Acne Vulgaris

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Learning Objectives

- Identify risk factors associated with acne
- Identify lesions and determine the severity of acne
- Describe the selection of treatment based on the pathophysiology of acne
- Recommend treatment appropriate to the type of lesions and severity of acne
- Outline advantages and disadvantages of acne treatments
- State time of resolution of lesions and efficacy of treatments as indicated

Case 1

- Susan is a 16 year old caucasian female requesting a stronger benzoyl peroxide gel since her current 2.5% product is not working. She has been applying this to her frequent pimples and blackheads for the past 2 weeks. She washes her face with a salicylic acid solution once a day and applies cover-up makeup to her entire face. She is experiencing dry skin and patchy peeling with her normally sensitive skin.
- On inspection, she has a few papules, pustules and numerous comedones involving her face. There is no scarring.
- Her parents would not approve of her using oral contraceptives for acne.
- How will you manage this patient?

Georgia

Acne Vulgaris

Definition

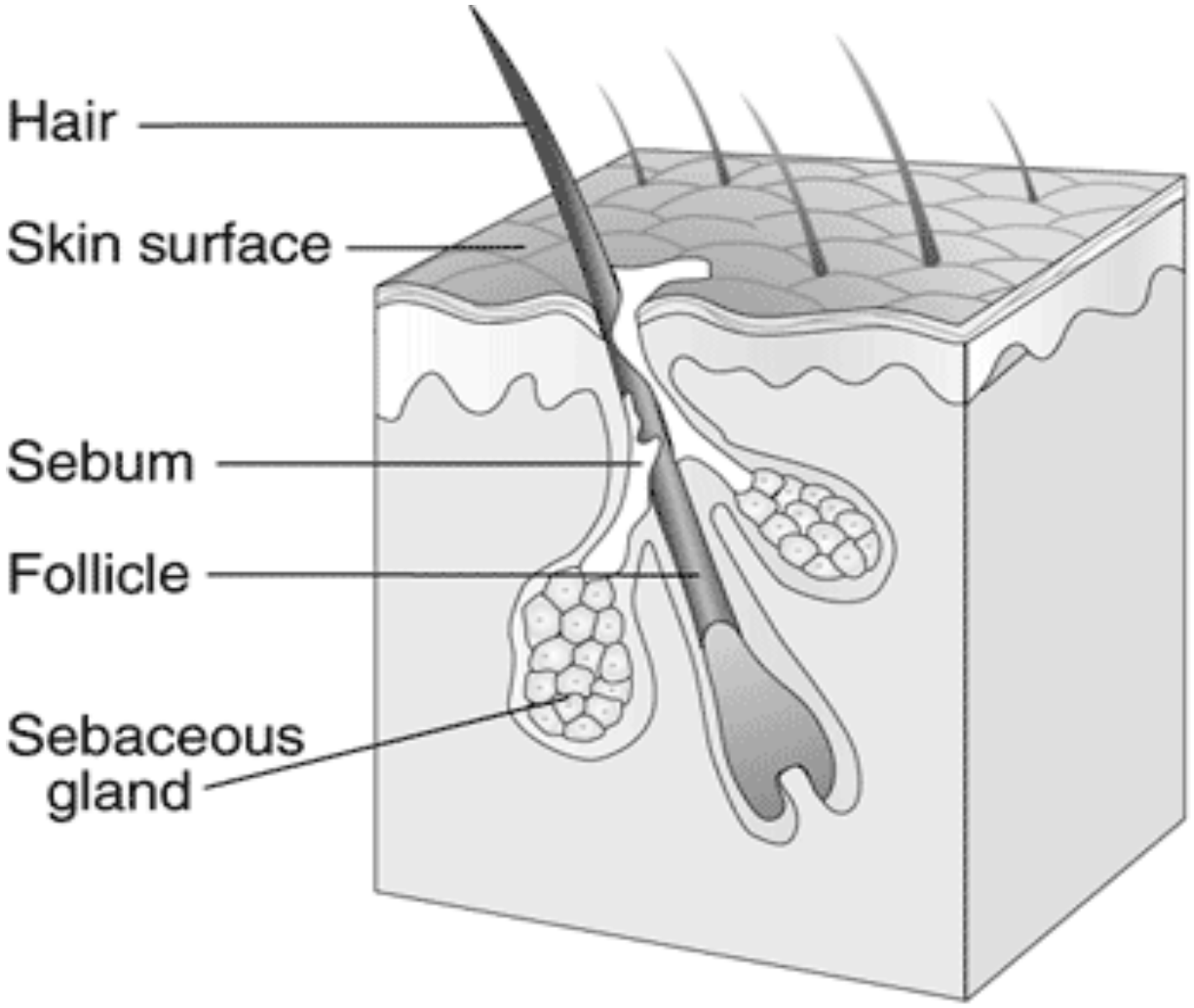
- Common acne is a chronic inflammatory disorder of the sebaceous glands and hair follicles of the skin, usually occurring in teenage years
- Key features
  - Non-inflammatory lesions
  - Inflammatory lesions
  - Lesion count
  - Presence of scarring
- Rule out acne rosacea and perioral dermatitis

Incidence

- Affects about 85 % of persons aged 12 to 24 with no gender, race or ethnicity variances.
- Clears in mid-20”s in males, but may persist through 3rd and 4th decade in females.
- 14% of patients receive professional help from general practitioner,and 0.3% from dermatologist
- Most use OTC medications

- J am Acad Dermatol 1998;39(2 Pt 3):S34-37.
- Pediatrics 2006l118(3):1188 -99

Pilosebaceous Unit



Pathogenesis

- Acne originates in the pilosebaceous unit
  - This unit consists of a hair follicle and a sebaceous gland that is connected to the surface of the skin by a duct through which the hair shaft passes
- Sebaceous glands:
  - are most common on face, upper chest and upper back
  - Produce sebum (a fat and wax mixture) that maintains proper hydration of the skin and hair
- Androgens
  - Increased levels during puberty, increase the size and activity of the sebaceous glands. However, patients with acne have exquisite end-organ sensitivity to androgens.

Pediatrics 2006;118(3):1188-99

The Lancet 1998 ;351:1871-6

Pathogenesis

- Under normal conditions, the keratinous lining of the follicle is continuously shed and carried to the surface by the flow of sebum
- In acne, this keratinization process is disrupted where:
  - **Epithelial cells (keratinocytes)** lining the follicle are overproduced and become cohesive (sticky) which results in retention within the follicle
  - **Sebaceous glands** produce excessive oil. Since the passageway is narrowed in the follicle, this sebum backs up

Pathogenesis…

- Eventually this accumulation of keratinous and sebaceous debris causes an impaction of the follicle and forms comedones (open and closed)
  - Closed comedones (whiteheads) are formed when the opening to the follicle is closed at the skin surface.
  - Open comedones (Blackheads) are formed when the follicle is open and the sebum is exposed to air. The top blackens due to a collection of melanin within the mass of horny cells.
- Acne characterized by open and closed comedones is called NON-INFLAMMATORY acne

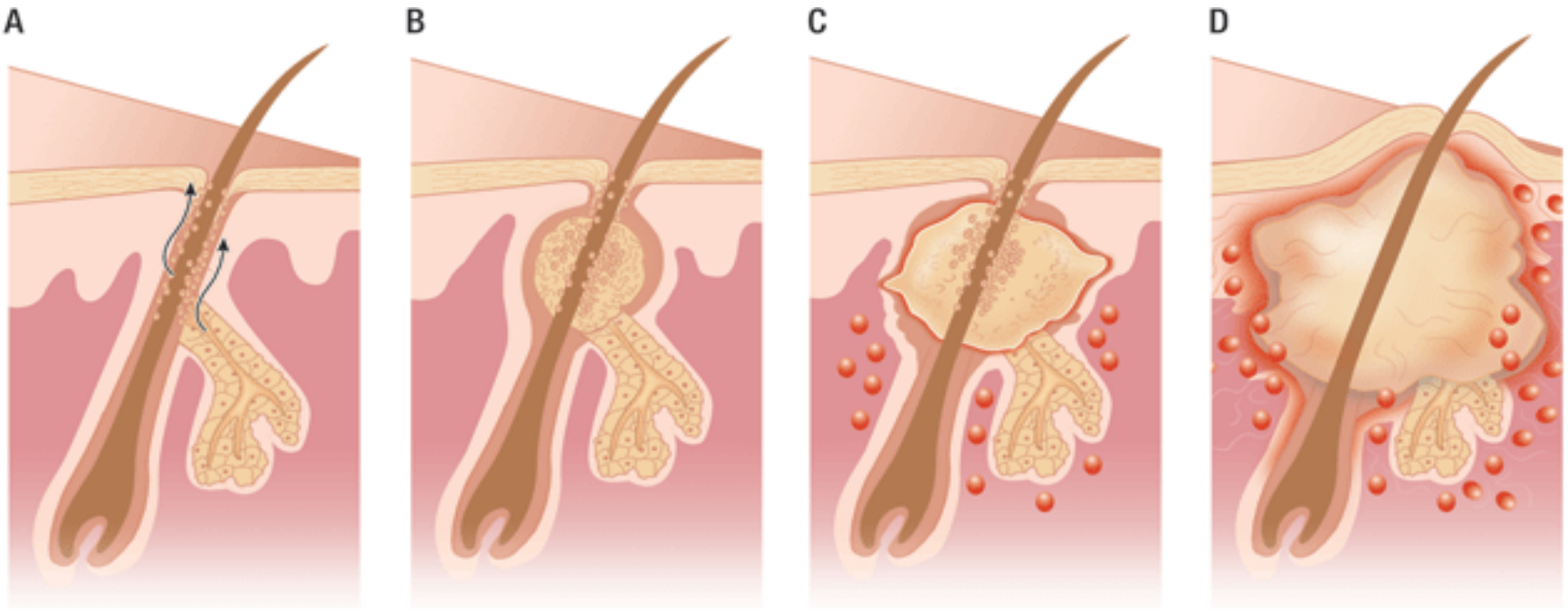
Pathogenesis…

- Local (gram +) anaerobic diptheroid bacteria, ***propionibacterium acnes*** (p. acnes), liberate lipases that hydrolyse triglycerides of the sebum to irritating free fatty acids
- This initiates an influx of white blood cells (**inflammation**) and ruptures follicle wall

Pathogenesis…

- INFLAMMATORY ACNE-is the result of bacterial lipolysis of triglycerides
- The closed comedone is the precursor of the inflammatory lesions:
  - Papules – red elevated solid and circumscribed lesions that precedes pustules
  - Pustules – small elevation of skin filled with pus
  - Cyst (Nodule) – a sac under skin with a definite wall around it and contains fluid or solid material. These lesions may heal with a scar (atrophic – valleys in skin)

Pathogenesis of Acne



Microcomedone
- hyperkeratotic infundibulum
- cohesive corneocytes
- sebum secretion

Comedone
- accumulation of shed corneocytes and sebum
- dilation of follicular ostium

Inflammatory papule/ pustule
- further expansion of follicular unit
- proliferation of *Propionibacterium acnes* perifollicular inflammation

Nodule
- rupture of follicular wall
- marked perifollicular inflammation
- scarring

Source: Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 6th Edition:* http://www.accessmedicine.com

Combined Acne Severity classification

Severity	Definition
Mild acne	Fewer than 20 comedones, or fewer then 15 inflammatory lesions, or Total lesion count fewer than 30
Moderate acne	20 – 100 comedones, or 15 – 50 inflammatory lesions, or total lesion count 30 – 125
Severe acne	More than 5 nodules, or Total inflammatory count greater than 50, or Total lesion count greater than 125 (presence of active scarring)

J Cutan Med Surg 2000;4 (Suppl 1:S2-3

Comedonal Acne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Perioral dermatitis- steroid, cosmetic cream induced papules and pustules around mouth area.

Acne Rosacea —vasodilation, telangiectasia, papules pustules involving central face. No comedones.

Acne Rosacea –glandular type - Rhinophyma
WC Fields

Risk Factors for Acne Vulgaris

- Stress, premenstrual flares, use of oil products, local friction, improper cleansing of hair and skin
- Drugs: androgens, barbiturates, corticosteroids, haloperidol, lithium, phenytoin, oral contraceptives (with levonorgestrel), bromides, iodides

Treatment Goals

- To prevent new lesions from forming, heal existing lesions and minimize permanent scarring by:
  - Reducing the keratinization process
  - Decreasing sebum production
  - Reducing microbial flora and thereby decreasing enzymes
- Prevent psychological distress

- Skin Therapy Letter Family Practice Edition 2005;1(3)

	Benzoyl Peroxide	Topical Retinoids	Antibiotics	Oral Isotretinoin	Hormonal therapy
Normalization of Follicular keratinization	X	X		X	X
Antibacterial	X		X		
Anti inflammatory	X	X	x Tetracycline	X	
Decreased Sebum production				X	X

Topical Treatment

- The cornerstone of acne treatment
- Must treat ALL skin areas daily not just the current lesions
- Takes at least 8 - 12 weeks to see improvement
- Maintenance is essential to prevent recurrence

- Am Fam Physician 2000;61(2):357-66
- Postgrad Med J 2006;82(970):500-506.

Exfoliants

- Phenol
- Resorcinol
- Sulfur 3 – 12%
- Salicylic Acid 3-6 %- washes are useful in young patients with recent onset acne
- Azelaic acid 15% (Finacea)

- Am Fam Physician 2000;61(2):357-66
- Postgrad Med J 2006;82(970):500-506.

Benzoyl Peroxide

- Mechanism of action: **antibacterial** – decomposed on skin by cysteine to liberate free oxygen radicals that oxidize bacterial proteins (↓FFA by 50% & P.acnes ↓ by 98%)
  - Also has minimal comedolytic effect
- Use: mild acne (alone) and adjunct for all types of acne
  - Apply once or twice daily
  - Reduces resistance of P.acnes when combined with topical antibiotics (*Br J Dermatol 134:107-13,1996)*
- Disadvantage:
  - dryness & irritation (redness) for first 1 -2 weeks (start low potency)
  - Contact dermatitis in 1 -3 %- patch test is advised
  - Bleaches fabrics and hair
  - Oxidizes tretinoin thus apply BP in a.m. and tretinoin in p.m.
- Products: 2.5%, 5%, 10% (4%) in water, acetone and alcohol gels (water least irritating)
  - Water base (Solugel, B, Benoxyl, Panoxyl Aquagel); Acetone base (Acetoxyl); Alcohol base (Panoxyl)
- Int J Clin Pract 2006;60(1):54-72

Topical Retinoid: Tretinoin (trans retinoic acid)

- Mechanism of action: decreases cohesiveness of follicular epithelial cells
  - Increases cell turnover in follicular wall resulting in expulsion of existing comedones
  - Decreases number of cell layers in stratum corneum from 14 to 5 (thins it)
- Use: possibly most effective comedolytic (apply hs)
- Disadvantage: irritation, erythema & peeling begin after 2 – 10 days usage & persists until adaptation occurs in 10 – 14 days. (start with low strength and frequency of application)
  - "flare of acne" appears after 3 to 6 weeks and clears by 8 – 12 weeks
  - Comedones take longest to respond
  - Need sunscreen SPF 15
  - Teratogenic (case reports) *Clin Evid 2006;15:2183-2201*
- Products: *Retin-A, Stieva-A, Vitamin A Acid, Vitinoin* 0.025%, 0.05%, 0.1% cream or gel
  - Cream is less irritating than the gel
- Products that have microspheres and polymerized products are not safer or more effective. *J Am Acad Dermatol 1998;38(4):S24-30*

Topical Retinoid: Adapalene

- a synthetic naphthoic acid derivative with retinoid activity (more receptor selective)
- Also inhibits arachidonic acid metabolism (less inflammatory response)
- Compared to tretinoin, comparable reduction in # lesions (both inflammatory and non-inflammatory) by 50% in 4 – 12 weeks; less erythema, scaling and dryness
- Dose: *Differin* 0.1% gel once daily at bedtime

- Cutis 2006 Jul;78(1 Suppl):26-33

Topical Retinoid: Tazarotene

- A synthetic retinoid (more selective binding to cause less local irritation)
- Once absorbed in skin, it is immediately converted to active metabolite, tazarotenic acid
- Mechanism of action: up-regulates 3 novel genes that modulate keratinocyte differentiation & inflammation
- Side effects: 5 – 13% dermatitis with erythema, stinging and burning (mild to moderate)
- Expensive
- Products: *Tazorac* 0.1% and 0.05% gels
- 68% reduction in # lesions versus 40% with control over 12 weeks.
- Most effective topical retinoid

- J Am Acad Dermatol 2000;43(2 Pt 3):S51-4
- J Drugs Dermatol 2006;5(9):921-22

General Principles for Topical Treatment

- Initiate with lowest strengths in water based products or apply every second or third night for adaptation to occur
- Apply to entire area affected by acne
- If using two different therapies, apply one in the morning and one in the evening
- Acne may initially worsen for the first few weeks
- Optimal effect is delayed up to 12 weeks
- Limited evidence suggests similar efficacy and tolerability

TOPICAL ANTIBIOTICS

- Mechanism: eliminate P.acnes from follicle thus get decreased free fatty acid production and subsequent inflammation
  - Concentrates medication in affected area and reduces risk of systemic side effects
  - (Tetracycline : Antiinflammatory effect by suppressing leukocyte chemotaxis)
- Use: mild to moderate acne (inflammatory lesions)
  - Not as effective on trunk (back and chest) as on face
  - Apply twice daily
- P.acne resistance with prolonged use (combine with benzoyl peroxide)

- Tan HH. Topical antibacterial treatments for acne vulgaris : comparative review and guide to selection. Am.J.Clin.Dermatol. 2004;5(2):79-84.

Topical Erythromycin

- Safest in pregnancy
- Greatest resistance risk
- Products :
  - *Staticin* 1.5 % lotion
  - *Erysol* 2% gel, *T-Stat* 2% solution, *SansAcne* 2% solution
  - Compounded as 1% or 2% in propylene glycol (25%) plus isopropanol 95% (75%)
- Combination Products:
  - *Stievamycin* Gel –erythromycin + retinoic acid
  - *Benzamycin* – erythromycin + benzoyl peroxide

- Am.J.Clin.Dermatol. 2004;5(2):79-84.

Topical Clindamycin

- Equal efficacy to topical erythromycin
- Rare cases of pseudomembranous colitis
- Disagreeable taste with topical use
- Products
  - *Dalacin-T* 1% lotion, *Clinda-T* 1% solution, *Clindasol* 1% cream and *Clindets*1% pledgets
  - Compounded as 1% or 2% in Duonalc or Duonalc-E lotion
- Combination Products

  Clindoxyl & BenzaClin– clindamycin 1% + benzoyl peroxide 5%

  Bianca –clindamycin + tretinoin
  - Am.J.Clin.Dermatol. 2004;5(2):79-84
  - ICSI May 2006 Acne guidelines

Systemic Antibiotics

- Mechanism of action: eliminate P.acnes from follicle
  (tetracycline inhibits chemotaxis, phagocytosis, complement activation and cell-mediated immunity –antiinflammatory)
- Use: best for moderate or severe inflammatory acne
  -best combined with topical benzoyl peroxide or retinoic acid
- Disadvantage: GI upset, vaginal candidiasis, gram negative folliculitis (proteus, klebsiella), photosensitivity reactions (tetracycline), refractoriness due to resistant p.acnes (especially erythromycin)
- **Discontinue once acne has improved and always combine with benzoyl peroxide**
- **Limit use to 6 months treatment to reduce resistance**
- If no response in 6 weeks, switch to a different antibiotic since individuals respond differently to different antibiotics.

- Tan HH. Antibacterial therapy for acne: a guide to selection and use of systemic agents. Am.J.Clin.Dermatol. 2003;4(5): 307-314.

Tetracycline

- Drug of first choice due to its effectiveness, low cost and less resistance
- Contraindicated in pregnancy
- Photosensitivity reactions, N,V,D, vaginal candidiasis, esophageal ulcerations, benign intracranial hypertension (pseudotumor cerebri)
- Starting dose: 250 mg qid or 500 mg bid on empty stomach for 2 – 3 weeks then reduce dose to 250 or 500 mg daily once formation of new lesions is stopped.

Erythromycin

- Useful in females contemplating pregnancy
- Causes GI distress (cramps)- motilin-like effect
- Drug interactions by P450 inhibition (anticoagulants, digoxin, carbamazepine, statins, theophylline)
- More *P.Acnes* resistance
- Dose: 250 mg qid (or 500 mg bid) then decrease with response to 250 – 500 mg daily

- Am Acad Dermatol 2003;49(Suppl 1):S1-37

Doxycycline

- Effective as it is highly lipid soluble
- A tetracycline that has improved absorption
- More photosensitivity reactions than tetracycline
- Dose – 50 -100 mg once daily

- Am Acad Dermatol 2003;49(Suppl 1):S1-37

Minocycline

- Considered highly effective due to its high lipid solubility and ability to penetrate follicle but evidence shows equal efficacy.(Cochrane Database Syst Reve2003l(1) (1):CD002086)
- Used in patients unresponsive to tetracycline
- Dizziness (vestibular irritation in 30 % patients)
- Blue- black color changes in acne scar (rarely)
- Drug-induced lupus reported
- Hypersensitivity reactions involving liver
- Dose: 50 mg bid or 100 mg once daily (200 mg daily max)
- Expensive - Caution recommended

- Cochrane Database Sust Rev 2003;(1) (1):CD002086
- Am Acad Dermatol 2003;49(Suppl 1):S1-37

Trimethoprim-Sulfamethoxazole

- Occasionally used for severe acne refractory to other antibiotics
- Used to treat gram-negative folliculitis
- Dose: one double-strength tablet (800/160 mg) once daily
- Can cause severe skin rashes (Stevens Johnsons Syndrome and Toxic epidermal necrolysis)

- Trimethoprim alone as 300 mg bid may also be used.

- Am Acad Dermatol 2003;49(Suppl 1):S1-37

Clindamycin

- Used for refractory acne
- May cause pseudomembranous colitis; diarrhea
- Dose: 150 mg once or twice daily

J Am acad Dermatol 2007;56(4):651-663

General Principles for Antibiotics

- Do not use topical and oral antibiotics together at the same time
- Always use benzoyl peroxide in combination with antibiotics to prevent bacterial resistance
- Use antibiotics judiciously for *inflammatory acne* and restrict the duration to less than 6 months
- Erythromycin is associated with greatest risk for resistance

Isotretinoin(Cis-retinoic acid)(oral vitamin A derivative) *Accutane and Clarus*

- Use: *For severe inflammatory acne unresponsive to conventional therapy
  - (nodulocystic acne – require isotretinoin, steroid injections to lesion or hormone therapy)
- Mechanism of action:
  - decreases sebum production (which results in decreased p.acnes and inflammation)
  - Normalizes keratinization

  - N Engl J Med 2005;352☹14):1463-72

Isotretinoin

- Dose: 0.5 mg/kg/day for 2 to 4 weeks then increase to 1 mg/kg/day (acne exacerbation occurs during first month of therapy)
  - 16 week course 70% success rate with prolonged remission of > 20 months
  - 20 week course 90% of patients achieve 80% improvement
  - 23% of cases relapse 2 months to several years after treatment
  - Can give second course after waiting 2 – 4 months

  - J Am Acad Dermatol 1984;10(3):490-6

Isotretinoin

- Side effects: 90% dry lips (chelitis)
  - 30% dryness and desquamation of face
  - 25% ↑ TG and cholesterol
  - Abnormal liver function tests (10% patients)
  - CNS - ↑ intracranial pressure (Pseudotumor cerebri)
  - Eyes- corneal opacities, irritation (conjunctivitis), decreased night vision
  - Musculoskeletal – pain 16% (catabolic effects on mesenchymal tissue)
  - Skeletal hyperostosis
  - Teratogenic (use 2 methods of contraception one month before, during & one month after therapy)
  - Depression- no causal link but should be discontinued
- Monitoring: CBC, LFT, Lipids (baseline, 4 & 8 weeks), pregnancy (2 weeks before and 6 weeks after)
- Product :10 mg and 40 mg capsules (usual 40 mg/day)
- Br J Dermatol 1993:129(3):292-6 and CMAJ 2004:55(3):165-8

Hormonal Therapy

- **OCs** (estrogen) decrease the amount of circulating androgens and increase serum binding hormone globulin
- Approved oral contraceptives for acne:
  - *Yasmin (drospirenone + EE) – thromboembolic risk*
  - *Tricyclen* (norgestimate +EE) – reduces lesions in 53% females versus 27% in controls over 26 weeks.
  - *Alesse* or *Aviane* (levonorgestrel +EE low doses)
  - *Diane* – 35 or *CyEstra - 35*(cyproterone acetate +EE)- indicated in women with severe androgenic symptoms (hirsuitism/acne) who have not responded to antibiotics and other treatments. Three-fold increased risk of DVT(deep vein thrombosis). Discontinue 3 to 4 cycles once acne has resolved. Not approved for contraception in Canada.
- All oral contraceptives have equal efficacy in acne. *Cochrane Database Syst Rev 2004;(3)(3):CD004425*
- Maximum effectiveness seen at 4 to 6 months
- **Spironolactone** (androgen receptor blocker)50 – 200 mg daily may be used when contraception is not required.
- *Contraception 2006:73(1):23-9*

Pharmacotherapy

- Mild acne
  - Topical agents alone or in combinations
  - Topical retinoid is most effective for comedones
  - Add topical antibiotics if inflammatory lesions present
  - Assess at 2 – 3 months
- Moderate Acne
  - Topical agents
  - Oral antibiotics for inflammatory lesions not responsive to topical or if involves areas other than face. Limit to 6 months treatment if possible.
  - Assess at 2 months for tolerability and 4 months for efficacy
- Severe Acne
  - Isotretinoin if other therapies have failed

  - J Cutan Med Surg 2000;4 (Suppl 1:S2-3

Tips for treatment

- Dispel myths
  - Acne is not caused by inadequate facial cleansing. Routine skin care should be gentle
  - Diet has little effect on acne
- Avoid picking, vigorous scrubbing and drying
- Topical treatment should be applied to entire area, use regularly. If irritation occurs, reduce duration and/or frequency of application.
- Antibiotic therapy should be combined with benzoyl peroxide to prevent *p.acnes* resistance
- Noticeable improvement may take 8– 12 weeks
- Use non-comedogenic cosmetics and moisturizers.

- Management of Acne. Summary, Evidence Report/Technology Assessment: Number 17. AHRQ Publication No. 01-E018. 2001. Rockville MC, Agency for Healthcare Research and Quality

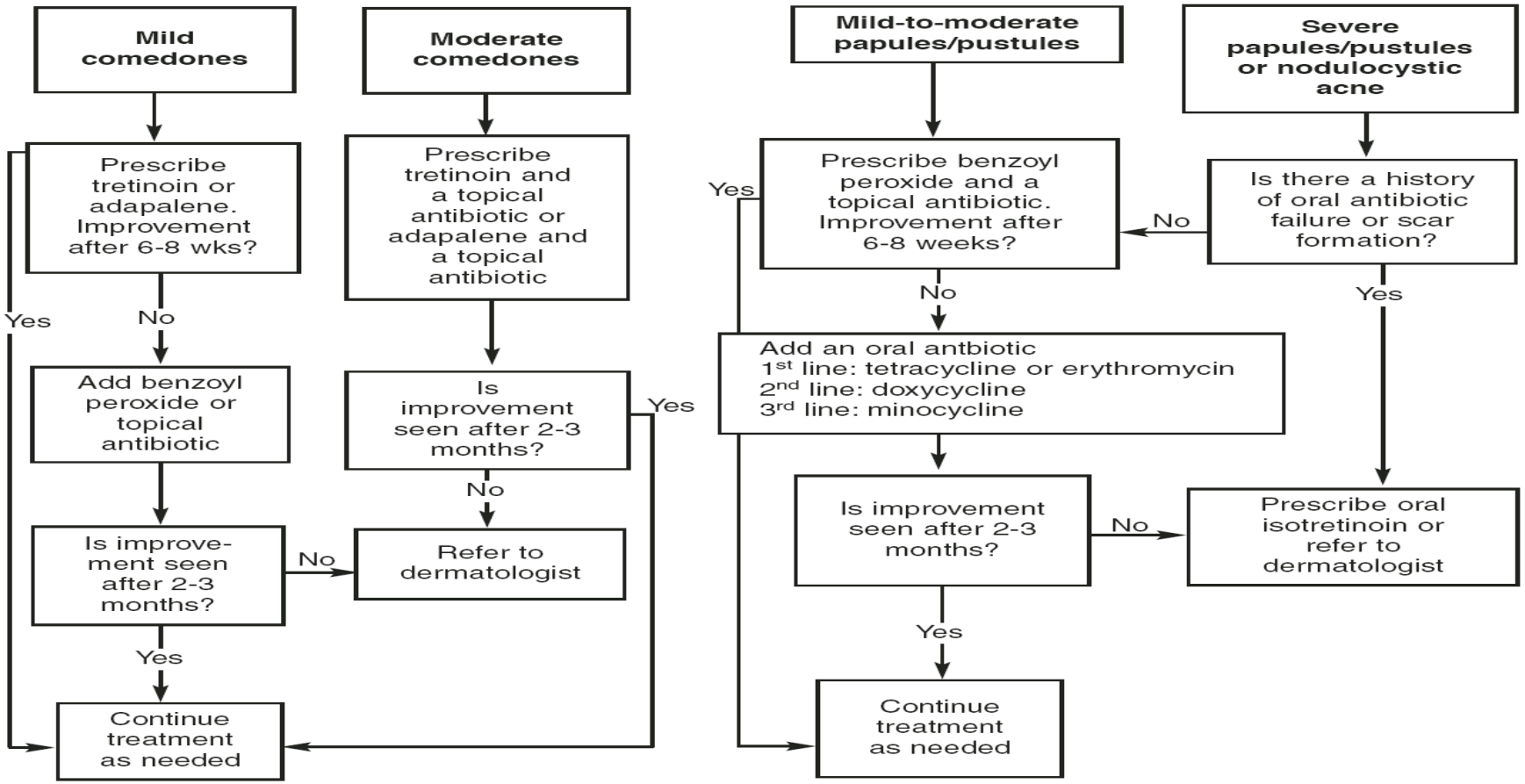
Susan- case resolution

"It's me acne Doc, it's gettin' so's i'm feelin' too ashamed to go out"

4to40

FIGURE

Treatment of acne according to type and severity



If patient is female:

Use oral contraceptives as adjunctive therapy to any treatments described above if patient desires contraception. [Note: There is only anecdotal evidence to suggest decreased oral contraceptive efficacy when combined with oral antibiotics typically used in the management of skin conditions.][44]

TABLE 4

Medication options for acne vulgaris

Evidence Strength*	Medication	Cost per month**	Relative efficacy	Comparator	Comment
Comedonal, papulopustular, or nodulocystic					
A	Norgestimate/ ethinyl estradiol	$31.08	>	Placebo	Decreases comedone and inflammatory lesion counts
Comedonal or papulopustular					
A	Adapalene	$34.47 (gel)	=	Tretinoin	Adapalene has better side-effect profile
A	Benzoyl peroxide	$7.99–$16.19	>	Placebo	Price depends on generic vs brand, not concentration
A	Clindamycin	$34.73 (gel)	>	Placebo	Topical
A	Erythromycin	$18.31 (gel)	>	Placebo	Topical
A or B	Tretinoin	$23.91	>	Placebo	Evidence strength A for noninflammatory and B for inflammatory
B	Azelaic acid	$44.40	>	Placebo	Topical
B	Azelaic acid	$44.40	=	Benzoyl peroxide	Azelaic acid has better side-effect profile
B	Azelaic acid	$44.40	=	Tretinoin	Azelaic acid has better side-effect profile
B	Clindamycin	$34.73	=	Erythromycin	Topical
B	Clindamycin	$34.73	=	Benzoyl peroxide	Topical
B	Salicylic Acid		>	Placebo	Topical
B	Tazarotene	$64.75 (.05%) $68.74 (0.1%)	>	Placebo	Side effects similar to those of topical retinoids
B	Tretinoin	$23.91	>	Benzoyl peroxide	Tretinoin: stronger effect on comedones; BPO: stronger effect on papules
Papulopustular or nodulocystic					
A	Tetracycline	$8.38	>	Placebo	Oral
B	Doxycycline	$24.82	>	Placebo	Oral
B	Erythromycin	$27.15	=	Tetracycline	Oral. Higher resistance levels of *P acnes* to erythromycin
B	Minocycline	$21.90	>	Placebo	Oral
B	Minocycline	$21.90	=	Tetracycline	Oral

KEY: > is more effective than; < is less effective than; = is equivalent to.

*Evidence Strength:
A = At least two trials of acceptable quality showing moderate to strong statistical evidence for clinically meaningful endpoint and effect.
B = Evidence is of modest strength, such as when only one trial addresses a comparison, there is significant heterogeneity, large differences are not statistically significant, or poor trial quality prevents accepting strong statistical evidence at face value.

**Cost: Referenced from a major on-line retail pharmacy.

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