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Antibiotic Use in *Acne vulgaris*: Pharmacological Perspectives and Emerging Resistance - A Brief Review

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ABSTRACT

Acne vulgaris (AV) is a chronic inflammatory skin condition that frequently affects adolescents and young adults. It is characterized by comedones, papules, pustules, and nodules. The primary etiological factors include hyperkeratinization, excessive sebum production, colonization of *Cutibacterium acnes* (*C. acnes*), and an inflammatory immune response. This review discusses the pharmacological aspects and challenges associated with the use of antibiotics in AV treatment, particularly in the context of rising antibiotics resistance. This mini-review was conducted using data collected from online academic databases, including Google Scholar, ScienceDirect, and PubMed. From an initial pool of 60 articles related to AV treatment,antibiotic mechanism, and resistance patterns, 31 publications (1999 – 2024) were selected based on relevance and quality. Results: The pathophysiology of AV is multifactorial, involving sebaceous hyperactivity, follicular hyperkeratinization, microbial colonization, and immune-mediated inflammation. Topical drugs (e.q., tetracyclines) remain central in AV management. However, increased antibiotic resistance, especially by C. acnes has compromised their efficacy. Combining antibiotics with agents like benzoyl peroxide (BPO) or topical retinoids may help mitigate resistance. Alternative treatments, including isotretinoin, hormonal therapies, and physical modalities, provide additional therapeutic options. Antibiotic use in AV treatment requires careful pharmacological consideration, balancing efficacy, safety, cost, and resistance risk. To preserve long-term effectiveness, antibiotics should be combined with non-antibiotic agents and used for limited durations. Tailoring treatment based on disease severity, location, and patient preference is essential for optimal outcomes.

Keyword: *Acne Vulgaris*, Antibiotic Therapy, Pharmacological Consideration, Antibiotic Resistance, *Cutibacterium acnes*, Isotretinoin, Acne Management

ABSTRAK

Acne vulgaris (AV) adalah kondisi kulit inflamasi kronis yang sering menyerang remaja dan dewasa muda. Penyakit ini ditandai dengan adanya komedo, papul, pustul, dan nodul. Faktor etiologi utama meliputi hiperkeratinisasi, produksi sebum berlebih, kolonisasi Cutibacterium acnes (C. acnes), serta respons imun inflamasi. Ulasan ini membahas aspek farmakologis dan tantangan penggunaan antibiotik dalam terapi AV, khususnya terkait meningkatnya resistensi antibiotik. Mini-review ini dilakukan dengan menggunakan data yang dikumpulkan dari basis data akademik daring, termasuk Google Scholar, ScienceDirect, dan PubMed. Dari 60 artikel awal yang terkait dengan terapi AV, mekanisme antibiotik, dan pola resistensi, sebanyak 31 publikasi (1999–2024) dipilih berdasarkan relevansi dan kualitas. Patofisiologi AV bersifat multifaktorial, mencakup hiperaktivitas sebasea, hiperkeratinisasi folikular, kolonisasi mikroba, dan inflamasi yang dimediasi imun. Antibiotik topikal (misalnya tetrasiklin) masih menjadi terapi utama dalam penatalaksanaan AV. Namun, meningkatnya resistensi antibiotik, terutama oleh C. acnes, telah menurunkan efektivitasnya. Kombinasi antibiotik

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dengan agen seperti benzoil peroksida (BPO) atau retinoid topikal dapat membantu mengurangi resistensi. Terapi alternatif, termasuk isotretinoin, terapi hormonal, dan modalitas fisik, juga memberikan pilihan tambahan. Penggunaan antibiotik dalam terapi AV memerlukan pertimbangan farmakologis yang cermat, dengan menyeimbangkan efektivitas, keamanan, biaya, dan risiko resistensi. Untuk menjaga efektivitas jangka panjang, antibiotik sebaiknya dikombinasikan dengan agen non-antibiotik dan digunakan dalam durasi terbatas. Penyesuaian terapi berdasarkan tingkat keparahan penyakit, lokasi, dan preferensi pasien sangat penting untuk mencapai hasil optimal.
Kata kunci: *Acne vulgaris, Terapi Antibiotik, Pertimbangan Farmakologis, Resistensi Antibiotik, Cutibacterium acnes, Isotretinoin, Manajemen Jerawat.*

1. Introduction

Acne vulgaris (AV) is a common, chronic inflammatory skin disorder that affects the pilosebaceous units (hair follicles and sebaceous glands), particularly among adolescents and young adults. It is characterized by skin lesions such as comedones, papules, pustules, and cysts [1]. The pathogenesis of AV is multifactorial, involving follicular hyperkeratinization, increased sebum production, colonization by *Cutibacterium acnes* (formerly known as *Propionibacterium acnes* (*P. acnes*)), and an inflammatory immune response [2]. Globally, AV ranks as the eighth most prevalent disease, affecting over 640 million people [3]. Although not life-threatening, it can cause significant physical and psychological distress, including anxiety, low self-esteem, and, in severe cases, suicidal ideation [4]. Around 20% of severe AV cases result in permanent scarring. In Indonesia, AV is a major dermatological concern, with prevalence rates reaching 87.5% [5]. The complex pathophysiology of AV involves four primary processes: (1) abnormal keratinization influenced by androgens leading to comedone formation; (2) hyperactivity of sebaceous glands under hormonal stimulation; (3) bacterial colonization by species such as *Staphylococcus epidermidis*, *Propionic acnes*, and lipid-dependent yeasts like *Pityrosporum*; and (4) inflammation mediated by the host immune [6-9]. Effective management requires targeting all four of these mechanisms [10].

Topical and systemic antibiotics are commonly used in AV treatment. However, growing resistance—especially among *P. acnes*—has reduced their efficacy, with over 50% of cases showing antibiotic resistance [11]. Consequently, combination therapies that include benzoyl peroxide (BPO) and topical retinoids are now recommended over monotherapy to reduce resistance development. Additional treatments include hormonal therapies, oral isotretinoin, laser and phototherapy, and lifestyle modifications. Patient-centered care and shared decision-making are crucial, taking into account severity, patient preferences, cost, and treatment risks [12]. This review aims to explore the role of antibiotic therapy in acne management, evaluate the efficacy and safety of commonly used antibiotics, and examine current challenges, particularly antibiotic resistance, in acne treatment.

2. Methods

This narrative review is based on a comprehensive literature search conducted through online databases including Google Scholar, ScienceDirect, PubMed, and supporting academic journals such as the British Journal of Dermatology, The Journal of the American Medical Association, The Lancet, and Microbiology Journal. Keywords used in the search included: “acne vulgaris,” “management of acne vulgaris,” “acne therapy,” “antibiotic resistance,” “clindamycin,” and “mechanism of antibiotic action.” An initial search yielded 60 articles. After screening for relevance, duplication, and quality, 34 journals were selected for final inclusion. These sources span from 1999 to 2024, providing both historical context and the latest advancements in AV treatment.

3. Result and Discussion

Pathogenesis of *Acne Vulgaris*

Several interconnected factors contribute to the development of AV:

a. **Hyperkeratinization.** Androgens disrupt the skin barrier, stimulating epidermal DNA synthesis and cell proliferation, leading to follicular plugging (Mohiuddin, 2019).
b. **Sebum Production.** Sebum Overproduction: Hormonal regulators—such as CRH, estrogen, GH, androgens, IGF-1, and ACTH play a significant role. Androgens and progesterone in particular are associated with increased sebaceous gland activity (Gollnick, 2015; Cong et al., 2019).

c. Bacterial Colonization. *P. acnes* thrive in oxygen-deprived, lipid-rich environments like clogged sebaceous follicles. It stimulates lipogenesis and intensifies sebum production via CRH pathways [13]. Anaerobic environments with high lipid content make P. acnes easy to grow.

d. Inflammation. *P. acnes* induced an immune response through Toll-like receptors (TLRs), protease-activated receptors (PARs), and antimicrobial peptides. This activates macrophages and keratinocytes to release inflammatory cytokines (e.g., IL-1, IL-6, IL-8, TNF-α), leading to neutrophil infiltration, oxidative stress, and tissue damage [14-16].

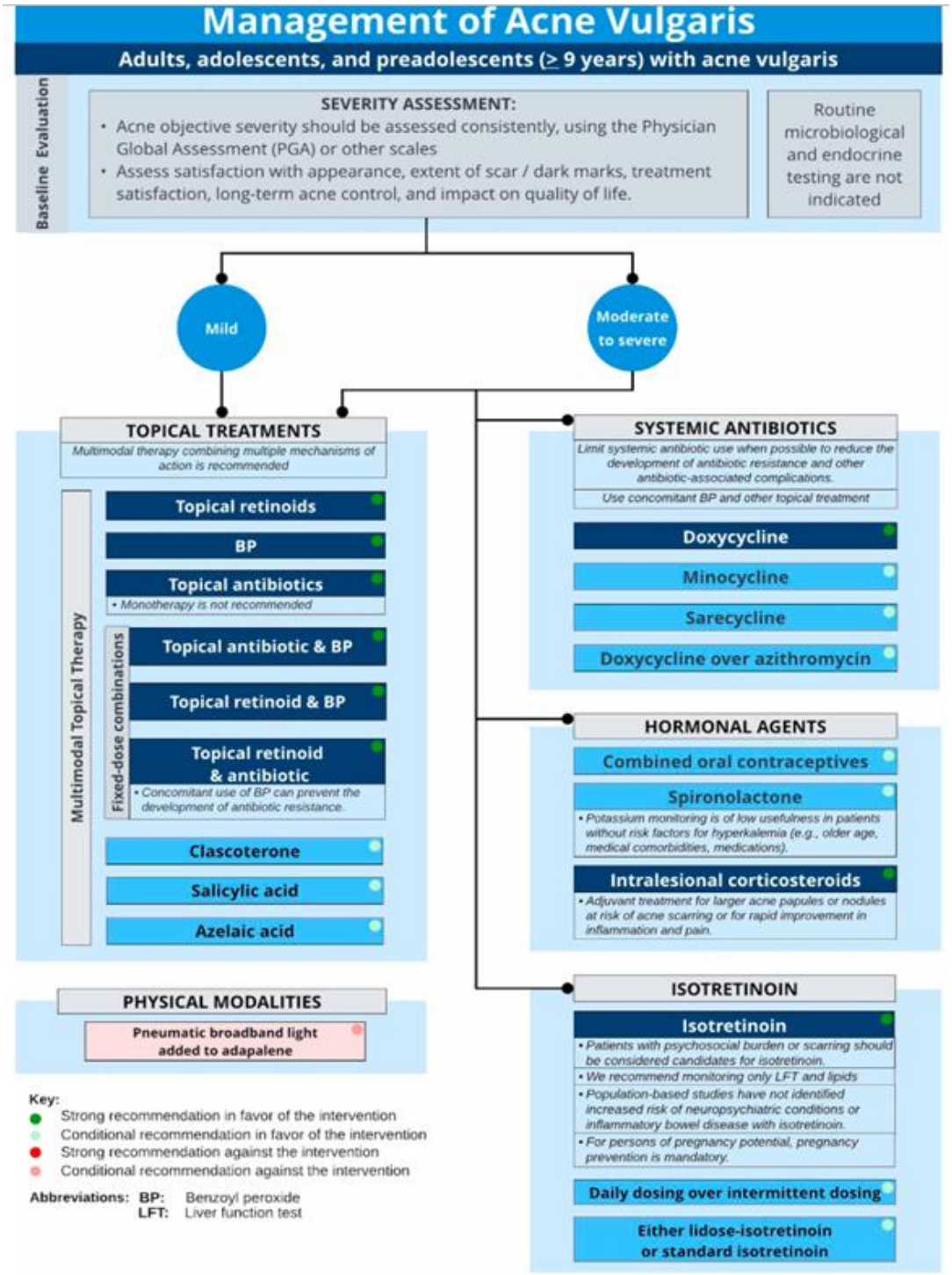

Figure 1. *Acne Vulgaris* Treatment (Reynolds *et al.*, 2024)

Topical antibiotics are used for milder cases that don't respond to standard topical treatments, while oral antibiotics are typically prescribed for moderate-to-severe forms of inflammatory acne.

e. Topical Antibiotics

Topical antibiotics are employed to treat acne of mild to moderate severity [17]. Topical antibiotics are antibiotics that have been manufactured into a cream or an ointment or gel, and can be applied directly to the skin. Antibiotics are medicines that destroy or inhibit the growth of susceptible bacteria. Antibiotics directed against *P. acnes* have remained the key approach in managing acne vulgaris over the last four decades. The most commonly prescribed antibiotics are macrolides, clindamycin, and tetracyclines [18]. Topical antibiotics, such as erythromycin, clindamycin, and minocycline, help treat acne by exerting antibacterial and anti-inflammatory effects [19]. Topical antibiotics work by possessing antibacterial and anti-inflammatory properties, and they accumulate in the follicles. Topical antibiotics applied as monotherapy in the treatment of AV are not recommended due to antibiotic resistance [20]. Thus, monotherapy with topical antibiotics should be restricted to 12 weeks and must be used alongside benzoyl peroxide, zinc, or retinoids to prevent the onset of bacterial resistance [17].

One percent of Clindamycin in solution or gel is currently the primary topical antibiotic for AV treatment, and 2% of erythromycin is available topically in cream, lotion, or gel forms; its effectiveness has declined compared to topical clindamycin due to resistance of *P. acnes* and *Staphylococcus aureus*. Antibiotics that will be stable and remain available are combinations of topical acne treatments, often involving fixed-dose combinations like erythromycin 3% combined with BPO 5%, clindamycin 1% combined with BPO 5%, or clindamycin 1% combined with BPO 3.75%. This formulation can improve alignment with the treatment regimen [20].

f. Oral Antibiotic

Oral systemic therapy involves using antibiotics to treat *P. acnes* bacteria and inflammation for moderate to severe acne [20-24]. Commonly used antibiotic choices include tetracycline antibiotics (doxycycline, minocycline, sarecycline) and macrolide antibiotics (erythromycin, clindamycin, azithromycin). Tetracyclines are still the mainstay of acne vulgaris treatment [21, 25-26]. Tetracyclines are widely used due to their proven efficacy and cost-effectiveness. Doxycycline and minocycline are the antibiotics of choice [23]. These antibiotics are favored for their better gastrointestinal tolerability and higher lipid solubility, and can penetrate the pilosebaceous follicle with greater efficiency. The onset of resistance in *P. acnes* and *Staphylococcus epidermidis* to erythromycin restricts its effectiveness in treatment [21]. *P. acnes* bacteria have also been reported to be resistant to clindamycin [18, 21]. As a result of the considerable increase in the resistance among the strains of *P. acnes* against erythromycin and clindamycin makes the sole application of these antibiotics should be avoided [18]. Tetracycline resistance has been reported to be lower than macrolides [20].

The mechanism of action of antibiotics is by blocking the proliferation of *P. acnes* and the release of mediators of inflammation produced by *P. acnes*. Antibiotic treatment success is determined by its potential to reach lipids within the pilosebaceous units of the dermis, which are known to be the area where *P. acnes* colonizes [20]. The utilization of systemic antibiotics should be confined to the shortest possible period, usually for a period not exceeding 3-4 months, as advised by international guidelines. Tetracycline antibiotics are contraindicated in pregnancy, breastfeeding, or children under 9 years of age during all phases of tooth development, prolonged exposure can lead to lasting tooth enamel damage or tooth staining [23].

Anti-Inflammatory Effects of Antibiotics

The anti-inflammatory properties of tetracyclines inhibit neutrophil chemotaxis and *matrix metalloproteinases* (MMPs) and downregulate inflammatory mediators [23]. Clindamycin also decreases pro-inflammatory cytokines [24].

Mechanism of Action of Antibiotics on *P. acnes* Bacteria

Inhibiting Bacterial Growth: Tetracycline antibiotics prevent protein synthesis in bacteria by attaching to the 30S portion of the ribosome, thereby blocking incorporation of tRNA molecules charged with amino acids [25]. Clindamycin stops the growth of gram-positive anaerobic bacteria mainly by preventing protein translation by targeting the 50S ribosomal component of *P. acnes*, thereby preventing translocation of peptide tRNA and formation of peptide bonds in the *P. acnes* ribosome [24]. Trimethoprim sulfamethoxazole (TMP/SMX) is another treatment option for acne. Sulfamethoxazole works by inhibiting bacterial folic acid synthesis, a process necessary for cell division, making it bacteriostatic. Trimethoprim functions as a folic acid analogue, blocking the action of the enzyme dihydrofolate reductase. Both agents function synergistically to prevent the formation of nucleotides and amino acids in bacteria. A blinded clinical study demonstrates that trimethoprim-sulfamethoxazole is equally efficacious as oxytetracycline [23].

Antibiotic Resistance in *P. acnes* Infections

Propionibacterium acnes resistance to antibiotics was initially identified in the United States in 1979; after that, resistant strains have been documented globally, and there is also a tendency to become more resistant to antibiotics [26]. According to research conducted by Moon et al. (2012), based on acne patients in Korea, P. acne isolates significantly showed erythromycin (26.7%) and clindamycin (30%) showed increased resistance when compared to the other antibiotics tested. The same trend was found in many countries worldwide. Variations in the 23S rRNA contribute to cross-resistance between erythromycin and clindamycin in *P. acnes*. The application of Clindamycin in South Korea was first available as an over-the-counter medication. Approved in 2001, this drug has been utilized as a topical antibiotic to treat acne vulgaris (AV). AV patients who use them carelessly can develop high resistance, and recently they have switched to prescription topical antibiotics [26].

Topical and systemic antibiotics like clindamycin and doxycycline have been effective in targeting *C. acnes*. However, resistance is a growing concern. Overuse and monotherapy practices have led to decreased antibiotic efficacy, making resistant strains more common [27]. To combat this, international guidelines recommend combination therapy, particularly using BPO alongside antibiotics to reduce resistance. Prolonged antibiotic treatment should always be paired with BPO, and monotherapy with antibiotics should be avoided.

Considerations for Antibiotic Use in Acne Vulgaris Patients to Avoid Resistance Formation

The President's Council for Science and Technology Advisors, established in 2014, in the United States recommended three ways to handle the growing concerns about antibiotic resistance: more effective control over the use of antibiotic, enhanced monitoring of antibiotic-resistant pathogens, combined with the progress in advanced antibiotics development [28]. *P. acnes* resistance may affect the prolonged treatment of AV using antibiotics. While much research is needed to comprehend the study of resistance patterns and the clinical significance of resistant strains, physicians do not wait to change their approach to treating acne vulgaris with antibiotics until the situation becomes urgent [28]. Four components should always be considered when determining the appropriate antimicrobial therapy: efficacy, safety, cost, and resistance.

The following seven-point checklist is created to assist in prescribing antibiotics that reduce the selection and transmission of resistant strains of *P. acnes*. (1) Apply antibiotics only when required, (2) Limit oral antibiotics to 6 months and topical therapy to 3 months, (3) use the same antibiotic if further treatment is needed (unless its efficacy has been lost), (4) adhere to antibiotic regimens, (5) do not use antibiotics as monotherapy, (6) educate patients not to self-administer topical or oral therapy when experiencing acne vulgaris, (7) emphasize the importance of good patient compliance and ensure that patients receive adequate advice on how to use and take their medications correctly [29].

Alternative and Adjunct Treatments

Antibiotics are especially effective when combined with other acne oral medications or topical treatments with different mechanisms of action, including: retinoids, benzoyl peroxide, isotretinoin, and oral contraceptives. Current treatments extend beyond antibiotics:

a. Topical Retinoids

Topical retinoids are vitamin A-related substances [23, 26-28]. Topical retinoids treat mild to moderate acne vulgaris (Leung et al., 2021; Reynolds et al., 2024). Topical retinoids reduce comedones and inflammation, improve pigmentation irregularities, and aid in the maintenance of AV scars. The results of placebo-controlled, double-blind, randomized trials support the implementation of this drug as a treatment for AV. Retinoids work by restoring the process of exfoliation of dead skin cells to run normally and in balance by reducing the proliferation of keratin cells (keratinocytes), encouraging differentiation, replacement of follicular epithelium and anti-inflammatory by blocking the inflammatory pathway of Toll Like Receptor, the movement of leukocytes and the activation of the AP-1 signaling pathway [29-32]. Three active topical retinoid-based agents are commercially on hand: tazarotene (0.05%, 0.1% in topical cream, gel, or foam), tretinoin (0.025%, 0.1% in cream and gel), and adapalene (0.1% in cream, 0.1%, 0.3% in gel, and 0.1% in lotion). Randomized studies have shown that monotherapy with topical retinoids markedly decreases the number of inflammatory skin lesions, accompanied by comparable effects on non-inflammatory lesions [30]. Tretinoin, the primary retinoid applied in the management of AV, successfully cleared mild to moderate levels of comedonal and inflammatory AV. The most irritating topical retinoid is tazarotene. Adapalene is better tolerated and does not cause significant irritation. In this recent comprehensive review, Jacobs et al. (2014) indicated the combination of BPO and adapalene are both effective in a fast-acting response (defined by the

duration needed to achieve, or a reduction of up to 25%, in the typical count of inflammatory lesions, in comparison with other retinoid compounds, including tretinoin and topical isotretinoin). Side effects and efficacy of retinoids vary by dose. In many cases, local side effects such as peeling, erythema, dry skin, burning, and itching appear in the first few weeks of treatment and then disappear. It is strongly recommended to use sunscreen daily because ultraviolet light can increase these effects. Irritation can be minimized by decreasing the number of treatments and beginning with a lower dose [28].

b. Benzoyl Peroxide (BPO)

BPO is an oxidizing compound with bactericidal properties against *P. acnes* [27]. BPO eliminates *P. acnes* by releasing free oxygen and has mild inflammatory-modulating and comedo-reducing activity. BPO does not lead to resistance, and adding BPO to antibiotic therapy regimens improves outcomes and may reduce the development of resistance. BPO is provided as a facial cleanser in foam, cream, or gel form. The concentration level of the treatment ranges between 2.5% and 10% [23, 25]. The effectiveness of BPO is constrained by its concentration and formulation, which depend on side effects such as burning, stinging, dry skin, redness, pain, peeling, and irritation. Lower concentrations of BPO formulations in water-based solutions and rinse-off are generally better tolerated [23]. Resistance occurs against P. acnes, which is generally observed during treatment with topical antibiotics alone, but no P. acnes resistance to BPO has been noted [23, 27]. BPO directly has toxicity against P. acnes, which can prevent the synthesis of bacterial proteins and nucleotides, alter metabolic pathways, and inhibit mitochondrial function. This mechanism enables BPO to function as a prolonged therapy for acne vulgaris, either on its own or combined with topical antibiotics, without the risk of inducing bacterial resistance [23, 25].

c. Hormonal Therapy

The Food and Drug Administration gave its first approval to Combination Oral Contraceptive Pills (COCs) for contraceptive use in the U.S. in 1960. COCs contain a combination of estrogen and progestin [23]. COCs prevent ovulation and pregnancy by suppressing the hormonal secretion of GnRH, FSH, and LH. Additionally, they treat acne vulgaris (AV) by inhibiting ovarian androgen production, increasing sex hormone-binding globulin (SHBG), and thus lowering free testosterone levels, which reduces activation of androgen receptors. COCs work by inhibiting 5α-reductase activity and blocking the interaction of androgens with their receptors, which determine how they work in the treatment of AV [23, 33]. Physicians should explain to patients that acne treatment with COCs typically takes 3–6 months for resolution, and they might evaluate the early integration of COCs with other therapies to hasten the treatment process. It is essential to assess the medical history and blood pressure levels before initiating COCs [23]. Given the numerous benefits, risks, and diverse patient preferences, patient-centered contraceptive counseling is essential, ensuring that decisions about initiating or discontinuing contraceptive methods are based on the patient's values, preferences, and personal experiences [34].

d. Systemic Isotretinoin (oral)

13-cis-retinoic acid systemic, as isotretinoin, has been authorized by the FDA for treating severe cases, refractory suffering from nodular-type AV since 1982. Though the exact mechanism of action is not yet fully understood, sebaceous gland size and secretion may be reduced by isotretinoin, indirectly reduce surface and follicular levels of sebum-dependent *P. acnes*, inhibit these agents, regulate keratinocyte keratinization to block comedogenesis, and provide anti-inflammatory benefits [31]. Potential side effects, including cardiovascular risks, ossification, tissue scarring, and bacterial colonization by S. aureus, were highlighted in the 2016 acne vulgaris protocols. The Society for Dermatologic Surgery in the United States expert consensus determined that whole-facial dermabrasion, rotary device-based mechanical dermabrasion, and laser skin ablation treatments of the whole facial and non-facial areas are discouraged within 6 months following the use of isotretinoin due to the elevated risk of side effects [33]. There is insufficient evidence to compare low- and high-dose Isotretinoin regimens, the treatment may consist of isotretinoin combined with systemic antibiotics, optionally with topical treatments, or isotretinoin as a monotherapy [23].

Alternative Therapies

Alternative therapies studied include botanicals and vitamins. There is insufficient evidence to develop recommendations for acne treatment with green tea, witch hazel, tea tree oil, oral pantothenic acid, oral or topical zinc, and niacinamide [23].

a. Physical Treatment Options

Physical treatment options encompass acne lesion removal, chemical peel treatments, lasers, light therapies, microneedling, radiofrequency, and phototherapy. Nevertheless, the existing evidence is inadequate to form guidelines for physical intervention in managing AV [23].

b. Diet

Existing evidence suggests that a low-glycemic diet has no significant impact on managing acne vulgaris. Recommendations to treat AV with omega-3 fatty acids, chocolate, low-dairy, and low-whey diets are also not sufficiently supported [23].

Table 1. *Acne Vulgaris* management approach [35].

	Mild	**Moderate**	**Severe**
Primary Treatment	Benzoyl peroxide (BPO)/retinoid topical -or- Topical combined therapy**BPO+antibiotic/retinoid+BPO/retinoid+BPO+antibiotic	Topical combined treatment** BPO+antibiotic/retinoid+BPO+ antibiotic -or- Oral antibiotic + topical retinoid+ BPO -or- Oral antibiotic+ topical retinoid+BPO+ topical antibiotic	Antibiotic oral + topical combined treatment** BPO+antibiotic/retinoid +BPO/retinoid+BPO+antibiotic -or- Oral Isotretinoin
Alternative Treatment	Addition of topical retinoid/BPO (if not already used) -or- Consider retinoid alternatives -atau- Consider topical *dapsone*	Consider combination therapy alternatives -or- Evaluate switching oral antibiotics -or- The addition of combined oral contraceptives /oral spironolactone (for women) -or- Oral isotretinoin considerations	Considerations for changes in oral antibiotics -or- Oral contraceptive/oral spironolactone (for women) -or- Consider isotretinoin

Note: **Drugs can be prescribed in Fixed Combination Products or as separate components.

4. Conclusion

Acne vulgaris is a prevalent dermatological condition with complex pathogenesis involving hormonal, microbial, and immune-mediated mechanisms. While antibiotics both topical and systemic have long been cornerstones of treatment, growing antimicrobial resistance necessitates a shift toward combination therapies and antibiotic stewardship. Incorporating agents like benzoyl peroxide, retinoids, and hormonal treatments, along with non-pharmacological options, can improve outcomes and minimize resistance risks. Ultimately, acne treatment should be personalized, weighing clinical effectiveness, side effects, patient expectations, and long-term sustainability.

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