an influence not only on the risk for psoriasis, but also on disease severity and type 2 diabetes mellitus associated with diabetes independent of sex, age, smoking, and body mass index (BMI) (OR 1.53, 1.03-2.27)
HYPERTENSION

- **Psoriasis is related to high blood pressure.**
- **Positive correlation between the severity of psoriasis and high blood pressure**
Hyperlipidemia

- **Total Cholesterol**, **LDL** and **HDL** may be very similar to the non psoriasis population.

- **Lipoprotein (a)**: A low-density lipoprotein (LDL)-like structure that is synthesized in the liver is elevated in Psoriasis.

- Elevation of Lp (a) levels >15 mg/dl increases the risk of atherosclerotic vascular disease.

- Lp (a) levels are genetically determined at a rate >90% and are not affected by dietary lipid or lifestyle changes.

- Measurement of the level of Lp(a) in psoriasis may be appropriate in the psoriatic population.
Myocardial Infarction

- **Significantly increased risk for MI in severe psoriasis aged <50; HR 1.74; 1.11-2.72).**

- **Elevated risk in patients with severe psoriasis with Psoriatic Arthritis aged <50 (HR 1.52; 1.03-2.25).**
Metabolic Syndrome

- Metabolic syndrome including abdominal obesity, hypertension, atherogenic dyslipidemia, type 2 diabetes, insulin resistance, and nonalcoholic fatty liver disease.
- The prevalence in psoriasis ranges from 20% to 50%, with a 2X risk in psoriatic vs non-psoriatic population.
- More common in severe psoriasis than in mild Psoriasis
Sleep Apnea

Psoriasis was associated with increased risk of sleep apnea.

Sleep apnea was associated with increased risk of psoriasis.
Reduced Life Expectancy

Psoriasis patients have a substantial comorbidity burden that can reduce life expectancy by 10 years or more.

On average, patients whose psoriasis was diagnosed before age 25 did not live to age 60.

In contrast, a psoriasis diagnosis at age 25 or afterward was associated with an average life expectancy greater than 70.
ATOPIC DERMATITIS
EPIDEMIOLOGY

Atopic Dermatitis (AD) affects up to 20% of children and up to 3% of adults.

Its prevalence is increasing in developing countries.

90% get AD before their 5th birthday and it precedes other allergic diseases such as asthma or allergic rhinitis.
**Atopic Dermatitis**

AD is a chronic, lifelong disease with a multi-dimensional patient burden

- **Pruritus is a defining feature of AD**
  - Its downstream effects are responsible for much of patients' disease burden
- **Sleep disturbance in AD patients worsens with greater severity of itch**
Atopic Dermatitis

Nocturnal itch leads to intense scratching.

This causes skin damage and poor sleep quality.

Early research attempting to understand the pruritus of AD focused on the role of histamine.

Unfortunately, clinical studies revealed that histamine receptor (H1, H2) blockade does not lead to significant improvement in itch or inflammation in AD.
**Atopic Dermatitis**

- **Family members have AD, asthma, or hay fever**: A family history of these remains conditions is the biggest risk factor. People often have asthma and hay fever for life, whereas AD may have remission.

- **Where child lives**: Living in a developed country, a city, or a cold climate increases risk.

- **Jamaican children raised in London are twice as likely to develop AD as those raised in Jamaica.**
Atopic Dermatitis

- **Gender:** Females are slightly more likely than males to get AD.

- **Mother’s age when child born:** When the mother gives birth to the child later in her childbearing years, a child is more likely to get AD.

- **Social class:** AD seems more common in higher social classes.
Key Inflammatory Mediators

- TH2 immune mediators
- IL-4 and IL-13 play a key role in AD pathogenesis.
- IL-4 decreases expression of multiple genes in the epidermal cell differentiation that regulates skin barrier function.
- This leads to increased skin damage with scratching.
- Increased damage decreased barrier protection.
Atopic Dermatitis

IL-4 and IL-13 exposed keratinocytes exhibited significantly reduced structural gene expression.

Structural proteins are reduced in lesional and nonlesional AD skin contributing to the defective skin barrier.

A compromised barrier allows penetration of bacteria and allergens in the skin, leading to infections and allergen sensitization.
The Atopic March
Atopic March

AD has been described as an allergic skin disease in the past.

It is no longer believed that multiple allergic reactions leads to the initiation of AD.

It is now proposed that allergy is rather a consequence of AD.

Altered skin barrier allows exposure to multiple allergens at a higher concentration.

This results in more allergy formation over time for the atopic patient.

As the entire system, including nasal mucosa becomes primed.
Do we expect multiple allergies at this age?
Compromised skin barrier?
Primed Immune Responses
PMH = LONG LIST OF ALLERGENS
Traditional Topical Therapies

Topical Soothing Agents

Barrier Creams

Topical Steroids

Topical Calcineurin Inhibitors

Topical PDE4 Inhibitors
Traditional Systemic Therapies

Antihistamines are mainly sedating agents to reduce nocturnal scratching.

Systemic steroids

Systemic immunosuppressants such as Cyclosporine, azathioprine, interferon-gamma, methotrexate, and Mycophenolate mofetil have been used, but are not FDA approved for Atopic Dermatitis.

These require extensive lab monitoring for side effects and have potential for teratogenicity.
What about the immune dysfunction?

Atopic Dermatitis is a systemic disease with a skin manifestation.

Topical therapy can help maintain or augment skin barrier function.

Topical barriers help slow the atopic march through the skin exposure.

Topical steroids and TCIs can help reduce pruritus and skin inflammation.

The system still remains primed for exposure through other immune surveillance measures.
**BILOGICS**

**Dupilumab**

The first FDA approved systemic treatment for Atopic Dermatitis.

- **Dupilumab is approved in the US for the treatment of adults with inadequately controlled moderate-to-severe AD who are candidates for systemic therapy, and in Asthma.**

- **Treatment with dupilumab significantly improves itch as well as sleep disturbance.**
MOA

• Dupilumab is a potent blocker of IL-4 and IL-13 pathways

• IL-4 and IL-13 are specific type 2 (Th2) cytokines that mediate many features of AD as well as asthma and other atopic and allergic diseases

• AD is more Th2-driven in pediatric patients than in adults.
COMORBID CONDITIONS
Asthma

Prevalence of allergic rhinitis and asthma in 2,270 children with physician-confirmed AD and found that by 3 years of age, nearly 66% of the subjects reported to have allergic rhinitis, asthma, or both.
Allergy

- **Allergic Rhinitis**
- **Eosinophilic Esophagitis** (The link between allergies and EE is threefold) Allergen driven
- **Increased TH2 cytokines at the site of inflammation in AD, AR, and EE**
Skin Infections

Decreased barrier function allows increased:

Staph. aureus

Eczema herpeticum (staphylococcal \( \alpha \)-toxin, may play a role in enhancing herpes simplex virus skin infections)

Eczema vaccinatum

Eczema coxsackium
**Atopic Keratoconjunctivitis**

- A chronic inflammatory disease of eye that affects patients with atopic dermatitis.
- AKC was first described in 1952 by Hogan, who described five cases of atopic eczema associated with bilateral keratoconjunctivitis. Peak incidence is between 30-50 years old. It is characterized by bilateral, non-infectious inflammation of the conjunctiva.
- It is estimated that 25-40% of patients with atopic dermatitis suffer from AKC.
Comorbidities Commonly shared in Systemic Inflammatory Diseases

Depression
Diabetes
Hypertension
Sleep Apnea
Obesity