

Acne Therapy

Overview & Drug Comparison Chart

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Comments welcome on or before October 24/06

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ACNE Therapy: Pharmacological Overview

- Benzoyl Peroxide (BP) is used as 1st line monotherapy for mild-moderate acne
 - BP produces powerful anaerobic antibacterial activity due to slow release of oxygen, comedolysis, and depression of sebum production
 - BP can also be used as an adjunct to topical retinoids, antibiotics (ABX)^{systemic/oral}, oral contraceptives (OCs) & spironolactone
- Topical retinoids (tretinoin, tazarotene, adapalene) slow the desquamation process, reducing the numbers of both microcomedones & comedones
 - Used for mild-moderate comedonal acne (inflammatory +/- non-inflammatory) or as adjunct with BP, ABX, OCs & spironolactone
- Topical ABX are best used in combination with retinoids or BP (monotherapy of topical ABX= more bacterial resistance compared to combination therapy)
- Systemic ABX (tetracycline, doxycycline, minocycline, erythromycin, & trimethoprim) are indicated for moderate-severe acne but resistance is increasing
- For females, OCs may be considered over antibiotics for moderate-severe acne. Spironolactone has been used for women with moderate-severe acne when OCs contraindicated or other treatments fail
- Isotretinoin is the most effective therapy for moderate-severe inflammatory acne
 - Isotretinoin can cause birth defects in the developing fetus of a pregnant woman
 - There have been reported suicides & suicide attempts in people taking isotretinoin, but direct correlation has not been established
- Other OTC agents include salicylic acid, sulphur, resorcinol, & Tea Tree Oil (all less efficacious than BP)

General Considerations for Topical Therapies

- Patient skin type (oily to dry)
 - For very oily skin consider a gel or solution
 - For very dry skin choose creams or lotions
- If 2 topicals are being used, apply one qam & the other qhs
- If multiple agents are used, they should be from different classes (eg. BP & topical ABX)
- Potency: Solution > Gel > Cream > Lotion

BP : Suggested routines to initiate therapy

- Wash the product off in the morning
 - Sunscreen is recommended during the day
1. Gently cleanse the skin & apply for 15 minutes the 1st evening. Each evening the time should be doubled until left on for 4 hours & subsequently all night. Once tolerance is achieved, the strength may be ↑ to 5% or the base changed to acetone or alcohol, gels or paste
 2. Alternatively, BP can be applied for 2 hours for 4 nights, 4 hours for 4 nights, and then left on all night.

Oral ABX: Reasons for Lack of Response

- Inadequate potency (eg. topical therapy for very severe disease)
- An inadequate duration of treatment (at least a month is needed)
- Improper education and poor compliance with medication
- The development of resistance to antibiotics
 - Resistance is most common with the use of erythromycin (50%), clindamycin (35%) & tetracycline (25%)
 - Resistance to ABX should be suspected in patients who do not have a response to treatment or who have a relapse during treatment, especially those who have been on multiple courses of ABX or have a history of variable compliance
 - If resistant to erythromycin and clindamycin → switch to tetracycline or doxycycline
 - If resistant to tetracycline → switch to minocycline (not doxycycline because of cross resistance)

OCs: Indications for optimal use in women with acne¹

- Acne accompanied by mild or moderate hirsutism
- Inadequate response to other acne treatments
- Acne that began or worsened in adulthood
- Premenstrual flares of acne
- Excessive facial oiliness
- Inflammatory acne limited to the “beard area”

What OCs have the official indication for acne tx?

- In Canada, Alesse, Tri-cyclen & Diane 35 have the official indications for acne in the monograph
- Yasmin is as efficacious as Tri-cyclen² & Diane 35³ for mild-moderate acne, but not officially indicated for acne
- ~~All OCs are beneficial in acne due to estrogens effect on sex hormone binding globulin~~

Can Diane 35 be used for OC monotherapy?

- Berlex Canada does not recommend that Diane 35 should be prescribed as contraception alone. They recommend the use of alternative contraception while on Diane 35. However, Diane 35 is indicated for OC monotherapy in other countries (e.g., Australia)

Isotretinoin (Accutane, Clarus) Indications:⁴

- Severe nodulocystic acne
- Extensive acne involving face and trunk, associated with scarring
- Failure to respond to or inability to tolerate systemic antibiotics and/or hormonal therapy
- Significant psychological distress because of acne
- Acne fulminans, gram-negative folliculitis, and/or pyoderma faciale

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Managing Adverse Effects

- Dryness can be managed with non-comedogenic moisturizers such as Cetaphil, Neutrogena, Moisturel & Neutrogena
- If irritation occurs with Tretinoin, switch to Adapalene
- If possible, ↓ the strength or contact time (topicals) initially to prevent further irritation, & gradually ↑ as tolerated
- For sensitive skin: 2% clindamycin in Complex 15 Lotion or Cetaphil Cleansing Lotion with 2.5% H₂O-based BP⁵

Possible contributing factors of Acne:

- Hormonal
 - Signs of androgen excess would include precocious puberty and hirsutism
 - Possible causes of androgen excess would include polycystic ovary disease, adrenal tumor, ovarian tumor and pituitary tumor
- Mechanical
 - Physical pressure from headbands, violins, chin straps, sports helmets, guitar straps and orthopedic braces have induced localized acne; wool and other rough textured fabrics and occlusive clothing may also be irritants
- Contact
 - Oil-based cosmetics, oil-based scalp lubricants, topical tar products, and hairspray
 - Occupational materials such as coal tar, pitch, mineral oil and petroleum oil
 - Ingestion, inhalation or transcutaneous penetration of halogenated aromatic hydrocarbons, including the polychlorobiphenyls in paint, varnishes, lacquers, fungicides, insecticides, herbicides, wood preservatives and various oils
- Environmental
 - Heat and humidity may induce comedones
 - Pressure, friction, and excessive scrubbing or washing can exacerbate existing acne by causing microcomedones to rupture
 - Hair styles low on the forehead/neck may cause excess sweating, occlusion & make acne worse
- Emotions
 - Intense anger or stress can exacerbate acne, causing flares or increasing mechanical manipulation⁶
- Drugs
 - Hormones: androgenic hormones in women, corticosteroids, corticotrophin (ACTH), oral contraceptives high in progestin
 - Bromides, chlorides, halothane, iodides (e.g., Kelp)
 - Antiepileptic drugs: phenytoin, phenobarbital, trimethadione, gabapentin
 - Tuberculostatic drugs: ethambutol, thionamide, isoniazid
 - Miscellaneous: cyclosporine, cyanocobalamin, dantrolene, gold salts, lithium salts, maprotiline, psoralens, quinidine, quinine, topical coal tar

Diet

- Chocolate – the evidence that chocolate is acneogenic has methodological flaws⁷, such as small sample size⁸; treatment duration and follow-up may not be long enough to detect changes^{9,10}; and high fat content of control bar may be acneogenic¹¹
- There are anecdotal evidence of patients that certain foods exacerbate acne¹²
- Therefore, advice regarding diet should be individualized

Facts for the Patient

- It can take at least 8 weeks of a prescribed treatment regimen for the patient to see any improvement. Acne may even get worse before it gets better
- Cleaning the skin too often may aggravate acne & cause flare ups. Acne is not caused by dirt or surface oil. Wash face twice per day with a mild non-alkaline soap and lukewarm water.
- Use the fingertips or a soft wash cloth to wash the face
- Picking at acne lesions may cause scarring – NO PICKING
- There is NO cure for acne.
- Stress may exacerbate psychological reaction to acne.
- There is no evidence to support that chocolate or sugar will cause acne. Certain foods may make some patients' acne worse and should be avoided. No specific food/diet has been proven to worsen or improve acne.
- Acne affects adults as well as children

Table 1: Topical acne therapies and their associated activities^{13,14,15}

Topical Therapy	Comedolytic activity	Sebostuppressive activity	Antimicrobial activity	Anti-inflammatory activity	Prevalence of resistant <i>P. acnes</i> strains
ERY	-	-	++	+	High
CLIN	-	-	++	+	High
TET	-	-	++	++	High
BP	+	-	+++	+	No
TRET	++	-	+	-	No
ADA	++	-	+	++	No
TAZ	++	-	+	-	No
(Ery or Cli) + BP	-	-	+++	++	Low
(Ery or Cli) + Tre	++	-	++	+	Low
(Ery or Cli) + Ada	++	-	++	++	Low

- = none; + = weak; ++ = moderate; +++ = strong **ERY** erythromycin **CLIN** clindamycin **TET** tetracycline **BP** benzoyl peroxide **TRET** tretinoin **ADA** adapalene **TAZ** tazarotene



Table 2: Acne Vulgaris VS Acne Rosacea

Acne variant	Open Comedones	Closed Comedones	Pustules	Papules	Nodules	Other distinguishing factors	Treatment Options
Acne Vulgaris	X	X	X	X	X	Most: ages 12-24	See drug charts
Acne Rosacea			X	X	+/-	Erythema, edema, telangiectasia, flushing, rhinophyma, ocular rosacea, ages 30-60	Metronidazole, oral antibiotics, isotretinoin

Closed comedone (whitehead): non-inflamed (non-red) follicular opening containing a keratotic plug with a thin overlying epidermal membrane; **Open comedone** (blackhead): non-inflamed (non-red) follicular opening containing a keratotic plug that appears black; **Papule**: small round to oval red elevation of the skin (1-4 mm); **Pustules**: resembles a papule with a central pocket of pus; **Nodule/Cyst**: poorly marginated red tender, sometimes draining 0.2-3.0cm, indurated mass in the skin

Table 2: Adverse drug reactions of topical agents in acne therapy ^{xvi}**{Removed from main text due to conflicting literature!}**

Agent	Erythema	Scaling	Burn- ing	Flare- up	Bacterial Resistance	Photo sensitivity
TRE	++++	++++	+++	+++	-	+++
ADA	++	++	++	++	-	-
TAZ	++	++	++	++	-	-
BP	+++	+++	++	++	-	-
Antibiotic	+	+	-	-	++++	+(TET)

- = none; + = weak; ++ = moderate; +++ = strong; ++++ = very strong **TOP** topical¹ Zouboulis CC and Piqero-Martin J. Update and Future of Systemic Acne Treatment. *Derm.* 2003;206(1):37-53² Thorneycroft H, Gollnick H, Schellschmidt I. Superiority of a combined contraceptive containing drospirenone to a triphasic preparation containing norgestimate in acne treatment. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial] *Cutis.* 74(2):123-30, 2004 Aug.³ van Vloten WA, van Haselen CW, van Zuuren EJ, Gerlinger C, Heithecker R. The effect of 2 combined oral Contraceptives containing either drospirenone or cyproterone acetate on acne and seborrhea. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial] *Cutis.* 69(4 Suppl):2-15, 2002 Apr.⁴ Katsambas A & Papakonstantinou A. Acne: Systemic Treatment. *Clin Derm.* 2004;22:412-8⁵ Dr. Lichtenwald, dermatologist, discussion, September 21, 2006⁶ Zouboulis CC, Bohm M. Neuroendocrine regulation of sebocytes -- a pathogenetic link between stress and acne. *Experimental Dermatology.* 13 Suppl 4:31-5, 2004.⁷ Magin P, Pnd D, Smith W, et al. A systematic review of the evidence for "myths and misconceptions" in acne management: diet, face-washing and sunlight. *Family Practice – an international journal;*2005(Jan 11):62-70⁸ Grant JD and Anderson PC. Chocolate and acne: a dissenting view. *Missouri Medicine* 1965;62:459-60⁹ Anderson PC. Foods as the cause of acne. *Am Fam Phys* 1971;3:102-3¹⁰ Fulton JE Jr, Plewig G, Kligman AM. Effect of chocolate on acne vulgaris. *J Am Med Assoc* 1969;210:2071-4¹¹ Fulton JE Jr, Plewig G, Kligman AM. Effect of chocolate on acne vulgaris. *J Am Med Assoc* 1969;210:2071-4¹² Magin P, Pnd D, Smith W, et al. A systematic review of the evidence for "myths and misconceptions" in acne management: diet, face-washing and sunlight. *Family Practice – an international journal;*2005(Jan 11):62-70¹³ Dreno B. Topical Antibacterial Therapy for Acne Vulgaris. *Drugs* 2004;64(21):2389-2397¹⁴ Krauthelm A and Gollnick HPM. Acne: Topical Treatment. *Clin Derm* 2004;22:398-407¹⁵ Zouboulis CC and Piqero-Martin J. Update and Future of Systemic Acne Treatment. *Derm.* 2003;206(1):37-53^{xvi} Krauthelm A and Gollnick HPM. Acne: Topical Treatment. *Clin Derm* 2004;22:398-407