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Advances in the Treatment of Acne Vulgaris: A Comprehensive Review of Current and Emerging Therapies

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Abstract
Background: Acne vulgaris is a common chronic inflammatory skin disorder affecting individuals of all ages, with a significant impact on quality of life. It results from increased sebum production, follicular hyperkeratinization, Cutibacterium acnes proliferation, and an inflammatory response. Despite the availability of numerous treatments, acne management remains challenging due to antibiotic resistance, patient adherence issues, and variable treatment responses. Emerging therapies, including biologics, androgen receptor inhibitors, and microbiome-targeted treatments, offer new possibilities for improving outcomes.
Objective: This narrative review provides a comprehensive evaluation of current and emerging acne treatments, including topical and systemic therapies, adjunctive procedures, and investigational approaches. Special considerations, such as acne in pregnancy, skin of color, and refractory cases, are also addressed.
Methods: A literature review was conducted, analyzing clinical studies, systematic reviews, and advancements in acne treatment. The review discusses the efficacy, safety, and limitations of topical retinoids, benzoyl peroxide, antibiotics, hormonal agents, isotretinoin, biologics, and novel interventions.
Conclusion: While existing therapies are effective, antibiotic resistance and treatment variability necessitate ongoing research. Personalized medicine, integrating genetic and microbiome-based approaches, may revolutionize acne treatment, optimizing outcomes and minimizing adverse effects.
Keywords: Acne vulgaris, topical retinoids, antibiotic resistance, androgen receptor inhibitors, biologics, JAK inhibitors, microbiome therapy, isotretinoin.

Introduction

Acne vulgaris is one of the most prevalent dermatological conditions worldwide, affecting individuals across various age groups, ethnicities, and geographic locations. Although it is commonly perceived as a transient issue of adolescence, acne can persist into adulthood, significantly affecting self-esteem and psychological well-being. The pathogenesis of acne is multifactorial, involving excess sebum production, follicular hyperkeratinization, microbial colonization by Cutibacterium acnes (formerly Propionibacterium acnes), and inflammation. [1]

Despite the availability of a wide range of treatment modalities, acne management remains challenging due to factors such as antibiotic resistance, patient adherence issues, and the varying response to treatments based on individual skin types. The continuous evolution of therapeutic options, including topical and systemic agents, light-based therapies, and emerging biologics, underscores the need for an updated and comprehensive review of available treatments. This article aims to provide a thorough discussion of the current and emerging treatment strategies for acne vulgaris, addressing their efficacy, safety profiles, and limitations. [2]

❖ Definition and Pathophysiology of Acne Vulgaris

Acne vulgaris is a multifactorial inflammatory disease of the pilosebaceous unit, predominantly affecting the face, back, and chest. It is primarily driven by four key pathogenic processes: sebaceous gland hyperactivity, abnormal keratinization leading to follicular plugging, colonization by Cutibacterium acnes (formerly Propionibacterium acnes), and an inflammatory immune response. Sebaceous glands, under the influence of androgens, produce excessive sebum, which combines with keratinocytes to form a microcomedone, the precursor to all acne lesions. [3] When these microcomedones enlarge and become clogged, they form open (blackheads) and closed (whiteheads) comedones. C. acnes, a commensal bacterium of the skin, thrives in the lipid-rich environment of blocked follicles, promoting inflammation through the activation of Toll-like receptors and the release of pro-inflammatory cytokines. This inflammation contributes to the development of papules, pustules, nodules, and cysts, which can lead to post-inflammatory hyperpigmentation and scarring. Hormonal fluctuations, particularly during puberty, menstruation, and conditions such as polycystic ovarian syndrome (PCOS), exacerbate acne severity by increasing androgen-driven sebum production. Other contributing factors include diet, stress, and the use of occlusive cosmetics. Understanding these underlying mechanisms is crucial for designing targeted and effective treatments. [4]

❖ Epidemiology and Impact on Quality of Life

Acne vulgaris is one of the most prevalent dermatological conditions worldwide, affecting approximately 85% of adolescents and young adults between the ages of 12 and 24 years. Although traditionally viewed as a disease of puberty, acne can persist into adulthood, with around 40% of adults, particularly women, experiencing acne beyond their teenage years. [1]

The prevalence varies across ethnicities and geographic regions, with environmental factors, genetics, and dietary habits influencing disease onset and severity. While acne is often self-limiting, it can have profound psychosocial implications. Studies have shown that individuals with acne are more likely to experience emotional distress, social withdrawal, and lower self-esteem, leading to an increased risk of depression and anxiety disorders. [5]

The stigma associated with acne can affect professional and personal interactions, particularly in individuals with severe or treatment-resistant cases. Moreover, post-inflammatory hyperpigmentation and scarring can have lasting effects, emphasizing the importance of early and effective treatment. Given the significant burden of acne on mental health and quality of life, a holistic approach to management, addressing both physical symptoms and psychological well-being, is essential. [6]

❖ Treatment Goals and Challenges

The primary goals of acne treatment are to reduce lesion count, prevent scarring, alleviate inflammation, and improve overall skin health. Effective treatment also aims to minimize recurrence and enhance the patient's psychological well-being. Current therapeutic approaches include topical agents such as retinoids, benzoyl peroxide, and antibiotics for mild acne, while moderate-to-severe cases often require systemic therapies such as oral antibiotics, hormonal agents, or isotretinoin. However, several challenges exist in the management of acne. One of the major concerns is antibiotic resistance, which has led to a shift in prescribing practices to minimize unnecessary antibiotic use and emphasize combination therapies. Hormonal treatments, such as oral contraceptives and spironolactone, are highly effective in certain patient populations but require careful consideration of contraindications and long-term effects. [2]

Isotretinoin remains the most effective treatment for severe, recalcitrant acne but is associated with potential adverse effects, including teratogenicity, mucocutaneous dryness, and mood alterations, necessitating strict monitoring protocols. Additionally, emerging therapies such as biologics, probiotics, and laser treatments are gaining traction but require further clinical validation. The individualized nature of acne therapy, patient adherence, and the risk of post-treatment relapse add further complexity to treatment decisions. [7]

The aim of this comprehensive review is to provide an in-depth evaluation of the current and emerging treatments for acne vulgaris, highlighting their mechanisms of action, efficacy, safety profiles, and limitations.

❖ Topical Therapies for Acne Vulgaris

Topical therapies serve as the cornerstone of acne treatment, particularly for mild-to-moderate cases. These treatments target the fundamental pathological mechanisms of acne, including follicular hyperkeratinization, Cutibacterium acnes proliferation, inflammation, and excessive sebum production. Topical therapies offer the advantage of localized treatment with minimal systemic side effects, making them suitable for long-term use. However, patient adherence can be a challenge due to the potential for irritation, delayed onset of action, and the necessity for consistent application. Among the most commonly prescribed topical agents are retinoids, antimicrobials, azelaic acid, and dapsone. More recently, fixed-dose combination therapies have been developed to enhance treatment efficacy and improve patient compliance. [8]

❖ Retinoids: Tretinoin, Adapalene, Tazarotene, Trifarotene

Retinoids are vitamin A derivatives that play a crucial role in acne management by regulating epithelial cell turnover and reducing comedone formation. They work by binding to nuclear retinoic acid receptors (RARs), which normalize keratinocyte differentiation, prevent follicular occlusion, and exert anti-inflammatory effects. As a result, they help in reducing both non-inflammatory and inflammatory acne lesions while preventing the formation of new lesions. [9]

Tretinoin, the first-generation retinoid, has been widely used for decades and remains one of the most effective topical treatments for acne. It is available in various formulations, including creams, gels, and microspheres, to enhance tolerability. However, its use is often associated with irritation, peeling, and increased photosensitivity, requiring patients to gradually introduce it into their skincare routine while using moisturizers and sunscreen. Adapalene, a third-generation synthetic retinoid, selectively targets RAR-β and RAR-γ, making it less irritating than tretinoin while maintaining similar efficacy. Its availability over the counter in lower concentrations has made it a popular option for mild acne. Tazarotene, another third-generation retinoid, exhibits higher potency but is also associated with increased irritation. It is typically reserved for more resistant cases of acne. The newest addition, trifarotene, is a fourth-generation RAR-γ selective retinoid, offering improved tolerability while effectively treating both facial and truncal acne. [10]

Retinoids remain a mainstay of acne treatment due to their ability to target multiple acne-causing mechanisms. They significantly reduce comedonal and inflammatory lesions, improve skin texture, and minimize post-inflammatory hyperpigmentation. However, they require careful patient education to mitigate

potential side effects such as dryness, erythema, and peeling. Proper skin care, including the use of non-comedogenic moisturizers and broad-spectrum sunscreen, is essential to enhance tolerability and adherence to treatment. [11]

- **Antimicrobials: Benzoyl Peroxide, Clindamycin, and Erythromycin**

Antimicrobial agents are essential in acne management as they help to control C. acnes proliferation and reduce inflammation. However, the increasing issue of antibiotic resistance has necessitated changes in prescribing patterns, emphasizing combination therapies and limiting the duration of antibiotic use.

Benzoyl peroxide is a powerful bactericidal agent that works by releasing free radicals, disrupting bacterial proteins, and eliminating C. acnes without inducing bacterial resistance. It also has mild keratolytic and anti-inflammatory effects, making it an excellent choice for inflammatory acne. Available in concentrations ranging from 2.5% to 10%, benzoyl peroxide can be used alone or in combination with antibiotics and retinoids. However, it can cause skin dryness, peeling, and irritation. Patients should be advised to start with lower concentrations and gradually increase usage to enhance tolerability. One of the notable drawbacks of benzoyl peroxide is its tendency to bleach fabrics, making it necessary for patients to be cautious with clothing, towels, and pillowcases. [12]

Topical antibiotics such as clindamycin and erythromycin are widely used in acne treatment due to their anti-inflammatory properties and ability to suppress C. acnes growth. Clindamycin is the preferred option due to its superior efficacy and lower resistance rates. It is available in various formulations, including gels, lotions, and foams, making it a versatile choice for different skin types. Erythromycin, once a first-line option, has seen a decline in use due to increasing resistance. However, when combined with benzoyl peroxide, it remains a viable option for acne treatment. Both antibiotics are best used in combination with benzoyl peroxide to minimize the risk of antibiotic resistance. Their monotherapy use should be avoided to preserve their long-term efficacy. [13]

- **Azelaic Acid: Anti-inflammatory and Keratolytic Properties**

Azelaic acid is a dicarboxylic acid with unique antimicrobial, anti-inflammatory, and keratolytic properties, making it a valuable option for acne treatment. Unlike retinoids and benzoyl peroxide, azelaic acid is well tolerated and suitable for patients with sensitive skin or those prone to post-inflammatory hyperpigmentation. It works by inhibiting Cutibacterium acnes growth through interference with microbial protein synthesis. Additionally, azelaic acid normalizes keratinization, preventing the formation of comedones, and exerts anti-inflammatory effects by reducing the production of pro-inflammatory cytokines. [14]

One of the most significant advantages of azelaic acid is its ability to reduce melanin production, making it particularly beneficial for patients with darker skin types who are prone to post-inflammatory hyperpigmentation. Unlike some other topical agents, it does not increase sun sensitivity, which allows for its safe use without the stringent requirement for sunscreen, although daily sun protection is still recommended. [15]

Azelaic acid is available in 10% to 20% concentrations in creams and gels. It is moderately effective in treating mild-to-moderate acne, especially in individuals with inflammatory lesions and hyperpigmentation. It can be used alone or in combination with other topical therapies, particularly for patients who cannot tolerate retinoids or benzoyl peroxide. While generally well tolerated, some individuals may experience mild stinging or burning upon application, but these effects usually subside with continued use. [16]

Table 1: Summary of Topical Therapies for Acne Vulgaris

Therapy	Mechanism of Action	Efficacy	Side Effects
Retinoids (Tretinoin, Adapalene, Tazarotene, Trifarotene)	Regulate keratinocyte differentiation, reduce comedogenesis, and exhibit anti-inflammatory properties.	Highly effective for both comedonal and inflammatory acne; prevents recurrence.	Dryness, peeling, erythema, and increased sun sensitivity.
Benzoyl Peroxide	Kills *Cutibacterium acnes* by generating free radicals, preventing bacterial resistance.	Fast-acting, effective in reducing inflammatory lesions, often combined with other therapies.	Dryness, irritation, and bleaching of fabrics.
Topical Antibiotics (Clindamycin, Erythromycin)	Inhibits bacterial protein synthesis, reducing inflammation and acne lesion formation.	Useful for mild-to-moderate inflammatory acne but requires combination with benzoyl peroxide to prevent resistance.	Potential for antibiotic resistance, dryness, and irritation.

Therapy	Mechanism of Action	Efficacy	Side Effects
Azelaic Acid	Has antimicrobial, anti-inflammatory, and keratolytic effects; reduces melanin production and post-inflammatory hyperpigmentation.	Moderate efficacy in mild-to-moderate acne; well-suited for patients with sensitive skin.	Generally well tolerated; may cause mild stinging or burning.
Dapsone Gel	Reduces neutrophilic inflammation rather than acting as a direct antimicrobial agent.	More effective in inflammatory papules and pustules, particularly in female adult acne.	May cause temporary yellow-orange discoloration when used with benzoyl peroxide.
Fixed-Dose Combination Therapies	Combines different mechanisms to enhance efficacy, prevent bacterial resistance, and improve patient adherence.	Improves efficacy, reduces resistance, and simplifies treatment regimens, enhancing adherence.	Lower side effects due to reduced individual agent concentration; potential for irritation depending on components.

❖ **Systemic Therapies for Acne Vulgaris**

Systemic therapies are primarily used for moderate-to-severe acne that does not respond adequately to topical treatments. These therapies are particularly beneficial in cases involving extensive lesions, nodulocystic acne, or significant scarring potential. The three main categories of systemic treatments for acne include oral antibiotics, hormonal therapies, and isotretinoin. While highly effective, systemic therapies must be carefully chosen based on individual patient needs, potential side effects, and long-term safety considerations. [17]

❖ **Oral Antibiotics: Doxycycline, Minocycline, and Sarecycline**

Oral antibiotics are commonly prescribed for inflammatory acne, particularly in moderate-to-severe cases where topical treatments alone are insufficient. These antibiotics work by reducing Cutibacterium acnes colonization and exerting anti-inflammatory effects, which help control papules, pustules, and nodules. The most frequently used antibiotics in acne management belong to the tetracycline class, including doxycycline, minocycline, and sarecycline. [2]

Doxycycline is widely used due to its broad antimicrobial and anti-inflammatory properties. It inhibits bacterial protein synthesis and reduces the production of inflammatory mediators such as interleukin-1 and tumor necrosis factor-alpha. It is generally well tolerated, but common side effects include gastrointestinal discomfort, photosensitivity, and esophageal irritation. To minimize side effects, patients are advised to take doxycycline with food and ample water and to avoid excessive sun exposure. [18]

Minocycline, another tetracycline derivative, is known for its enhanced lipid solubility, allowing better penetration into sebaceous glands. It has strong anti-inflammatory properties and is slightly less likely to cause photosensitivity compared to doxycycline. However, minocycline has been associated with more severe adverse effects, including dizziness, skin hyperpigmentation, and, in rare cases, autoimmune reactions such as drug-induced lupus. [19]

Sarecycline is a newer-generation tetracycline antibiotic designed specifically for acne treatment. It has a narrower spectrum of activity, primarily targeting C. acnes, which reduces the risk of antibiotic resistance and disruption of normal gut flora. Sarecycline is well tolerated, with fewer gastrointestinal side effects and a lower likelihood of causing photosensitivity, making it a promising option for long-term acne management. [20]

Despite their efficacy, prolonged use of oral antibiotics raises concerns about antimicrobial resistance. To mitigate this risk, antibiotics should be used for the shortest effective duration, typically three to six months, and should always be combined with topical therapies such as benzoyl peroxide or retinoids to reduce bacterial resistance. [21]

❖ **Hormonal Therapies: Oral Contraceptives, Spironolactone, and Cyproterone Acetate**

Hormonal therapies are particularly beneficial for female patients with hormonally driven acne, often characterized by flares around the menstrual cycle, jawline involvement, and resistance to conventional treatments. These therapies work by counteracting androgen activity, which plays a key role in sebum production and acne pathogenesis. [22]

Oral contraceptives containing a combination of estrogen and progestin help regulate androgen levels, reducing sebaceous gland activity and preventing new acne lesions. The most effective formulations contain anti-androgenic progestins, such as drospirenone, norgestimate, or desogestrel. It typically takes three to six months to see significant improvement, and oral

contraceptives are often used in combination with other acne treatments for optimal results. While generally well tolerated, potential risks include venous thromboembolism, breast tenderness, and mood changes, necessitating careful selection in patients with risk factors for cardiovascular disease. [23]

Spironolactone, a potassium-sparing diuretic with anti-androgenic properties, is commonly used off-label for hormonal acne in women. It works by blocking androgen receptors and reducing sebum production, leading to significant improvement in acne lesions. It is particularly effective in adult female acne that is resistant to other treatments. Doses typically range from 50 to 200 mg per day, with results becoming noticeable within a few months. Potential side effects include menstrual irregularities, breast tenderness, and hyperkalemia, although serious adverse events are rare. Patients are often advised to use reliable contraception while on spironolactone due to concerns about potential fetal effects. [24]

Cyproterone acetate is an anti-androgen that is frequently combined with ethinylestradiol in certain oral contraceptives specifically formulated for acne treatment. It works by directly inhibiting androgen production and blocking androgen receptors in sebaceous glands. While highly effective, its use is somewhat limited due to concerns about increased risk of thromboembolic events compared to other hormonal treatments. [25]

Hormonal therapies are a valuable option for women with acne, particularly those with signs of androgen excess, such as hirsutism or polycystic ovary syndrome (PCOS). However, their use requires individualized risk assessment, particularly in patients with a history of blood clotting disorders, hypertension, or migraines. [26]

- **Isotretinoin: Indications, Efficacy, Safety Concerns, and Monitoring**

Isotretinoin is the most effective systemic therapy for severe, recalcitrant, or nodulocystic acne. As a retinoid derivative, it works by dramatically reducing sebaceous gland size and activity, normalizing follicular keratinization, decreasing C. acnes proliferation, and exerting potent anti-inflammatory effects. Unlike other acne treatments, isotretinoin offers long-term remission in many patients, making it a preferred choice for severe cases. [13]

Isotretinoin is typically prescribed at cumulative doses ranging from 120 to 150 mg/kg over four to six months. The response is often dose-dependent, with higher cumulative doses associated with lower relapse rates. Although highly effective, isotretinoin requires careful monitoring due to its potential for significant adverse effects. [27]

The most common side effects include mucocutaneous dryness, cheilitis, dry eyes, and nasal irritation. More serious concerns include elevated liver enzymes, dyslipidemia, and musculoskeletal symptoms. Routine laboratory monitoring is recommended, particularly during the first few months of treatment. The most critical safety concern with isotretinoin is its teratogenicity, necessitating strict pregnancy prevention measures, including enrollment in risk management programs such as iPLEDGE in the United States. [28]

Psychiatric side effects, including mood changes and depression, have been a subject of debate. While studies have not conclusively established a direct link between isotretinoin and depression, patients should be monitored for mood disturbances, particularly those with a history of mental health disorders. Given its powerful effects, isotretinoin is generally reserved for severe acne that has failed conventional therapies, but when used appropriately, it provides unparalleled efficacy in achieving long-term acne clearance. [29]

- **Adjunctive and Emerging Therapies for Acne Vulgaris**

In addition to traditional pharmacologic treatments, several adjunctive and emerging therapies have been explored to enhance acne treatment outcomes. These include laser and light-based therapies, chemical peels, microneedling, platelet-rich plasma (PRP), and even botulinum toxin injections. These interventions are particularly useful in patients seeking alternative or supplementary treatments, especially for post-inflammatory hyperpigmentation and acne scarring. [30]

- **Lasers and Light-Based Therapies**

Photodynamic therapy (PDT) utilizes photosensitizing agents activated by light exposure to reduce sebaceous gland activity and kill C. acnes. Blue light and red light therapy work by targeting bacterial porphyrins and reducing inflammation, respectively. These treatments are non-invasive and can be used in patients who cannot tolerate conventional therapies. Nd:YAG and fractional laser treatments help in collagen remodeling, making them effective in treating both active acne and post-acne scarring. [31]

- **Chemical Peels**

Chemical peels using salicylic acid, glycolic acid, and Jessner's solution are frequently employed in acne treatment. These agents exfoliate the skin, unclog pores, and improve overall skin texture. Salicylic acid is particularly beneficial due to its lipophilic nature, allowing it to penetrate sebaceous follicles and exert anti-inflammatory effects. [32]

- **Microneedling and Platelet-Rich Plasma (PRP)**

Microneedling creates controlled micro-injuries that stimulate collagen production,

improving acne scars and skin texture. PRP, which contains growth factors that promote tissue regeneration, is sometimes used in conjunction with microneedling to enhance healing and skin rejuvenation. [33]

- **Botulinum Toxin in Sebaceous Gland Suppression**

Recent research has explored the use of botulinum toxin (Botox) in reducing sebaceous gland activity. By inhibiting acetylcholine-mediated sebaceous gland stimulation, Botox may help decrease excessive oil production, making it a potential novel therapy for acne. While these adjunctive and emerging therapies continue to evolve, their role in acne treatment is becoming increasingly significant, particularly for patients with treatment-resistant acne or those seeking non-pharmacologic interventions. [34]

- **Novel and Investigational Therapies for Acne Vulgaris**

As our understanding of acne pathophysiology evolves, novel and investigational therapies continue to emerge, offering potential breakthroughs for patients with treatment-resistant acne. Many of these treatments target underlying hormonal influences, immune responses, and the skin microbiome, aiming to provide more effective and personalized management strategies. [35]

- **Topical and Systemic Androgen Receptor Inhibitors**

Since androgens play a crucial role in stimulating sebum production, androgen receptor inhibitors have become a promising area of research. While hormonal therapies such as oral contraceptives and spironolactone are commonly used in female patients, newer therapies targeting androgen receptors are being explored for both men and women. Topical androgen receptor inhibitors, such as clascoterone, work by blocking androgen signaling in sebaceous glands, reducing sebum production and inflammation. Systemic androgen receptor inhibitors, including experimental drugs like proxalutamide and apalutamide, are being investigated for their ability to control severe hormonal acne. These therapies may offer an alternative for patients who cannot tolerate traditional hormonal treatments. [22]

- **Biologics and Immunomodulatory Approaches**

Acne has increasingly been recognized as an inflammatory disease, leading to the exploration of biologic therapies that modulate immune responses. Biologics targeting cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), and interleukin-1 (IL-1) have shown potential in reducing acne-related inflammation. Drugs like secukinumab and ixekizumab, both IL-17 inhibitors approved for psoriasis, are being studied for their effects on severe acne. These targeted therapies may provide a valuable option for patients with inflammatory and recalcitrant acne who have not responded to conventional treatments. [36]

- **Probiotics and Skin Microbiome-Based Treatments**

The role of the skin microbiome in acne pathogenesis has gained significant attention, leading to the development of probiotic-based treatments. Probiotics help restore the balance of beneficial and pathogenic bacteria on the skin, reducing inflammation and sebum production. Both oral and topical probiotics, including Lactobacillus and Bifidobacterium species, have been investigated for their potential to improve acne symptoms. Additionally, microbiome-based therapies, such as bacteriophage-based treatments targeting C. acnes, are being explored as a novel way to control bacterial overgrowth without contributing to antibiotic resistance. [37]

- **JAK Inhibitors and IL-17 Inhibitors in Severe Acne**

Janus kinase (JAK) inhibitors, which target intracellular signaling pathways involved in inflammation, have shown promise in treating inflammatory skin diseases. Drugs like tofacitinib and ruxolitinib, originally developed for autoimmune conditions, are being studied for their potential role in severe acne by reducing inflammation at the molecular level. Similarly, IL-17 inhibitors, which have been successful in psoriasis treatment, are now being explored for patients with severe nodulocystic acne. These emerging therapies represent a shift toward precision medicine, offering new hope for patients with chronic and treatment-resistant acne. [38]

- **Special Considerations in Acne Management**

Acne presentation, severity, and treatment response can vary significantly based on factors such as age, pregnancy status, skin type, and underlying medical conditions. Personalized approaches to acne management are essential to optimize treatment efficacy and minimize risks. [39]

- **Acne in Different Age Groups: Adolescents vs. Adults**

Acne is most prevalent during adolescence due to increased androgen production during puberty, which leads to excessive sebum secretion. Adolescent acne typically presents as comedonal and inflammatory lesions on the forehead, nose, and cheeks. First-line treatments include topical retinoids, benzoyl peroxide, and oral antibiotics for moderate cases. [40]

Adult acne, particularly in women, often manifests as inflammatory papules and nodules along the jawline and chin. Hormonal fluctuations, stress, and dietary factors contribute to its persistence. Hormonal therapies, such as oral contraceptives and spironolactone, are commonly

used in female adult acne, whereas isotretinoin may be necessary for persistent or severe cases. [41]

- **Acne in Pregnancy: Safe Treatment Options**

Managing acne during pregnancy presents unique challenges due to the teratogenic risks associated with many acne medications. Isotretinoin and oral tetracyclines are contraindicated due to their potential to cause birth defects and fetal complications. Safe alternatives include topical azelaic acid, which has antimicrobial and anti-inflammatory properties, and limited use of benzoyl peroxide and glycolic acid. In severe cases, erythromycin or cephalexin may be used under medical supervision. Hormonal therapies are not recommended during pregnancy, and all treatments should be carefully selected to ensure maternal and fetal safety. [42]

- **Acne in Skin of Color: Post-Inflammatory Hyperpigmentation Considerations**

Patients with darker skin tones are more prone to post-inflammatory hyperpigmentation (PIH), a common sequela of acne that can be more distressing than the acne itself. Treatments must be chosen carefully to minimize irritation, as excessive inflammation can worsen hyperpigmentation. Topical retinoids, azelaic acid, and niacinamide are beneficial in both treating acne and reducing PIH. Laser and light-based therapies must be used cautiously in darker skin tones to prevent unwanted pigmentation changes. [42]

- **Acne Fulminans and Recalcitrant Acne: Therapeutic Approaches**

Acne fulminans is a rare but severe form of acne characterized by sudden onset of ulcerating nodules, systemic symptoms such as fever, and musculoskeletal pain. This condition requires aggressive treatment with systemic corticosteroids to control inflammation, followed by isotretinoin to prevent relapse. Recalcitrant acne, which does not respond to conventional treatments, often necessitates high-dose isotretinoin or novel biologic therapies targeting inflammatory pathways. These cases require specialist intervention and long-term follow-up to prevent complications. [43]

- **Treatment Challenges and Future Directions**

Despite significant advances in acne treatment, several challenges remain, including antibiotic resistance, variability in treatment response, and the need for personalized approaches. [12]

- **Antibiotic Resistance and Stewardship**

The widespread use of oral and topical antibiotics has contributed to increasing resistance in C. acnes, making antibiotic stewardship a priority in acne management. To reduce resistance, antibiotics should be used for the shortest duration necessary and always in combination with benzoyl peroxide or retinoids. Novel non-antibiotic alternatives, such as bacteriophage therapy and antimicrobial peptides, are being developed to address this growing concern. [12]

- **Personalized Medicine Approaches**

Acne treatment is increasingly moving toward personalized medicine, where therapies are tailored based on an individual's genetic, hormonal, and microbial profile. Pharmacogenomic testing may help predict treatment response to isotretinoin and hormonal therapies, improving patient outcomes while minimizing adverse effects. Machine learning algorithms and artificial intelligence are also being integrated into acne treatment planning, allowing for more accurate diagnosis and treatment recommendations. [44]

- **Role of Genetic and Molecular Research in Future Therapies**

Advances in genetic research have identified potential molecular targets for acne treatment, including androgen receptor gene variations and inflammatory cytokine pathways. Future therapies may focus on selectively modulating these pathways to provide highly targeted treatments with minimal side effects. Additionally, gene-editing techniques, such as CRISPR, hold potential for correcting genetic predispositions to severe acne, although further research is needed before clinical applications can be realized. [8]

Conclusion

Acne vulgaris remains a complex and multifactorial condition that requires a comprehensive and individualized approach to treatment. Current therapies, including topical and systemic agents, have significantly improved acne management, but challenges such as antibiotic resistance, treatment adherence, and recurrence persist. Adjunctive and emerging therapies, including biologics, probiotics, and laser treatments, offer new possibilities for patients with resistant or refractory acne.

Looking ahead, the integration of personalized medicine, genetic research, and microbiome-based therapies may revolutionize acne treatment, providing more effective and tailored interventions. Future breakthroughs in pharmacogenomics and immunomodulatory approaches hold the potential to enhance long-term outcomes while minimizing side effects. By continuously refining treatment strategies and embracing novel therapeutic innovations, clinicians can optimize acne management and improve the quality of life for patients worldwide.

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