Acne Therapy

Supplement to the Acne Drug Comparison Chart

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The RxFiles **Academic Detailing Program**
Saskatoon City Hospital
701 Queen Street, Saskatoon, SK S7K 0M7
www.RxFiles.ca

Key Messages, Tips and Pearls

1) **Acne drug therapies require consistent use for several weeks before optimal results are seen.**
2) **Topical therapies need to be applied to the entire affected area, not just specific lesions.**
3) **Benzoyl Peroxide (BP) is a very effective and relatively inexpensive acne therapy. Strengths greater than 5% are no more effective but more irritating than strengths ≤ 5%.**
4) **Topical retinoids are an effective first line option for comedonal acne.**
   a. **Tretinoin** (e.g. Retin-A, Stieva-A, Vitamin A Acid)**:**
      i. **0.025-0.05% products are most useful; lower concentrations do not work; higher concentrations are seldom tolerated**
   b. **Adapalene** (Differin) **may be preferred if:**
      i. **less skin irritation is important**
      ii. **part of a combination regimen where morning application of agent causing minimal sun sensitivity is important (e.g. BP+ABX at night, retinoid in am)**
5) **Topical antibiotic monotherapy should be avoided. Addition of BP to antibiotic regimens is strongly recommended to reduce bacterial resistance.** (Combo products useful: Benzamycin, BenzaClin / Clindoxyl)
6) **Oral antibiotics should be used for shorter "pulses" of therapy (e.g. 8-16 weeks) to reduce the development of bacterial resistance.**
7) **Any combination oral contraceptive (COC) may result in improvement in acne.**
8) **Oral isotretinoin** (Accutane, Clarus) **is the most effective therapeutic option for severe acne. Physicians should be familiar with cost effective dosing strategies, pregnancy precautions, required monitoring and side effect management.**
9) **Acne can cause significant stress, psychosocial concerns to the patient. Early intervention is recommended when presentation or family history suggests a severe course is likely.**
10) **Identification of sensitive skin issues is important so that steps can be taken to reduce drug related irritation {e.g. patients with non-oily skin, previous eczema or a history of sensitivity}.**

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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 and comedolysis.
  - BP is also a useful adjunct to topical retinoids, antibiotics (ABX) topical/oral, combination oral contraceptives (COCs) & spironolactone.
- Topical retinoids (e.g. tretinoin, adapalene) are important in acne treatment.[1] They affect the desquamation process, reducing the number of microcomedones & comedones.
  - Used for mild-moderate comedonal acne (inflammatory or non-inflammatory) or as adjunct with BP, ABX, COCs & spironolactone.
- Topical ABX are best used in combination with topical retinoids or BP (↓ potential for antimicrobial resistance).[1]
- Systemic ABX (tetracyclines, erythromycin, & trimethoprim) are indicated for moderate-severe acne. Due to resistance concerns monotherapy should be avoided and therapy courses limited where possible to short durations or "pulses" of 8-12 weeks.[2]
- COCs may be considered over antibiotics for females with moderate-severe acne. Spironolactone has been used for adult women with moderate-severe acne when COCs are contraindicated or other treatments fail.
- Isotretinoin monotherapy is the most effective therapy for moderate-severe inflammatory acne; care must be taken to ensure potential serious adverse events are avoided/recognized.
  - Isotretinoin causes a high rate of birth defects in the developing fetus of pregnant woman.
  - Depression & suicide have been reported in people taking isotretinoin; direct correlation not established.
- Other OTC agents: salicylic acid, sulphur, resorcinol, glycolic acid & tea tree oil (limited data; all less efficacious than BP).[1]
  {Tea tree oil 5%: 1 trial showed effectiveness but slow onset.[3]}

General Considerations for Topical Therapies

- If two topicals are being used, apply one qam & the other qhs
- Multiple agents are useful if from different therapeutic classes
- Potency: Solution > Gel > Cream / Lotion
- Patient skin type:
  - For very oily skin consider a solution or gel
  - For very dry skin choose a cream or a lotion (or add a moisturizer)

Topical Retinoids: Initiation Considerations

- Apply a thin layer to dry skin 30 minutes after gently cleansing. Rub in gently. {For creams and gels, medication should become invisible within a minute; if not, patient may be using too much.}
- Begin by applying only on every 3rd night, moving up to every 2nd night and eventually every night if tolerated.
- In some cases, a shorter application time may be useful.
- A non-comedogenic skin moisturizer (various e.g. Complex-15, Moisturel) may be applied in the morning to manage skin dryness.
- Sunscreen with SPF-15 or greater protection (e.g. Ombrelle) is important especially with tretinoin and tazarotene.

BP: Initiation Routines to Minimize Irritation

- Less frequent (every 2-3 night) application may be useful early in therapy; begin with low concentration [2.5%]; avoid more irritating formulations (e.g. acetone- & alcohol- based gels) unless skin is oily.
- Alternatively, 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 increased to 5%.
- Alternatively, BP can be applied for 2 hours for 4 nights, 4 hours for 4 nights, and then left on all night.

Managing Adverse Effects (Skin)

- Dryness can be managed with non-comedogenic moisturizers; avoid use of scrubs and astringents.
- If irritation occurs with tretinoin, switch to adapalene.
- If possible, ↓ the strength or contact time (topicals) initially to prevent further irritation, and gradually ↑ as tolerated.
- For sensitive skin: 2% clindamycin in Complex 15 Lotion or Cetaphil Cleanser qHS + 2.5% H_2O-based BP qAM.[4]

Facts for the Patient

- Stress may exacerbate psychological reaction to acne.
- It can take at least 8 weeks of a prescribed treatment before the patient sees any improvement. Acne may even get worse before it gets better. Focus on less new lesions.
- Wash the face no more than twice per day with a mild non-alkaline soap / soap-free cleanser & lukewarm water. Cleaning the skin too often may aggravate acne & cause flare ups. Acne is not caused by dirt or surface oil.
- 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.
- 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.

Acne Vulgaris Versus Acne Rosacea

- Acne rosacea is a chronic skin eruption with flushing and dilation of small blood vessels in the face, especially nose and cheeks. Its etiology differs significantly from acne vulgaris and should not be confused given the different approach to treatment (See Table 2).
- Effective treatments include topical metronidazole, benzoyl peroxide 5%/erythromycin 3% gel, benzoyl peroxide 5%/clindamycin 1% gel, benzoyl peroxide (BP) alone, azelaic acid, and sodium sulfacetamide10%/sulfur 5%. Oral tetracycline was effective by physician assessment, but not by patient assessment.[5]

Antibiotics (ABX): Considerations

- Using BP with topical ABX is strongly recommended to reduce the risk of bacterial resistance!
- Oral ABX are useful for more extensive/severe inflammatory acne; however, due to bacterial resistance concerns, shorter "pulse" courses may be preferred over longer-term maintenance therapy.
- Topical antibiotics are useful as follow-up to an oral ABX course.

COCs: Role in women with acne [6]

- 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 COCs have the official indication for acne tx?

- In Canada, Alesse, Tri-cyclen & Diane 35 have official indications for acne in the product monograph.
- Yasmin is as efficacious as Tri-cyclen[7] & Diane 35[8] for mild-moderate acne, but not officially indicated. {Yaz in the USA recently got acne FDA indication}
- All COCs are generally beneficial, likely due to estrogens effect on sex hormone binding globulin (SHBG) resulting in an antiandrogenic effect.[9,10] Limited and conflicting evidence does not support the superiority of one progestin over another.

Can Diane 35 be used as contraceptive?

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

Isotretinoin (Accutane, Clarus) Highlights[11]

- Official indications: severe nodular and/or inflammatory acne, acne conglobata & recalcitrant acne.
- Other considerations:
  - ♦ extensive acne involving face and trunk, associated with scarring; failure to respond to or inability to tolerate systemic antibiotics and/or hormonal therapy; family history
  - ♦ Significant psychological distress because of acne
- Due to common side effects, avoid concurrent acne topicals, vitamin A supplements, and follow-up topical retinoids for about 4 months

Diet

- There is anecdotal evidence that certain foods exacerbate acne[12]
- Chocolate – the evidence that chocolate is acnegeic had several methodological flaws[12]: small sample size[13]; treatment duration and follow-up not long enough to detect changes[14,15]; and high fat content of control bar may have been acnegenic[16]
- Advice regarding diet should be individualized.

Table 2: Acne Vulgaris vs Acne Rosacea

Acne variant	Comedones		Pustules	Papules	Nodules	Other distinguishing factors	Treatment Options
	Open	Closed					
Acne Vulgaris	X	X	X	X	X	Most: ages 12-24; may improve in sunshine; may affect chest & back	See RxFiles Acne Drug Comparison Chart at www.RxFiles.ca
Acne Rosacea			X	X	+/-	Ages 30-70; erythema, edema, telangiectasia, flushing, rhinophyma, ocular rosacea; head area	metronidazole topical, BP+/- Clinda gel, sulphur topical, isotretinoin if severe; other azelaic acid; tetracycline?

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

Possible Contributing Factors for 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 components in paint, varnishes, lacquers, fungicides, insecticides, herbicides, wood preservatives and 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 and make acne worse
- Emotions
  - Intense anger or stress can exacerbate acne, causing flares or increasing mechanical manipulation [16]
- Drugs (see also Acne Comparison Chart)
  - Hormones: androgenic hormones in women, corticosteroids, corticotrophin (ACTH), oral contraceptives high in progestin
  - Topical steroid induced perioral acne
  - Bromides, chlorides, halothane, iodides (e.g., Kelp)
  - Antiepileptic drugs: gabapentin, phenytoin, phenobarbital & trimethadione
  - Tuberculostatic drugs: ethambutol, isoniazid & thionamide
  - Miscellaneous: cyclosporine, cyanocobalamin, dantrolene, gold salts, lithium salts, maprotiline, psoralens, quinidine, quinine & topical coal tar
  - Select cancer drugs: cetuximab, erlotinib & gefitinib
- Family history (genetics) often provides prognostic clues

Table 1: Topical acne therapies and their associated activities[17,18,6]

Topical Therapy	Comedolytic activity	Sebosuppressive activity	Antimicrobial activity	Anti-inflammatory activity	Prevalence of resistant *P. acnes* strains
ERY	-	-	++	+	High
CLIN	-	-	++	+	High
TET not used	-	-	++	++	High
BP	+	-/+	+++	+	No
TRE	++	-	-	-	n/a
ADA	++	-	-	++	n/a
TAZ	++	-	-	-	n/a
(Ery or Cli) + BP	+	-	+++	++	Low
(Ery or Cli) + Tret	++	-	++	+	Low
(Ery or Cli) + Ada	++	-	++	++	Low

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

Table 3: Adverse drug reactions of topical agents in acne therapy [18]
{Removed from main text due to conflicting literature!}

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

- = none; + = weak; ++ = moderate; +++ = strong; ++++ = very strong

References – RxFiles Acne Newsletter

{for additional references – see those specific to RxFiles Acne Drug Comparison Chart}

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