Acne Vulgaris:

Pathophysiology, diagnosis, and treatment of a common dermatologic condition

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Learning Objectives

- Define acne and describe its epidemiology
- Explain the pathophysiology of acne
- Describe the clinical presentation of acne
- Explain how acne is diagnosed
- Discuss the various treatment options for acne, both pharmacologic and non-pharmacologic

What is Acne?

- Acne vulgaris is a chronic, inflammatory disease of the pilosebaceous units of the skin.
  - Pilosebaceous unit
    = hair + hair follicle + sebaceous gland
  - Sebaceous gland
    - Found in hair-covered areas
    - Functions to secrete sebum, an oily substance that acts to protect and waterproof skin and hair, and keep it from being dry, brittle, and cracked

Epidemiology

- Age
  - Acne can present at any point during a person's life
  - Adolescent acne usually presents prior to the onset of puberty
- Sex
  - During adolescence, acne is more common in males than females
  - During adulthood, acne is more common in females than males

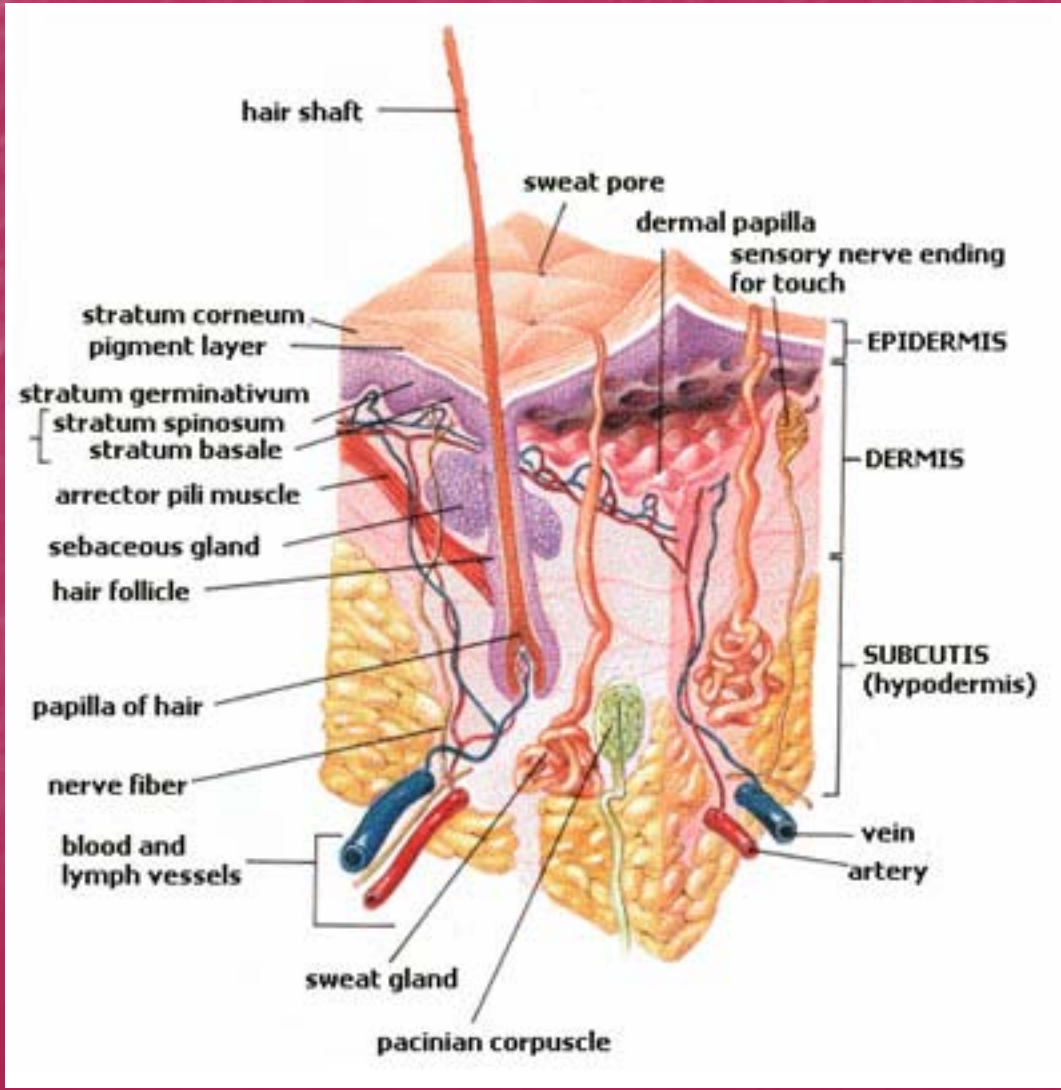
Epidemiology cont…

- US population
  - Acne affects more than 85% of teenagers
  - Results in more than 2 million visits to the doctor per year for patients 15-19 years of age
  - Mean age at presentation for treatment is 24 years
  - 10% of doctor's visits take place when patients are between the ages of 35 and 44 years.
- Financial impact
  - Direct cost of acne in the US is estimated to exceed $1 billion per year
  - Of this amount, it is estimated that $100 million is spent on over-the-counter acne products

Epidemiology cont…

- Psychosocial impact
  - Social, psychological, and emotional impairment that can result from acne has been reported to be similar to that associated with other chronic medical conditions like arthritis, asthma, diabetes, and epilepsy
  - Patients are prone to depression, social withdrawal, anxiety, and anger
  - Scarring associated with acne can lead to lifelong problems with regards to self-esteem
  - Patients with acne are more likely to be unemployed

The Skin


hair shaft
sweat pore
dermal papilla
sensory nerve ending for touch
stratum corneum
pigment layer
EPIDERMIS
stratum germinativum
stratum spinosum
stratum basale
DERMIS
arrector pili muscle
sebaceous gland
hair follicle
SUBCUTIS (hypodermis)
papilla of hair
nerve fiber
blood and lymph vessels
vein
artery
sweat gland
pacinian corpuscle

Pathophysiology

- Primary Causes
  - Increased sebum production
  - Abnormal epithelial desquamation
  - Bacterial growth
  - Inflammation

- Secondary Triggers
  - Mechanical obstruction (e.g., helmets, shirt collars)
  - Increased hormonal activity (e.g., menstrual cycles, puberty)
  - Stress (due to increased output of hormones from the adrenal gland)
  - Cosmetics and emollients (occlude follicles and cause an acneiform eruption)
  - Medications with halogens (iodine, chlorine, bromine)
  - Lithium, barbiturates, androgens
  - Anabolic steroids

1. Increased Sebum Production

- Maturation of the adrenal gland or an increase in the number of cells of the sebaceous gland can lead to excess sebum production

2. Abnormal Epithelial Desquamation

- Hyperkeratinization of the hair follicle prevents the normal shedding of follicular keratinocytes
- This results in follicular canal widening and increased cell production
- Sebum mixes with excess loose cells in the follicular canal to form a keratinous plug, or microcomedo
  - "Blackhead" – aka, open comedo; color due to the oxidation of tyrosine to melanin upon exposure to air
  - "Whitehead" – aka, closed comedo; due to inflammation or trauma to the follicle

3. Bacterial Growth

- The occluded follicle is rich in lipids as this is a major component of sebum
- This environment fosters the growth of *Propionibacterium acnes*, a bacteria that is part of the normal flora of the skin

4. Inflammation

- *P. acnes* provokes an inflammatory response by breaking down triglycerides found in sebum to free fatty acids and glycerol, and these compounds are proinflammatory

- *P. acnes* leads to further inflammation by releasing chemotactic factors that result in WBC activity

Clinical Presentation

- Acne may present on the face, neck, chest, back, shoulders, or upper arms
- Acne can be described in terms of:
  - Type of lesion
  - Classification of severity
- Lesions can take months to heal completely, and fibrosis associated with healing may lead to permanent scarring

Type of Lesion

- Non-Inflammatory
  - Comedonal
    - "Whitehead" – dilated hair follicle filled with keratin, sebum, and bacteria, with an obstructed opening to the skin
    - "Blackhead" – dilated hair follicle filled with keratin, sebum, and bacteria, with a wide opening to the skin capped with a blackened mass of skin debris
- Inflammatory
  - Papulo-pustular
    - Papule – small bumps less than 5mm in diameter
    - Pustule – small bump with a visible central core of purulent material
  - Nodulocystic
    - Nodule – bump greater than 5mm in diameter

Severity

Table 1. Classification of Acne.*

Severity	Description
Mild	Comedones (noninflammatory lesions) are the main lesions. Papules and pustules (Fig. 1) may be present but are small and few in number (generally <10).
Moderate	Moderate numbers of papules and pustules (10–40) and comedones (10–40) are present (Fig. 2). Mild disease of the trunk may also be present.
Moderately severe	Numerous papules and pustules are present (40–100), usually with many comedones (40–100) and occasional larger, deeper nodular inflamed lesions (up to 5). Widespread affected areas usually involve the face, chest, and back (Fig. 3).
Severe	Nodulocystic acne and acne conglobata with many large, painful nodular or pustular lesions are present, along with many smaller papules, pustules, and comedones (Fig. 4A).

* The information is from Cunliffe et al.[12]

Mild Acne

Moderate Acne

Moderately Severe

Severe Acne

Diagnosis

- The diagnosis of acne is established by observation of acne lesions
- The presence of 5-10 comedones is usually considered to be diagnostic

Therapeutic Objectives

- To prevent the formation of new acne lesions
- To heal existing lesions
- To prevent or minimize scarring

Treatment Options

- Non-pharmacologic
  - Surface skin cleansing
- Pharmacologic
  - Topical products
  - Oral antibiotics
  - Isotretinoin
  - Hormonal agents

Non-Pharmacologic Treatment

- Surface skin cleansing with soap and water has a relatively small effect on acne because it has minimal impact within follicle
- Skin scrubbing or excessive face washing does not necessarily open or cleanse pores and may lead to skin irritation
- Use of gentle, nondrying cleansing agents is important to avoid skin irritation and dryness during some acne therapies

Pharmacologic Treatment: *Topical Products*

- Benzoyl peroxide
- Retinoid analogues
- Topical antibiotics
- Azelaic acid

Benzoyl Peroxide

- Role in Acne Treatment:
  - Non-antibiotic antibacterial agent that is bacteriostatic against *P. acnes*
  - Increases the sloughing rate of epithelial cells and loosens the follicular plug structure
  - Proven effective in the treatment of acne
- Availability
  - Available in a wide variety of dosage forms (e.g., soaps, lotions, creams, washes, and gels) and dosages (e.g., 2.5% to 10%
- Dosing
  - To limit irritation and increase tolerability, begin with lowest concentration and increase either the strength or application frequency
  - Patients should apply the product to cool, clean, dry skin no more than twice daily
- Common Side Effects
  - Dryness and irritation
  - May bleach or discolor some fabrics

Retinoid Analogues

- Role in Acne Treatment
  - Increases cell turnover in the follicular wall
  - Decreases cohesiveness of cells, leading to extrusion of the comedones and inhibition of new comedo formation
  - Effectiveness in the treatment of acne is well documented

Retinoid Analogues cont…

- Examples
  - Tretinoin (topical vitamin A acid)
    - Availability – wide variety of dosage forms and concentrations, including Retin-A-Micro
    - Dosing – applied once nightly
    - Side Effects – skin irritation, erythema, peeling, increased sensitivity to sun exposure, wind, or cold
  - Adapalene (Differin)
    - Availability – 0.1% gel, cream, alcoholic solution, and pledgets
    - Dosing - applied once daily at night or in the morning
    - Side Effects – minimal irritation
  - Tazarotene (Tazorac)
    - Availability – 0.05% and 0.1% gel or cream
    - Dosing – applied once nightly
    - Side Effects – irritation, erythema, burning, stinging

Topical Antibiotics

- Role in Acne Treatment
  - Both erythromycin and clindamycin have demonstrated efficacy and are well tolerated
- Availability
  - Wide variety of dosage forms and concentrations
  - Also available in combination with benzoyl peroxide
- Dosing
  - Erythromycin – applied once or twice daily
  - Clindamycin – applied once or twice daily
  - In combination with benzoyl peroxide – applied once or twice daily
- Common Side Effects
  - Development of resistance by *P. acnes*

Azaleic Acid

- Role in Acne Treatment
  - Reported to possess comedolytic, anti-inflammatory, and antibacterial properties
- Availability
  - 20% cream
- Dosing
  - Applied twice daily on clean, dry skin
- Side Effects
  - Mild transient burning, pruritus, stinging, and tingling

Pharmacologic Treatment: *Oral Antibiotics*

- Role in Acne Treatment
  - Standard of care in the management of moderate and severe acne as well as in treatment-resistant forms of inflammatory acne

- Examples
  - Minocycline – reserved for patients who do not respond to other oral antibiotics or topical products; superior to doxycycline in reducing *P. acnes*
  - Doxycycline – more effective than tetracycline
  - Tetracycline – least expensive and most often prescribed for initial therapy
  - Erythromycin – effective, but use is limited to those who cannot use the tetracyclines (e.g., pregnant women or children under 8 y.o.)
  - Trimethoprim-Sulfamethoxazole – effective, but use is limited to those who cannot use the tetracyclines or erythromycin, or in case of resistance to these antibiotics
  - Clindamycin – use is limited by diarrhea

Oral Antibiotics cont…

- Dosing
  - Minocycline – 50-100mg once to twice daily
  - Doxycycline – 50-100mg once to twice daily
  - Tetracycline – 250-500mg twice to four times daily
  - Erythromycin – 250-500mg twice daily
  - Trimethoprim-Sulfamethoxazole – 160/800mg twice daily
  - Clindamycin – use is limited by diarrhea
- Common Side Effects
  - Vaginal candidiasis, photosensitivity, diarrhea

Pharmacologic Treatment: *Isotretinoin*

- Role in Acne Treatment
  - Indicated for severe nodular or inflammatory acne in patients unresponsive to conventional therapies, for scarring, for those with chronic relapsing acne, and for acne associated with severe psychological distress
  - Decreases sebum production, changes in sebum composition, inhibits *P.acnes* growth within follicles, inhibits inflammation

- iPLEDGE
  - This agent is a potent teratogen, and thus should only be prescribed by physicians knowledgeable in its appropriate administration and monitoring
  - Female patients of child-bearing potential must only be treated with this agent if they are participating in iPLEDGE, the approved pregnancy prevention and management program
  - Physician enters the patient's information into the iPLEDGE website
  - Dispensing pharmacist interviews patient and verifies patient information on website
  - Patient has to sign a consent form to comply with the program

Isotretinoin cont…

- Dosing
  - 0.5-2.0mg/kg/day
  - Drug is usually given for a 20 week course of therapy
  - Lower doses can be used for a longer time period, with a total cumulative dose of 120-150mg/kg
- Common side effects
  - Dry mouth, nose, and eyes
  - Increases in cholesterol, triglycerides, glucose, and transaminases
- Other reported effects
  - Mood disorders, depression, suicidal ideation,

Pharmacologic Treatment: *Hormonal Agents*

- Role in Acne Treatment
  - Estrogen-containing oral contraceptives can be useful in the treatment of acne in some women
  - Currently FDA-approved products for the treatment of acne include Ortho Tri-Cyclen (norgestimate with ethinyl estradiol) and Estrostep (norethindrone acetate with ethinyl estradiol)
  - These products have been shown to be equally efficacious
  - The effect of other estrogen-containing contraceptives (e.g., transdermal patches, vaginal rings) has not been studied

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