First Line Acne Treatment: Comparison of Cost and Efficacy

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First-Line Acne Treatment:

Comparison of Cost and Efficacy

Michael P. McNeil

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Master of Science

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ABSTRACT

First-Line Acne Treatment: Comparison of Cost and Efficacy

Michael P. McNeil
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Acne vulgaris is a common skin concern that may cause permanent disfiguration and encumbering effects on self-esteem and mental health. Additionally, it is often associated with expensive treatment costs for patients. When selecting the most appropriate therapeutic approach, nurse practitioners must also consider the price of the medication. For the majority of mild to moderate cases of acne (both comedonal and inflammatory), effective first-line treatment recommendations include a combination of a topical retinoid, benzoyl peroxide, and a topical antibiotic such as clindamycin. Generic and compounded medications are typically more cost-effective for patients than brand name formulations.

Keywords: acne vulgaris, retinoids, benzoyl peroxide, clindamycin, cost-benefit analysis
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First-Line Acne Treatment: Comparison of Cost and Efficacy

Introduction

Acne vulgaris is the most common dermatological condition in the United States (U.S.) and affects approximately 50 million Americans each year (Bickers et al., 2006). Acne is characterized by inflammatory skin lesions, including open and closed comedones, papules, pustules, nodules, and cysts, all with varying degrees of severity and presentation (Zaenglein et al., 2016). Left untreated, acne may result in permanent scarring, post-inflammatory hyperpigmentation, or both (Tan et al., 2017). Acne may have debilitating effects on quality of life, self-esteem, and mental health (Sood et al., 2020). Therefore, early intervention by the nurse practitioner (NP) is essential to prevent short and long-term complications.

For most patients with inflammatory, comedonal, or combination acne, first-line treatment includes topical retinoids, benzoyl peroxide (BPO), and topical clindamycin in combination with BPO (Kolli et al., 2019; Thiboutot et al., 2018; Zaenglein et al., 2016). These topicals are highly effective agents, often resulting in a high degree of acne resolution, and should be promoted by providers. Research indicates, however, that dermatologists prescribe topical retinoids for only 58.8% of acne patients, while non-dermatologist providers prescribe topical retinoids in 32.4% of cases (Pena et al., 2016).

While vital to treatment, acne medications can be expensive and are often not fully covered by insurance. Indeed, the most common barrier to initiating acne treatment is cost (Ryskina et al., 2018). Beyond considering cost, NPs must also evaluate vehicles, efficacy, and tolerability of medications. The purposes of this paper are to assess evidence-based first-line topical medications for mild to moderate acne vulgaris and to provide comparisons of effectiveness and price.
Methods

CINAHL, MEDLINE, PubMed, Cochrane Library, Epocrates, and UpToDate were searched to identify studies related to first-line topical treatment of acne vulgaris using retinoids, BPO, and clindamycin. Additionally, government and professional organization websites, such as the American Academy of Dermatology and the U.S. Food and Drug Administration (FDA) were also reviewed. Search terms included acne vulgaris, treatment, topical retinoid, benzoyl peroxide, clindamycin, efficacy, cost, and price. Inclusion criteria were English language articles published between 2016 and 2021, however several seminal articles containing pertinent data were included. Articles that deviated from topical retinoids, BPO, clindamycin, or concentrated on alternative or novel therapies were excluded. Oral antibiotic therapies were not included in this paper due to concerns of antibiotic resistance when used long-term (Kircik, 2013; Thiboutot et al., 2018).

Prescription drug prices were evaluated using data from UpToDate. Data were also collected via phone from seven individual, private compounding pharmacies in each region of the U.S. to assess typical costs of non-branded compounded formulations that might not be listed online. Pharmacy prices were used in a range comparison. Pharmacies were also asked if their compounded formulas could be covered by insurance, or if they were cash price only.

Costs of over-the-counter (OTC) products (adapalene 0.1% and BPO) were identified from websites of three large and popular national drugstore chains: CVS, Walgreens, and Walmart. The three competing prices were used to determine the average price per gram of product and then rounded to the nearest hundredth. Exact products and brands were used to compare costs between retailers (see Table 1).
Results

Topical Retinoids

Retinoids are Vitamin A derivatives that act on two of the four key pathogenic factors in the development of acne by (a) normalizing follicular hyperkeratinization and (b) blocking inflammatory pathways. The other two contributing factors include (c) hyperproduction of sebum and (d) microbial colonization of *Cutibacterium acnes* (*C. acnes*), formerly referred to as *Propionibacterium acnes* (Kraft & Freiman, 2011; Latter et al., 2019). Each retinoid binds to a distinctive set of retinoic acid receptors (RAR): alpha, beta, and gamma; thus presenting minor differences in its mechanism, tolerability, and efficacy (Zaenglein et al., 2016).

The U.S. FDA currently approves four topical retinoids: adapalene, tretinoin, tazarotene, and trifarotene. Although each is well-studied in acne treatment, limited head-to-head studies compare these medications. For example, Kakita (2000) suggests that tazarotene is more effective than tretinoin and adapalene, while Shalita et al. (1996) support the efficacy of adapalene over tretinoin. However, drug concentrations and vehicles used in studies varied greatly and complicated comparison. Due to the limitations in the current literature, there is insufficient evidence to conclude the absolute efficacy of one retinoid over another (Zaenglein et al., 2016).

Topical retinoids may be sufficient monotherapy in treating acne vulgaris, particularly in comedonal acne (Zaenglein et al., 2016). In cases where inflammatory pustules are present, retinoids are most efficacious when combined with a potent antimicrobial agent, such as BPO. Combination therapy of a retinoid with BPO is especially preferred over the monotherapy use of topical or oral antibiotics due to the risk of developing antibiotic resistance (Kolli et al., 2019). In contrast, there has been no published evidence of antimicrobial resistance occurring with the use
of BPO (Yang et al., 2020). Additionally, improved acne outcomes result when the concentration of individual retinoids increases (Pariser et al., 2005). The choice of retinoid molecule prescribed is less important than selecting an appropriate concentration of the retinoid and then combining it with an antimicrobial vehicle (Kolli et al., 2019).

**Adapalene**

Adapalene is a third-generation retinoid that targets beta and gamma-Retinoic acid receptors (RARs) (Zaenglein et al., 2016). In 1996, the FDA approved this molecule for acne treatment in patients 12 years and older. In 2016, 0.1% adapalene gel (Differin®) became FDA approved OTC use for acne and is currently the only topical retinoid available without a prescription (Tolaymat & Zito, 2020). However, vehicles containing a 0.3% concentration still require a prescription.

Adapalene may yield enhanced treatment compliance in patients due to its decreased potential for skin irritation and dryness. Data suggest that adapalene is the most well-tolerated retinoid compared to tretinoin and tazarotene (Kolli et al., 2019). Adapalene gel 0.1% is highly cost-effective due to its OTC availability, with an average price below $0.62 per gram. However, its higher concentration at 0.3% is 10 times the cost in generic form at $6.60 per gram, with the 0.3% brand name (Differin®) at $14.64 per gram (see Table 1).

**Tretinoin**

Tretinoin is a first-generation retinoid (all-trans-retinoic acid) that binds to alpha, beta, and gamma-RAR and was approved by the FDA in 1971 (Zaenglein et al., 2016). It is not only the first retinoid molecule developed, but it is also the most well-studied and has the most formulations available. Generic and brand (Retin-A®) cream formulations range from $4.75 to
$8.35 per gram, while generic and brand (Retin-A®, Atralin®) gel preparations range from $5.32 to $15.00 per gram, respectively (see Table 1).

Generic and compound formulations of tretinoin are more cost-effective than brands, but side effects often involve erythema, peeling, and irritation, thus contributing to reduced patient compliance. Newer formulations, such as Altreno® and Retin-A Micro®, include technologically advanced delivery systems that include micronization and encapsulation. These formulations improve photostability, optimize topical application and spreadability on the skin surface, and decrease irritation and dryness (Latter et al., 2019). Altreno® and Retin-A Micro® have a much higher cost than their generic counterparts, from $3.00 up to $21.96 per gram, respectively (see Table 1). These formulations are also much less likely to be covered by insurance than generic tretinoin.

**Tazarotene**

Tazarotene is a third-generation retinoid that binds selectively to beta and gamma-RAR (Zaenglein et al., 2016). This retinoid molecule has only been approved in the U.S. to treat acne vulgaris (Kassir et al., 2020). Tazarotene cream and gel vehicles are currently available at 0.05% and 0.1% strengths in brands Tazorac®, Avage®, and generic formulations. Drug costs vary from $12.99 per gram for generic cream to $18.87 per gram for brand-name cream and gels (see Table 1).

Tazarotene, like other retinoids, can produce treatment-related adverse events such as erythema, pruritis, burning, and scaling (Kassir et al., 2020). Novel vehicles such as a 0.1% foam, Fabior® and more recently, a lotion formulation, Arazlo® at 0.045%, were developed to provide enhanced efficacy and skin spreadability. Increased patient compliance may also be seen due to fewer side effects (Tanghetti et al., 2020; Smith et al., 2016). Respective costs average
$14.84 and $12.72 per gram (see Table 1). Although expensive, these medications may cost less than the potentially more irritating other brand-name creams and gels.

**Trifarotene**

Trifarotene (Aklief®) is the newest retinoid molecule approved in over 20 years for the treatment of acne and is the first retinoid to be FDA approved for truncal acne (Bell et al., 2021). Approved in October 2019, it is a fourth-generation retinoid potent in its affinity for the gamma-retinoic acid receptor only (Kassir et al., 2020). While safe and effective for acne treatment, future clinical studies to compare effectiveness and tolerability to existing retinoids are warranted (Bell et al., 2021). As there is currently no generic formulation available, trifarotene is more expensive than other retinoids, with an average cost of $16.26 per gram (see Table 1). Its high cost may be a barrier to patient access and use.

**Benzoyl Peroxide**

BPO is an oxidizing agent and bactericidal against *C. acnes*. It is lipophilic, allowing it to penetrate the pilosebaceous follicle, where it releases free radicals and oxidizes bacterial proteins. BPO also promotes comedolytic and anti-inflammatory properties in the skin (Dutil, 2010). It significantly reduces the amount of *C. acnes* in as little as two days (Bojar et al., 1995). Due to its direct toxicity to *C. acnes*, bacterial resistance to BPO has not been reported (Yang et al., 2020), which permits BPO to be used long-term in acne management.

BPO is available in OTC vehicles such as gels, creams, and cleansers. It can also be found in several fixed combination vehicles alongside other medications for synergistic effects. Concentrations of BPO range from 2.5% to 10%. Mills et al. (1986) reported that BPO of lower concentrations (2.5-5%) showed a similar reduction in lesion count but with fewer occurrences of dermatologic side effects, including erythema, peeling, and irritation. However, BPO may
cause bleaching when in contact with clothing, fabrics, and hair (Zaenglein et al., 2016). To avoid this side effect, it is recommended that patients use white towels and bed linens and avoid contact with any fabric until the product has thoroughly dried. Any contact with hair, facial hair, and eyebrows should also be avoided.

Water-based vehicles of BPO are designed to be less irritating to the skin (Fyrand & Jakobsen, 1986). Leave-on BPO products come in creams, lotions, and gels. Brands such as Neutrogena®, PanOxyl®, Cerave®, and Differin® have BPO cleanser formulations ranging from strengths 3.5 to 5%, with an average cost ranging from $1.80 to $3.08 per ounce. Neutrogena® also has two BPO cream products at 2.5% strengths. One cream product is marketed as a spot treatment, while the other is a micronized formulation. These cost $9.58 and $5.58 per ounce, respectively. The brand Clean & Clear® offers a Persa-Gel® 10 product, a BPO gel at 10%, widely available in most drugstores. Its average price is $6.52 per ounce. CVS, Walgreens, and Walmart and their respective generic brands each have a 10% BPO gel with an average cost of $4.35 per ounce (see Table 1).

**Clindamycin**

Clindamycin is a lincosamide antibiotic used topically at a 1% concentration to treat inflammatory acne. Its mechanism of action involves accumulation in follicles and contains both anti-inflammatory and antibacterial properties (Zaenglein et al., 2016). It can be prescribed in singular vehicles or fixed-combination formulas. Unlike retinoids and BPO, clindamycin is typically well-tolerated (Wolf et al., 2003). Clindamycin should not be used as monotherapy, but rather in concert with BPO to minimize the risk of antibiotic resistance and assist in maintaining clindamycin’s potency against *C. acnes* (Jackson et al., 2010). Generic versions of clindamycin...
are affordable. The topical solution formulation has an average price between $0.33-$1.36 per milliliter, and the gel formulation costs as low as $1.80 per gram (see Table 1).

**Fixed Combinations**

BPO and adapalene can be found together in fixed-combination vehicles. EpiDuo®, which combines 2.5% BPO and 0.1% adapalene, has an average cost of $10.99 per gram. Its generic counterpart costs between $2.67 and $9.89 per gram. EpiDuo Forte®, which contains 2.5% BPO with a higher percentage of adapalene (0.3%), comes at a higher price point of $16.26 per gram (see Table 1). However, it should also be noted, that a more cost-effective option would be to use these two active ingredients in separate products, but at the same time.

Clindamycin and BPO may also be prescribed in fixed-dose formulas. Because clindamycin needs to be used in combination with BPO, fixed combinations of the two medications are more convenient for patient use. Generic formulations can be found for as little as $3.12 to as high as $12.03 per gram, while the brand Onexton® costs an average of $15.98 per gram (see Table 1). These two medications may also be purchased individually and used in separate vehicles, at significantly less cost.

**Discussion and Implications for Practice**

Clinical treatment of mild acne vulgaris starts with a proper diagnosis and by ruling out other potential medical conditions (rosacea, polycystic ovarian syndrome, folliculitis, etc.) via physical examination and thorough history. The decision on which topical medication(s) should be prescribed along with dosing, frequency, and application can vary depending on the cost of the medication, the potential to enhance compliance, availability, and shelf-life.
Cost

The most cost-effective ways to obtain clindamycin, BPO, or a retinoid are stand-alone prescriptions. Insurances are more likely to cover non-compounded formulations. If a patient’s insurance does not cover a medication, coupons from GoodRx.com are free, accessible to all, and highly recommended for additional savings on generic and brand formulas. For example, a GoodRx coupon on generic tretinoin 0.05% cream yielded a savings of 61%, bringing the cost from $2.91 per gram to $1.13 per gram (Tretinoin Prices and Tretinoin Coupons - GoodRx, 2022.)

Combination formulations with either BPO, clindamycin and/or a retinoid are typically more expensive. But price difference may be worth it to patients who feel they are better able to adhere to their regimen with a fixed-combination formula.

Compliance

In addition to considering costs, NPs should assess a patient’s motivation to follow a consistent skincare routine. Some patients may be willing to apply topical medications in both the morning and evening. This type of patient would be an excellent candidate for having their medications prescribed in separate vehicles, which is typically more cost-effective. Alternatively, fixed-combination topical medications, which are typically more expensive, can increase compliance and ease of use, as some patients may only be willing to apply topical medications once a day.

Compliance is also highly related to tolerability. Any addition of drying medications such as BPO and/or retinoids should be accompanied by a moisturizing agent, preferably free from fragrance or dyes. Knowing additional prescription and/or OTC medications a patient is currently using will be helpful in reducing potential irritation and adverse effects.
Availability

Both brand name and generic acne medications are widely available throughout the U.S. However, the availability of specific brands and manufacturers' coupons vary from pharmacy to pharmacy. Allowing substitutions between similar formulations (such as 1% clindamycin gel vs. 0.75% clindamycin lotion) may allow greater availability between regions or pharmacies.

Shelf-life

While not extensively studied, many providers feel that brand-name drugs such as EpiDuo® and Onexton® have a longer shelf-life due to their packaging and preservatives when compared to their generic compounded equivalents (C. Platt, personal communication, January 10, 2022). Shelf-life may be a factor for patients who use their medication infrequently.

Limitations

Similarly to all clinically-focused articles, there were limitations. When addressing the pricing of medications, pricing can easily change based on product demand and supply from pharmacy to pharmacy. The out-of-pocket cost after insurance and incentive programs can change quickly. While general recommendations are given, NPs must assess the individual patient’s needs. Skin sensitivity and acne type may affect specific recommendations.

Furthermore, this review was limited in that it excluded treatment types beyond topical first-line acne treatments for mild to moderate acne. Our investigation did not include a comprehensive list of prices using different insurance plans across the U.S. However, the inquiry into cash prices of both individual medications and compounded formulas across different U.S. regions gives providers a practical guide to cost-effective topical acne treatments.
Treatment Recommendations

For mild comedonal or inflammatory acne cases, adapalene 0.1% gel is recommended as the initial retinoid of choice. Adapalene is effective, affordable, accessible without a prescription, and is considered the least irritating retinoid available (Kolli et al., 2019). In cases where a patient does not respond to adapalene after 3 months, or in cases of more moderate acne, a different retinoid or adapalene 0.3% may be prescribed (see Figure 1). Utilizing generic or compounded formulations of these medications is recommended, as they tend to be more cost-effective but equivalent in efficacy to brand names.

BPO is recommended for inflammatory and pustular types of acne in both mild and moderate cases (see Figure 1). BPO may also be used in comedonal types of acne, as it promotes mild comedolytic effects (Zaenglein et al., 2016). A significant amount of literature supports the efficacy of leave-on BPO products as opposed to BPO washes. However, leave-on BPO is more likely to cause skin irritation (Yang et al., 2020). It is recommended to use lowest concentration of BPO products (2.5-5%) possible, as increased concentrations are more irritating and are not more effective at reducing lesions (Mills et al., 1986). Generic, leave-on BPO products are the most cost-effective per ounce (see Table 1). BPO products are widely available OTC.

Topical clindamycin is recommended for both mild and moderate types of inflammatory acne (see Figure 1). Clindamycin should always be given alongside a BPO product to reduce the risk of bacterial resistance (Jackson et al., 2010). Clindamycin is typically the most affordable when prescribed as a separate vehicle, as opposed to a fixed-dose formulation alongside BPO.

Conclusion
Acne is the most common skin disease in the U.S., but therapeutics are often costly to the patient which may delay treatment. NPs should be informed about practical and cost-effective drug therapy options. When prescribing medication(s), careful consideration of the drug, cost, patient compliance, drug availability, and shelf-life should be carefully appraised. Depending on the type and severity of acne, a combination of a topical retinoid, a BPO product, and topical clindamycin is recommended for first-line treatment. Generic medications are often the most cost-effective. Because all NPs will undoubtedly encounter patients with acne, they must be knowledgeable of treatment options and cost factors, thus enhancing patient outcomes and lives.
References


https://www.statpearls.com/ArticleLibrary/viewarticle/919


 group=price_page_refresh_1_5&slug=tretinoin&form=tube-of-cream&dosage=45g-of 0.05%25&quantity=1&label_override=tretinoin


Appendix A

Figure 1

_Treatment Algorithm for Mild to Moderate Acne_
Table 1

*Cost Comparison of First-Line Acne Treatments*

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name or Generic</th>
<th>Vehicle</th>
<th>Strength (%)</th>
<th>Average Cost/Gram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tretinoin</td>
<td>Generic</td>
<td>Cream</td>
<td>0.025, 0.05, 0.1</td>
<td>$5.02-$6.38, $5.63-$7.15, $6.57-$8.35</td>
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<tr>
<td>Retin-A</td>
<td>Cream</td>
<td>0.025, 0.05, 0.1</td>
<td>$4.75</td>
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</tr>
<tr>
<td>Retin-A</td>
<td>Gel</td>
<td>0.01, 0.025, 0.05</td>
<td>$5.32-$6.75, $5.36-$6.81, $7.50-$9.52</td>
<td></td>
</tr>
<tr>
<td>Retin-A</td>
<td>Gel</td>
<td>0.01, 0.025</td>
<td>$6.33</td>
<td></td>
</tr>
<tr>
<td>Atralin</td>
<td></td>
<td>Gel</td>
<td>0.05</td>
<td>$15.00</td>
</tr>
<tr>
<td>Compounded</td>
<td>Cream, Gel</td>
<td>0.05-0.1</td>
<td></td>
<td>$0.95-$3.33</td>
</tr>
<tr>
<td>Tretinoin Microsphere</td>
<td>Generic</td>
<td>Gel pump</td>
<td>0.04, 0.1</td>
<td>$5.00</td>
</tr>
<tr>
<td>Retin-A Micro</td>
<td>Gel pump</td>
<td>0.04, 0.06, 0.08, 0.1</td>
<td>$21.96, $21.87, $21.87, $21.96</td>
<td></td>
</tr>
<tr>
<td>Altreno</td>
<td>Lotion</td>
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<td></td>
<td>$3.00</td>
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<td>Generic (OTC)</td>
<td>Gel</td>
<td>0.1</td>
<td>$0.37</td>
</tr>
<tr>
<td>Differen (OTC)</td>
<td>Gel, Gel pump</td>
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<td>$0.62, $0.71</td>
<td></td>
</tr>
<tr>
<td>Generic</td>
<td>Gel</td>
<td>0.3</td>
<td>$6.60-$6.88</td>
<td></td>
</tr>
<tr>
<td>Differin</td>
<td>Gel</td>
<td>0.3</td>
<td>$14.64</td>
<td></td>
</tr>
<tr>
<td>Adapalene/Benzoyl Peroxide</td>
<td>Generic</td>
<td>Gel pump</td>
<td>0.1/2.5</td>
<td>$2.67-$9.89</td>
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<td>Epiduo</td>
<td>Gel pump</td>
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<td>$10.99</td>
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</tr>
<tr>
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<td>Gel pump</td>
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<td>$16.26</td>
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<td>Foam</td>
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<td>Cream pump</td>
<td>0.005</td>
<td>$16.26</td>
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<td>Trade Name or Generic</td>
<td>Vehicle</td>
<td>Strength (%)</td>
<td>Average Cost/Gram</td>
</tr>
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<td>Generic</td>
<td>Topical solution</td>
<td>1</td>
<td>$0.33-$1.36 (per mL)</td>
</tr>
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<td>$1.80-$3.46</td>
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<td>Gel</td>
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<td>$3.12-$9.85</td>
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<td>$4.80-$12.03</td>
<td></td>
</tr>
<tr>
<td>Onexon</td>
<td>Gel pump</td>
<td>1.2/2.5</td>
<td>$15.98</td>
<td></td>
</tr>
<tr>
<td>Generic Name</td>
<td>Brand and Product Name</td>
<td>Vehicle</td>
<td>Strength (%)</td>
<td>Average Cost/Ounce</td>
</tr>
<tr>
<td>Benzoyl Peroxide</td>
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<td>Cleanser</td>
<td>3.5</td>
<td>$1.80</td>
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<td>Benzoyl Peroxide</td>
<td>PanOxyl Creamy Wash</td>
<td>Cleanser</td>
<td>4</td>
<td>$1.89</td>
</tr>
<tr>
<td>Benzoyl Peroxide</td>
<td>Cerave Acne Foaming Cream</td>
<td>Cleanser</td>
<td>4</td>
<td>$2.56</td>
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<tr>
<td>Benzoyl Peroxide</td>
<td>Differin Daily Deep</td>
<td>Cleanser</td>
<td>5</td>
<td>$3.08</td>
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<tr>
<td>Benzoyl Peroxide</td>
<td>Neutrogena On-The-Spot</td>
<td>Cream</td>
<td>2.5</td>
<td>$9.58</td>
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<td>Benzoyl Peroxide</td>
<td>Neutrogena Stubborn Acne</td>
<td>Cream (Micronized)</td>
<td>2.5</td>
<td>$5.58</td>
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<tr>
<td>Clean&amp;Clear Persa-Gel</td>
<td>Gel</td>
<td>10</td>
<td>$6.52</td>
<td></td>
</tr>
<tr>
<td>CVS/Walgreens/Equate BPO</td>
<td>Gel</td>
<td>10</td>
<td>$4.35</td>
<td></td>
</tr>
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