Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Treatment of Acne vulgaris***

-January 2020-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) reviewed the medical management of acne vulgaris at their January 2020 meeting. This review included topical therapies (retinoids, antibiotics, bactericidal and other anti-comedonal or anti-inflammatory agents) and oral therapies (antibiotics, isotretinoin, oral contraceptives, antiandrogens). Topical clindamycin, topical tretinoin, spironolactone, and combined estrogen-containing oral contraceptives are currently on the IHS National Core Formulary (NCF). Following clinical review, pharmacoeconomic evaluation and internal deliberation, the NPTC voted to **ADD (1.) benzoyl peroxide (any topical formulation)** and **REPLACE** topical clindamycin with **(2.) combination clindamycin and benzoyl peroxide gel** to the NCF.

Discussion:

Acne is the most common skin disorder in the United States (US), affecting 40-50 million persons of all ages. It can have significant sequelae from physical scarring, persistent hyperpigmentation, and psychological issues. Small studies focused on acne among American Indian/Alaska Native (AI/AN) populations suggest that the prevalence of acne is similar to other racial/ethnic groups in the US, but that the sequelae of scarring is significantly higher (55% in AI/AN vs. 3% among US white populations) and access to specialty care services is disproportionately low[1]. Acne is a chronic inflammatory disease of the pilosebaceous unit involving increased sebum production by sebaceous glands, hyperkeratinization of the follicle, colonization of the follicle by *Propionobacterium acnes*, and an inflammatory reaction. Acne is manifested with both non-inflammatory (open and closed comedones) and inflammatory lesions (papules, pustules, and nodules). Inflammatory acne is graded as mild, moderate, or severe based on the frequency of the various inflammatory lesions. The goals of treatment are to reduce inflammation, the number of lesions, scarring, and psychological sequelae.

Treatment of acne involves the use of various topical medications (prescription and OTC), oral therapies, and a multitude of physical agents/procedures and complementary/alternative therapies which are outside the scope of this review. Guidelines from the American Academy of Dermatology were updated in 2016 and serve as the major recommendations for current approaches to the treatment of acne in the US[2]. The following chart summarizes the 1st line and alternative treatment recommendations:

	Mild	Moderate	Severe
1st Line Treatment	Benzoyl Peroxide (BP) or Topical Retinoid **-or-** Topical Combination Therapy BP + Antibiotic *or* Retinoid + BP *or* Retinoid+ BP + Antibiotic	Topical Combination Therapy BP + Antibiotic *or* Retinoid + BP *or* Retinoid + BP + Antibiotic **-or-** Oral Antibiotic + Topical Retinoid + BP **-or-** Oral Antibiotic + Topical Retinoid + BP + Topical Antibiotic	Oral Antibiotic + Topical Combination Therapy BP + Antibiotic *or* Retinoid + BP *or* Retinoid + BP + Antibiotic **-or-** Oral Isotretinoin
Alternative Treatment	Add Topical Retinoid or BP (if not on already) **-or-** Consider Alternate Retinoid **-or-** Consider Topical Dapsone	Consider Alternate Combination Therapy **-or-** Consider Change in Oral Antibiotic **-or-** Add Combined Oral Contraceptive or Oral Spironolactone (Females) **-or-** Consider Oral Isotretinoin	Consider Change in Oral Antibiotic **-or-** Add Combined Oral Contraceptive *or* Oral Spironolactone (Females) **-or-** Consider Oral Isotretinoin

Topical Retinoids: Topical retinoids are vitamin A derivatives that variably bind to retinoic acid receptors, preventing the formation and reducing the number of comedomes, as well as providing an anti-inflammatory effect. Their main role is monotherapy for non-inflammatory acne or combined with

antibiotics (oral or topical) for the various severities of inflammatory acne. They also have utility in maintenance after initial goals of therapy are met. There are three agents in this class: adapalene, tazarotene, and tretinoin. Each is available in varying strengths, formulations, and some in combination products with other topical acne treatments. Tazarotene has limited evidence that it is more effective than the other two agents, whereas adapalene is better tolerated. All of these agents can cause localized skin reactions, especially during initial use, and all cause increased sun sensitivity.

Topical Antibiotics: Topical antibiotics reduce colonization of the pilosebaceous units with anaerobic bacteria (*P. acnes*) and reduce inflammation. They have a role in the treatment of mild to moderate inflammatory acne, especially in combination with topical retinoids. The two main agents used in acne are clindamycin and erythromycin, also available in varying strengths, formulations, and in combination products with other topical acne treatments. Both topical and oral antibiotics are not recommended for monotherapy due to the risk associated with antibiotic resistance. Antibiotic use in the treatment of acne has been associated with a shift in antibiotic resistance in *P. acnes* from 20% in 1978 to ~ 66% in 2016[3,4]. Antibiotic use in acne has been associated with changes to normal skin flora, including increased Gram-negative bacterial overgrowth in nares and overgrowth of *Streptococcus pyogenes* and *Staphylococcus aureus* in the oral pharynx. Additionally, there is an increased incidence of antibiotic-resistant bacteria seen in family members of patients treated with antibiotics for acne. The use of these agents together with benzoyl peroxide reduces the risk for the development of antibiotic resistance.

Other topical agents:
Azelaic acid- This agent exhibits mixed comedolytic, antimicrobial, and anti-inflammatory effects, primarily being used in mild to moderate inflammatory or mixed acne. As it can be associated with hypopigmentation, this can be a good option for patients with dyspigmentation associated with their acne.

Benzoyl Peroxide (BP)- BP is a bactericidal agent that functions through the release of free radicals. No formulation of this OTC product has been found to be superior. Unlike antibiotics, this agent is not associated with the development of bacterial resistance. It is used for the treatment of mild to moderate mixed acne in combination with topical retinoids, or added to regimens including topical or oral antibiotics to reduce resistance.

Dapsone- Although this is an antibiotic, it appears to improve acne by reducing inflammation. This agent is minimally more effective than placebo in reducing inflammatory and non-inflammatory lesions. When co-applied with BP, dapsone may oxidize, causing an orange-brown coloration to skin that can be brushed or washed off.

Oral Antibiotics: Various oral antibiotics have been used in the treatment of acne, including tetracyclines (tetracycline, doxycycline, minocycline), macrolides (erythromycin, azithromycin) and sulfa agents (trimethoprim/sulfamethoxazole). Dosing regiments vary, but typically involve taking agents twice daily. This off-label use is effective for the treatment of moderate to severe inflammatory acne, with tetracyclines (primarily doxycycline or minocycline) considered first-line. Monotherapy with oral antibiotics is discouraged due to the risk for antibiotic resistance (see above). As such, these agents should be used in combination with benzoyl peroxide. Guidelines recommend limiting therapy to 3 months, and/or switching to topical retinoids for maintenance after goals are met.

Oral Isotretinoin: Isotretinoin is FDA-approved for treatment of severe, recalcitrant acne, though it also has a role in treating less severe, treatment-resistant acne. Like the topical retinoids, it is a vitamin A derivative and has similar mechanisms of action. Dosing typically starts at 0.5 mg/kg/day for 1 month, then 1.0 mg/kg/day to complete 20 weeks or a cumulative dose of 120-150 mg/kg. Total cumulative doses of <120 mg/kg are associated with increased risk for relapse and >150 mg/kg are associated with increased adverse effects without greater treatment benefits. Moderate acne may respond to lower doses (0.25-0.4 mg/kg/day). Patients should have baseline and monthly monitoring of fasting lipids and transaminase levels. Of note, CBC monitoring is no longer recommended.

A 2018 Cochrane systematic review evaluated 31 randomized control trials of isotretinoin compared to placebo or other acne treatments. Three studies (400 participants) showed no evidence that isotretinoin decreases trial investigator-assessed inflammatory lesion counts more than antibiotics (Relative Risk [RR] 1.01, 95% confidence interval [CI]: 0.96 to 1.06). However, isotretinoin did improve acne severity as assessed by physician's global evaluation (RR 1.15, 95% CI: 1.00 to 1.32; 351 participants; 2 studies) but

resulted in more adverse effects such as dry lips/skin, cheilitis, vomiting, and nausea (RR 1.67, 95% CI: 1.42 to 1.98; 351 participants; 2 studies)[5].

Previously, concerns were raised about the potential for isotretinoin to increase depression/suicidality, especially among teens. A 2017 systematic review and meta-analysis evaluated 31 studies where depression scales were collected for patients treated with isotretinoin. In the controlled studies, the change in depression scores from baseline was not significantly different between patients receiving isotretinoin treatment and those receiving an alternative treatment (standardized mean difference [SMD] -0.33, 95% CI: -0.68 to 0.01). The prevalence of depression after isotretinoin significantly declined (RR 0.59, 95% CI: 0.38 to 0.90) and the mean depression scores significantly decreased from baseline (SMD -0.34, 95% CI: -0.50 to -0.17). The authors concluded that isotretinoin treatment for acne does not appear to be associated with an increased risk for depression and that the treatment of acne appears to ameliorate depressive symptoms[6].

Because of the significant teratogenic effects of isotretinoin, physicians, distributors, pharmacies, and patients are required to register in iPLEDGE, a program established to prevent pregnancy in patients taking isotretinoin. In addition to frequent pregnancy testing and counseling, women of childbearing potential must commit to using two forms of effective contraception simultaneously. The iPLEDGE program has not resulted in a significant decrease in fetal exposure to isotretinoin, with ~150 isotretinoin-exposed pregnancies in US each year[7]. Nearly 1/3 of women participating in iPLEDGE admitted noncompliance with pregnancy prevention requirements (29% did not comply with use of condoms when agreed to as one method and 39% missed ≥1 contraceptive pill in last month)[8]. This emphasizes the importance of long-acting reversible contraceptives as an option for women using isotretinoin.

Oral contraceptives: Combined oral contraceptive pills (OCPs) prevent acne through several mechanisms that reduce androgen impacts on acne. There are four FDA-approved, branded contraceptives for the treatment of acne: Estrostep Fe®, OrthoTri-Cyclen®, Yaz®, and Beyaz®. All include a low-to-moderate dose of ethinyl estradiol combined with various progestins. There is insufficient evidence to recommend approved agents over other estrogen-containing OCPs. A 2012 Cochrane review of 9 trials showed no consistent differences in the efficacy of OCPs[9]. Additionally, meta-analyses comparing OCPs to antibiotics show no significant differences in acne improvement[9,10]. This makes OCPs a potential preferred option for women of child-bearing age with acne who also desire contraception.

Spironolactone: Spironolactone is an aldosterone receptor antagonist which decreases testosterone production by competitively inhibiting binding of testosterone and dihydrotestosterone to androgen receptors in the skin. It is considered a second or third-line agent in acne treatment or alternative to isotretinoin. Side effects include risk for severe hyperkalemia and potential feminization of male fetuses.

Findings:

In summary, topical retinoids are first-line therapy for non-inflammatory and mild to moderate inflammatory acne. Topical or systemic antibiotics are first-line therapy used in combination with topical retinoids for moderate and severe acne, but should be used in combination with BP to reduce the development of antibiotic resistance. Oral isotretinoin is useful in severe and treatment-resistant acne, but needs to be carefully monitored and utilized by clinicians skilled in its use. Other agents (OCPs, spironolactone, topical dapsone or adapalene) may have a role in certain specific patient populations.

References:

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