The Prudent Prescriber

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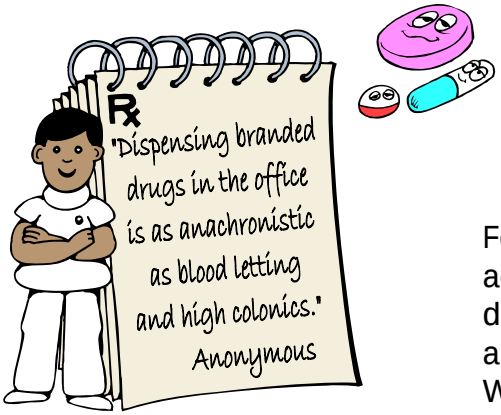

February 2017

Acne: A Guide to Cost-effective Management

Few adolescents, if any, have ever died of acne, but some of us may have developed a death wish when a huge golden pustule announced itself unexpectedly on our chins. With a typical course of 4-6+ years, some clinicians consider acne a chronic illness. This review will consider management of acne in that light.

Three of you faithful readers (about 30% of our CNN reported crowd size) have decried the increasing costs of acne treatment and asked for answers. This review is an attempt to provide guidelines for cost effective management of adolescent acne.

The First Acne Visit

The first clinical visit with an acne patient should include gaining an understanding of the patient's (and her parents') concept of the disease, the degree of psychosocial morbidity and the patient's personal preferences. (Minerva Pediatrica, August 2011)

Take home: The level of psychological suffering from acne is quite variable and often does not correspond to disease severity. (Minerva Pediatrica, August 2011)

CHF?

Think:
Ace
Aldactone
B-blocker
Dig
Diuretic

Avoid these expensive "me-too" drugs:

Intermezzo
Vimovo
Livalo
Pristiq
Viibyrd
Edarbi
Daliresp

Pharm Reps ≠ Rational Prescribing (PR) (RP)

Antibiotics do NOT help acute bronchitis

ß-blockers in post-MI save lives

Pill splitters save BIG

Need to ask: What has been tried in the past? What has worked? What has not worked? What is the patient's skin type? This helps determine the best drug vehicle. Is there evidence of scarring or post inflammatory hyperpigmentation? What is the current skin care regimen?

What is this going to cost? Office visits, over-the-counter meds? Prescription drugs?

Take home: As with other chronic conditions, it is extremely important to thoroughly explain the timing of the positive therapeutic effects and the side effects of the acne treatment prescribed.

Unrealistic expectations are the most common reason for poor adherence. It takes 4-8 weeks to demonstrate visible results from any acne treatment. Up to Date (referenced February 1, 2017) suggests that 2-3 months of consistent attendance to the therapeutic regimen is necessary prior to concluding that therapy is ineffective. Adolescents are impatient!

In one small study, it was found that non-adherence with acne treatment was 52% after three months. (Enhancing acne medication compliance: a comparison of strategies. Behav Res Ther 1985; 23(2):225–227)

Diet

There are some recent data (fair-poor quality) that high glycemic diets and dairy indigestion increase the risk for exacerbations of acne.

In general, dietary restrictions are not appropriate due to lack of convincing clinical data. (Minerva Pediatrica, August 2011)

Medications

Combination therapy with two active ingredients has been shown to hasten improvement of lesions, particularly early in the disease. (Minerva Pediatrica, August 2011)

Take home: Knowledge of the "invisible micro-comedo" helps patients understand why topical meds should be applied to the entire face.

All acne therapy primarily works by preventing outbreaks of NEW lesions. (Prescriber's Letter, August 2013)

Topical Medications

*** Benzoyl Peroxide(BENZOYL PEROXIDE) OTC**
Benzoyl peroxide is the most cost-efficient single substance for topical acne treatment. (Prescriber's Letter, August 2013)

Benzoyl Peroxide is the first line option in U.S., British and German acne guidelines. (Sao Paulo Med J 2013;131 (30:193-7))

Take home: Lower concentrations of benzoyl peroxide are less irritating and 2.5% has been found as effective as 10%. (Clin Exp Dermatol, 2009; 8: 657-61) If low dose Benzoyl Peroxide is irritating, go to every other day until the irritation resolves.

Benzoyl peroxide works faster with inflammatory lesions than topical retinoids. (Clin ExpDermatol, 2009; 8: 657-61.)

Benzoyl peroxide may bleach clothing, bedding and hair.

All retinoids except adapalene are unstable with benzoyl peroxide. They need to be applied separately.

Take Home: To decrease the risk of antibiotic resistance, topical benzoyl peroxide should always be included in the regimen when either topical or systemic antibiotics are prescribed. (AAD Guidelines for Acne, publ J Am Acad Dermatol May 2016)

*** Retinoids**

Mild non-infectious comedome acne may be treated with retinoid monotherapy. (BMJ May 8, 2013)

Topical retinoids are effective in reducing the number of comedones and inflammatory lesions by 40 to 70%. Higher concentrations work better, but are more irritating. (JAMA 2004; 292(6); 726-35.) Start with low concentrations.

Up to Date comments that retinoids should be a part of the regimen of most acne patients. Of the retinoid products on the market, adapalene works as well as tretinoin and is a little less irritating. Tazorac (tazarotene) is more effective than tretinoin or adapalene for acne, but is more irritating and is pregnancy category X.

Choose a formulation based on skin type: oily skin: use solutions or gels; dry skin: use creams.

Start with conservative dosing every other evening and increase to daily.

Differin (0.1% adapalene gel) OTC was almost as effective (48% reduction in total lesions counts) as prescription adapalene 0.3% gel (56% reduction) in a 12 week study of 653 acne patients. (Thiboutot et al J Am Acad Dermatol 2006;54: 242.)

Apply a moisturizer like CeraVe before retinoid to avoid skin irritation.

Apply tretinoins and adapalene at night. They are deactivated by sunlight.

Use a pea sized amount to cover the entire face! (Evidence-based Recommendations for the Diagnosis and Treatment of Pediatric Acne in Pediatrics volume 131, Supplement, May 2013) Patients often told me that this was not enough medicine, but taking that pea sized amount on an index finger and dotting it on the forehead, cheeks and chin and then rubbing it around **will** cover the whole face.

Retinoids are useful for maintenance therapy as they prevent development of micro-comedomes.

Take home: Skin irritation and actual acne flare are common with initiation of topical retinoid treatments, but typically improve in 8 to 12 weeks. Clinicians need to make patients and their parents aware of this phenomenon so as not to misinterpret flares and irritation as intolerance and discontinue the medication. (Minerva Pediatrica, August 2011)

***Topical Antibiotics**

Systematic reviews show that antibiotic efficacy decreases over time with both topical clindamycin and erythromycin. Not only P. acnes, but also Staph and Strep resistance may develop resistance. Limit topical antibiotics to 12 weeks. (BMJ May 8, 2013)

Take home: Clindamycin 1% solution or gel is currently the preferred topical antibiotic for acne therapy. Topical erythromycin in 2% concentration is available as a cream, gel, lotion or pledget, but has reduced efficacy in comparison with clindamycin because of resistance of cutaneous Staphylococci and P acnes. (J Am Acad Derm May 2016)

Avoid concurrent use of topical and oral antibiotics. (Clin Exp Dermatol 2011: 36: 840-3) Interestingly 2016 AAD Guidelines say that concomitant use of topical and oral antibiotics is OK.

Take home: Combination topical products: antibiotic/retinoids and antibiotics/benzoyl peroxide decrease antibiotic resistance and improve treatment outcomes through improved adherence. The biggest drawback is cost! (see Table 2). Individual generic products can be applied simultaneously with equivalent effects.

* Other topicals

Over the counter salicylic acid preparations are less effective then benzoyl peroxide. (Evidence-based Recommendations for the Diagnosis and Treatment of Pediatric Acne in Pediatrics volume 131, Supplement, May 2013) Salicyclic acid compounds may have a role in those unable to tolerate retinoids.

Topical dapsone is most effective against inflammatory lesions. In two randomized trials of dapsone 5% gel with a total of 3010 patients, the percent reduction of inflammatory lesions after 12 weeks of twice daily treatment was significantly greater in patients treated with topical dapsone than those treated with the vehicle (48% vs 42%) (Draelos et al J Am Acad Dermatol 2007; 56:439.e1) I am underwhelmed!

Topical tea tree oil has some antibacterial properties. There is minimal data to support its efficacy. Some patients become allergic to it. (www.aad.org/media/news-releases/dermatologists)

Systemic Meds

*Oral Antibiotics

Systemic antibiotics are effective for modest– severe acne. Although minocycline has been touted as the drug of choice, a Cochrane review showed no clear evidence of superiority of any antibiotic over others and minocycline has a greater potential for adverse events. (Gamer et al Cochrane Database Syst Rev 2012; :CD002086)

Take home: Doxycycline: all salts and formulations are equally effective at recommended doses. The low dose Oracea (40 mg) sells for $24.50 per capsule with no increase in efficacy and a modest decrease in gastric irritation. All doxycycline products may be taken with food or milk if G.I. irritation occurs. (Prescriber's Letter, August 2013)

Oral erythromycin and azithromycin are effective, but should be limited to those who cannot take tetracycline. There are limited data regarding the efficacy of penicillin, cephalosporins and trimethoprim sulfa. (J Am Acad Derm May 2016)

Take home: Try to limit systemic antibiotics to a course of three months. If repeated antibiotic courses are necessary, use antibiotics from the same class to prevent multidrug resistance. (Minerva Pediatrica, August 2011)

There is no consensus as to whether antibiotics should be tapered or stopped abruptly. (Up to Date, referenced Feb 2017)

* Isotretinoin

Isotretinoin targets all four components of the development of acne. It is prescribed as monotherapy. Usually involves a 16 – 24 week course starting with 0.5 -1mg/kg/day to a cumulative dose of 120 – 150 mg/kg. Patients need to be advised that they will see no positive effect for 1 to 2 months.

Oral isotretinoin is the most effective treatment for severe active. Its main obstacle is teratogenicity. Side effects also include dryness, paronychia, abnormal liver function tests, myalgias and questionably depression. It is difficult to sort out depression causation as suicidal ideation and depression are 2 to 3 times more frequent in patients with severe acne. (Minerva Pediatrica, August 2011)

A meta-analysis shows that half of patients are "permanently" cured after a single course of isotretinoin. Only 20% required repeat therapy. Relapse is most common in younger patients. (BMJ May 8, 2013)

Other oral meds

*** Oral contraceptives**

Oral contraceptives are very effective in reducing acne activity in severely affected women, particularly in those with involvement of the lower jaw and face when systemic antibiotics have failed.

The FDA has approved three oral contraceptives for use in acne:

- OrthoTriCyclen (norgestinate/ethinyl estradiol)
- EstroStep(norethindrone acetate/ethinyl estradiol)
- Yaz (drospirenone/ethinyl estradiol

Take home: A Cochrane review (Cochrane Database System Rev 2012; 7: CD004425) showed little difference in efficacy between different types of pills. Progesterone only contraception may worsen acne.

Combining oral contraceptives with antibiotics is fine with the exception of rifampin, where decreased contraceptive effect may occur. (Journal of the American Academy of Dermatology 2002; 4–6:917-123)

A Cochrane Database Systematic Review (209; (2): CD 000194) showed no benefit of spironolactone over placebo in treating acne.

Other Therapies

***Light therapy**

There is no significant high-quality evidence for the effectiveness of light therapy for acne.
(Cochrane Database Syst Rev 2016 Sept 27; 9:CD007917)

My Take:

I set out to find a singular, spectacular cost-effective way to treat acne and I failed. The keys to treating acne and most chronic illnesses more efficaciously are often a litany of tiny steps:

- Listen to what the patient is telling you about her illness and what her expectations are.
- Correct inappropriate expectations!
- Set optimistic, but realistic treatment goals.
- In follow-up, listen for evidence of wavering adherence.
- Change the treatment plan to fit with the patient's motivations.
- Be sure the patient knows to cover his entire face with medication.
- These meds are expensive. Use a pea-sized amount of medicine to cover the entire face. Convince the patient of this fact.
- Tune into selecting the appropriate topical vehicle. Oily skin: use solutions or gels; dry skin: use creams.
- Balance the trade-offs of seeing acne patients more frequently to improve adherence with the downsides of increased costs.
- Balance the use of combination products and their apparent increased inherence with their increased costs.
- The OTC benzoyl peroxide and adapalene products offer good value.
- If I were convinced that an expensive combination topical was the only way to go, I would check with GoodRx, call my favorite mom and pop pharmacy (not part of GoodRx and often the best game in town in Grand Junction) and then go straight to PharmacyChecker.com and buy Canadian! Safe, effective, half the price and free shipping!
- Finally, Do No Harm! I have included the now quickly outdating pregnancy category table for many of the medications that have been discussed. In spite of the iPledge program requiring two forms of contraception, approximately 120-150 women become pregnant in the US each year while taking isotretinoin. Among pregnant women exposed to isotretinoin, the risk of spontaneous abortion is approximately 20 percent; among pregnancies that progress, approximately 20 to 30 percent of neonates have evidence of embryopathy.

The AAD (American Academy of Dermatology) acne treatment guidelines (2016) are not unlike those of the ADA (American Diabetes Association) where a lack of high quality data makes treatment after benzoyl peroxide (acne) or metformin (diabetes) a smorgasbord of medications.

Table 1 AAD Acne Treatment Guidelines 2016

Severity of disease	Mild	Moderate	Severe
1st line treatment	benzoyl peroxide or topical retinoid or combo benzoyl peroxide & topical retinoid or topical antibiotics & topical retinoid or topical antibiotics and benzoyl peroxide or benzoyl peroxide & topical retinoid or topical antibiotics & benzoyl peroxide & topical retinoid	As with mild disease, all combinations of topical antibiotics & benzoyl peroxide & topical retinoid, plus add oral antibiotics	Oral antibiotics plus topical combo of topical antibiotics & benzoyl peroxide & topical retinoid or oral isotretinoin
Alternative treatment	consider alternative topical retinoid or consider topical dapsone	Consider changing oral antibiotic or add oral contraceptive or spironolactone or oral isotretinion	Consider changing oral antibiotic or add oral contraceptive or oral spironolactone

Table 2 Acne Medication Costs

drug(s)	strength/ quantity	Good Rx	Canadian pharmacies
benzoyl peroxide OTC	2.5% 8 oz	$18.97 Amazon	----
tretinoin gel	0.1% 60 gm	$66	$50
adapalene OTC Differin	0.1% 15gm	$13 Target	$55
clindamycin gel	1% 30 gm	$31	$ 21
clindamycin/benzoyl peroxide Benzaclin	1% / 5% 45 gm	$140	$66
erythromycin benzoyl peroxide	3% / 5% 46 gm	$81	$58
clindamycin/tretinoin Ziana, Veltim	1%/.025% 60gm	$253	$429
benzoyl peroxide/adapalene Epiduo	2.5%/0.1% 45 gm	$290	$100
doxycycline caps	100mg #100	$110	$38
OrthoTriCyclen	28tabs	$4	$32

Good Rx app consulted for Grand Junction, CO on February 6, 2017, least expensive pharmacy. Canadian pharmacies researched via PharmacyChecker.com on February 6, 2017, least expensive pharmacy, usually free delivery. All prices are US dollars.

Table 3 Old FDA Pregnancy labeling

Drug	Pregnancy category
topical tretinoin	C
topical adapalene	C
topical tazarotene	X
topical erythromycin	B
topical clindamycin	B
topical BP	C
topical dapsone	C
oral doxycycline	D
oral erythromycin, azithromycin	B
oral isotretinoin	X

A = Adequate, well controlled studies: no risk to fetus in 1st trimester or in later trimesters.

B = Animal studies have not demonstrated risk to fetus; no well controlled studies in humans.

C = Animal studies: adverse effect on fetus; no well controlled studies in humans, but potential benefits may warrant use.

D = Positive evidence of human fetal risk based on adverse data (marketing or studies in humans) but potential benefits may warrant use in pregnant women.

X = Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience. The risk involved in the use of these drugs in pregnant women clearly outweighs potential benefits.

The new FDA pregnancy labeling changed effective June 30, 2015. Over the next 18 months, the letter labeling will entirely disappear and be replaced with narrative sections to include data from pregnancy exposure registries, risk summaries, and clinical considerations.

For example, for the drug doxycycline, the new clinical summary for pregnancy is, ”avoid use during pregnancy; risk of permanent bone/teeth discoloration, enamel hypoplasia based on human data with tetracycline class; possible risk of embryo – fetal toxicity based on conflicting animal data with tetracycline class.”

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