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Review

# Differentiated approach to external acne therapy

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ABSTRACT

Acne is a serious medical and social problem due to the widespread prevalence of the disease. Localized mainly on the face, acne leads to the development of disorders in the psycho-emotional sphere, significantly reducing the quality of life.

The aim of the study was to study the effectiveness and safety of Epiduo/Effezel gel (adapalene 0.1% and benzoyl peroxide 2.5%) in patients with papulopustular acne.

The Clinic of Skin and Sexually Transmitted Diseases of the Clinical Hospital No. 2 of Sechenov University has accumulated extensive experience in the treatment of acne. In the diagnostic and treatment department, patients with mild to moderate acne receive consultations and treatment almost every day. A dermatological examination is carried out visually with a simple count of eruptive elements: papules, pustules and nodes, on the basis of which the degree of severity is determined. Patients with severe forms of acne receive systemic retinoids with corrective therapy until a certain cumulative dose is reached, and then patients receive topical maintenance therapy intermittently for 12 months.

Despite the development of effective methods for treating this dermatosis, patient adherence to treatment remains low. This is due, first of all, to the duration of therapy, not always the rapid achievement of the expected result, and to the development of psycho-emotional disorders in patients. In the latest edition of the Russian Society of Dermatovenerologists and Cosmetologists clinical guidelines for the treatment of mild to moderate acne with a high level of evidence A1, it is recommended to use benzoyl peroxide and a fixed combination of adapalene and benzene peroxide. When prescribing benzene peroxide (Baziron AS), we observed the best results in clearing the skin of rashes in the presence of a few papulopustular elements in the clinical picture due to the triple action of benzoyl peroxide — antimicrobial, keratolytic and sebostatic. In our experience, it usually took 4 to 6 weeks to achieve clinical remission, and we did not note a single case of the development of bacterial resistance during treatment. For moderately widespread papulopustular acne rashes of moderate severity, as well as in cases of severe forms of the disease, when it is impossible to prescribe systemic isotretinoin or there is a tendency to scarring of the primary elements, we used a fixed combination of adapalene 0.1% and benzoyl peroxide 2.5% (Effezel) with anti-inflammatory, antimicrobial, keratolytic, sebostatic, comedolytic and anticomedogenic effects.

In the arsenal of dermatologists and cosmetologists there are drugs for the external treatment of mild to moderate papulopustular acne with a high level of evidence. Thus, for papulopustular acne with a few inflammatory (papules and pustules) rashes, benzoyl peroxide gel may be recommended. For moderately widespread papulopustular acne with the presence of comedones (moderate severity), a fixed combination of adapalene and benzoyl peroxide can be recommended as the first line of therapy.

**Keywords:** acne; adapalene; benzoyl peroxide; papulopustular stage.

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Научный обзор

# Дифференцированный подход к наружной терапии акне

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АННОТАЦИЯ

Акне представляет собой серьёзную медико-социальную проблему в связи с широкой распространённостью заболевания. Локализуясь в основном на лице, акне приводит к развитию нарушений в психоэмоциональной сфере, существенно снижая качество жизни.

Цель данного обзора — изучение эффективности и безопасности геля Epiduo/Эффузул, в состав которого входят адапален 0,1% и бензоила пероксид 2,5%, у пациентов с папулопустулёзной формой акне.

Клиникой кожных и венерических болезней УКБ № 2 Сеченовского Университета накоплен большой опыт лечения акне. В лечебно-диагностическом отделении практически ежедневно получают консультации и лечение пациенты с лёгкой и средней степенью тяжести акне. Дерматологический осмотр проводится визуально с простым подсчётом высыпных элементов (папул, пустул и узлов), на основании чего определяется степень тяжести. Пациенты с тяжёлыми формами акне получают системные ретиноиды с корригирующей терапией до достижения определённой кумулятивной дозы, а затем в течение 12 месяцев — наружную поддерживающую терапию по интермиттирующей схеме.

Несмотря на разработанные эффективные методы терапии акне, приверженность пациентов к лечению остаётся по-прежнему низкой. Это связно, в первую очередь, с длительностью терапии, далеко не всегда быстрым достижением ожидаемого результата и развитием у больных расстройств психоэмоционального характера. В последней редакции клинических рекомендаций Российского общества дерматовенерологов и косметологов для лечения акне лёгкой и средней степени тяжести с высоким уровнем доказательности (А1) рекомендовано применять бензоила пероксид и фиксированную комбинацию адапалена и бензола пероксида. Назначая антисептик бензоила пероксид (Базирон АС), наилучшие результаты в очищении кожных покровов от высыпаний мы наблюдали при наличии в клинической картине немногочисленных папулопустулёзных элементов в связи с тройным действием препарата — антимикробным, кератолитическим и себостатическим. Как показывает наш опыт, для достижения клинической ремиссии обычно требовалось от 4 до 6 недель, при этом случаев развития бактериальной резистентности не отмечено. При умеренно распространённых папулопустулёзных высыпаниях акне средней степени, а также тяжёлых формах заболевания, когда невозможно назначить системный изотретиноин или имеется тенденция к рубцеванию первичных элементов, мы применяли фиксированную комбинацию адапалена 0,1% и бензоила пероксида 2,5% (Эффезел) с противовоспалительным, антимикробным, кератолитическим, себостатическим, комедонолитическим и антикомедогенным эффектом.

В арсенале врачей-дерматологов и косметологов имеются препараты для наружного лечения папулопустулёзных акне лёгкой и средней степени с высоким уровнем доказательности. Так, при папулопустулёзных акне с немногочисленными воспалительными высыпаниями (папулы и пустулы) может быть рекомендован гель бензоила пероксид. При умеренно распространённых папулопустулёзных элементах акне с наличием комедонов (средняя степень тяжести) в качестве первой линии терапии может рекомендоваться фиксированная комбинация адапалена и бензоила пероксида.

**Ключевые слова:** акне; адапален; бензоила пероксид; папулопустулёзная стадия.

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# INTRODUCTION

## Acne: prevalence, etiology, pathogenesis

Acne is a chronic inflammatory disease of the pilosebaceous unit, characterized by the formation of open or closed comedones and the presence of inflammatory elements in the form of papules, pustules, and nodules. Acne represents a significant medical and social issue, largely due to its pervasive prevalence. According to existing literature, the condition affects approximately 80% to 85% of adolescents and young adults [1]. However, acne may persist or manifest at a later age (late acne occurs in approximately 20% of adult women [2]). Conversely, acne, which is primarily localized on the face, has been linked to the onset of psychological and emotional disturbances, which significantly impair the patient's quality of life. A correlation has been found between acne and the development of obsessive-compulsive disorder and dysmorphic reactions [3]. Even mild forms of acne have been demonstrated to cause psychoemotional disorders, including anxiety, social withdrawal, and severe depression. In addition, the chronic course and formation of post-acne symptoms aggravates the situation, having an even more significant psychological impact. All this calls for the improvement of existing treatment methods and the development of new ones.

In the majority of cases, acne is regarded as a constitutionally determined disease, with an increased sensitivity of sebocytes to androgenic stimuli [4, 5]. It has been established that the initial link is hereditary hyperandrogenism, which leads to changes in both the quantitative and qualitative composition of sebum. However, genetic factors can only play a role in the development of sebaceous gland disease when environmental factors (hormonal disorders, medications, cosmetics, smoking, ultraviolet irradiation, environmental pollution, food, etc.) overlap with the genetic predisposition. Furthermore, among the interrelated pathogenetic factors, pathological follicular keratinisation, *Cutibacterium acnes* proliferation in the ducts of sebaceous glands and the development of an inflammatory response play a significant role in the pathogenesis of acne. Notably, inflammation represents the primary link in this process, occurring prior to keratinisation [6, 7].

An increase in the production of interleukin 1 (IL) results in enhanced proliferation of keratinocytes, while the excessive generation of nuclear factor NF-κβ leads to the release of tumor necrosis factor alpha (TNF-α), IL-1, IL-8, and IL-10. The synthesis of proinflammatory cytokines is mediated by toll-like receptors (TLR), which in turn release antimicrobial peptides (β-defensins) and metalloproteinases that cause the inflammatory and scarring processes observed in acne [8].

# ACNE THERAPY: HIGHLY RECOMMENDED AGENTS— BENZOYL PEROXIDE AND ITS FIXED COMBINATION WITH ADAPALENE

The current approach to acne treatment is based on both Russian and foreign guidelines. Similar treatment schemes have been developed worldwide, with variations depending on the severity of the condition. However, there is currently no unified classification of acne by severity. Nevertheless, there are ongoing developments in this direction, including by Russian experts who consider counting rashes as an additional option [9]. The severity of papulopustular acne can be classified into three degrees: mild (up to 10 papulopustular elements), moderate (from 10 to 20 papules and pustules), and severe (more than 20 papulopustular elements). In cases where there are lesions on the trunk, scars or the inflammatory rash extends beyond the seborrheic areas, the severity is increased by one point [9].

In the treatment of papulopustular acne, external agents are used, the selection of which is somewhat limited. These include retinoids, benzoyl peroxide, antibiotics, and azelaic acid. However, in cases where the condition is mild, only external agents may be prescribed. In medium conditions, external therapy is combined with systemic drugs when necessary. In cases of severe acne, the foundation of therapy is systemic drugs, including isotretinoin, antibiotics, and hormonal agents [10].

## Study of the effectiveness of drugs in the publications by Russian and international authors

In recent years, the range of treatments available to dermatologists has expanded to include highly recommended products, particularly, benzoyl peroxide (Basiron AC, Galderma, France) and a fixed combination of adapalene 0.1% and benzoyl peroxide 2.5% (Effezel and Epiduo, Galderma, France). The effectiveness of benzoyl peroxide has been demonstrated in many clinical studies and scientific papers [11, 12]. According to several authors, benzoyl peroxide is equally effective in different concentrations (2.5%, 5.0%, and 10%). However, the use of a high concentration (10%) may result in dermatitis. Consequently, benzoyl peroxide gel (Basiron AC) 2.5% and 5% is more commonly used in global and Russian clinical practice [13, 14].

In a separate study, the mean percentage reduction in total acne lesions was 44.3% (standard deviation (SD) = 9.2) and 27.8% (SD = 21.0) in the active benzoyl peroxide and placebo treatment groups, respectively. The mean percentage reduction in non-inflammatory lesions was 41.5% (SD = 9.4) and 27.0% (SD = 20.9), while the mean percentage reduction

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in inflammatory lesions was 52.1% (SD = 10.4) and 34.7% (SD = 22.7), respectively [15].

M.A. Samgin and S.A. Monakhov were among the first researchers in Russia to publish data on the use of benzoyl peroxide in patients with the papulopustular form of acne (*n = 20*; 14 men and 6 women) in 2003 [16]. By the end of the sixth week of benzoyl peroxide administration, all patients exhibited complete regression of the pustular elements. Furthermore, the number of papules decreased by approximately 80% by the end of the third month.

Benzoyl peroxide[1] is a potent and highly lipophilic oxidant with keratolytic and, to a lesser extent, sebostatic properties [17]. The drug has a nonspecific bactericidal mechanism of action, forming reactive oxygen species that prevent the emergence of antibiotic-resistant microorganisms. Benzoyl peroxide is primarily effective in the treatment of acne due to its bactericidal activity, particularly against *C. acnes*. This is achieved by the release of active or free oxygen radicals, which are capable of oxidizing bacterial proteins. The free radical reaction of benzoyl peroxide can destroy keratin, thereby allowing sebum drainage [18]. Additionally, some evidence suggests that the drug exerts anti-inflammatory effects at micromolar concentrations, where it has been observed to impede the release of reactive oxygen species by neutrophils, which is a part of the inflammatory response in acne [19].

In the guidelines of the Russian Society of Dermatovenereologists and Cosmetologists (RSDC) for the treatment of mild and moderate papulopustular acne, benzoyl peroxide and fixed combination of adapalene and benzoyl peroxide have the highest level of evidence and grade of recommendation, classified as A1 (Figure 1). A clinically noticeable therapeutic effect of benzoyl peroxide is observed after four weeks, with a persistent result achieved after three months of treatment. Significant improvement in therapy with the fixed combination of adapalene/benzoyl peroxide is evident after one to four weeks[2] [10, 18].

During treatment with benzoyl peroxide and a fixed combination of adapalene/benzoyl peroxide, dose-dependent cutaneous redness and/or dryness may manifest in the initial days, which typically resolve with the application of moisturizers or through the implementation of an intermittent regimen. The incidence of adverse effects associated with these formulations is low, as the excipients present in the benzoyl peroxide composition include methacrylic acid copolymer and glycerol. The process of glycerol exposure is based on the principle of delivery through displacement,

## Treatment regimens for papulopustular lesions[1–4]

Topical monotherapy and fixed combination: Level A recommendations

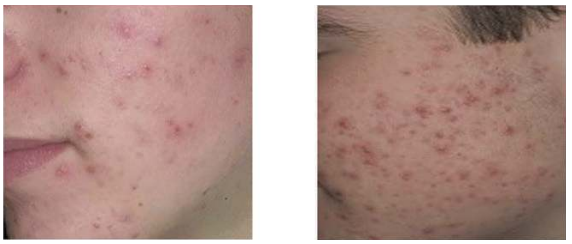
**Scheme 1**

Patients (12 years and older) with isolated acne in the form of papules and pustules on the face
Once or twice daily (morning and/or evening)[1, 3, 4]

Benzoyl peroxide (BPO) 2.5% and 5% gel

**Scheme 2**

Patients (9 years and older) with a moderate number of acne elements in the form of papules and pustules on the face (comedones, without nodules) once daily in the evening[2–4]



Fixed combination (FC) of adapalene 0.1% gel + BPO 2.5%

Adapted from
1. Instructions for medical use of Basiron AC, gel for external use, 2.5%, 5% Marketing authorization No. P N014057/01
2. Instructions for medical use of Effezel Marketing authorization No. LP-000738
3. Clinical guidelines. Acne. Developer of the clinical guidelines: RSDC
4. Diane Tiboutol (USA), Brigitte Dreno (France), Elena Araviiskaia (Russia), Jerry Tan (Canada) et al. Practical management of acne for clinicians: an international consensus from Global Alliance to improve outcomes in acne. J An Acad Dermatol 2018

**Fig. 1.** Russian Society of Dermatovenerologists and Cosmetologists clinical guidelines (2020): acne treatment regimen.

[1] Instructions for medical use of Basiron AC, marketing authorization: P N014057/01. Available at https://www.basiron.ru/sites/default/files/2020-10/Базирон%20АС_Имент ация_07.2020.pdf?ysclid=ls4l8jk8cy740357471.

[2] Instructions for medical use of Effezel, authorization number: LP-000738. Available at http://galderma.tmweb.ru/uploads/file/effezel_instrukciya_(1).pdf.

whereby sebum is absorbed by the copolymer, displacing glycerol and resulting in the softening and moisturizing of the skin at the application site [16, 18].

The efficacy and safety of Epiduo/Effezel gel, comprising a fixed combination of adapalene (0.1%) and benzoyl peroxide (2.5%), are presented in various clinical trials and publications. In an international, randomized, double-blind, placebo-controlled clinical trial involving 1670 patients aged 12 years and older with moderate-to-severe acne, a fixed combination of adapalene 0.1% and benzoyl peroxide 2.5%, adapalene 0.1%, benzoyl peroxide 2.5% or a gel base (placebo) was applied daily at night for 12 weeks. The study demonstrated that the fixed combination of adapalene 0.1% and benzoyl peroxide 2.5% led to a clinically significant reduction in the number of non-inflammatory and inflammatory acne lesions as early as the first week of therapy [20].

A meta-analysis of data from 179 randomized clinical trials (35,000 observations) revealed that a combination retinoid with benzoyl peroxide was the most effective topical therapy for mild to moderate acne [21].

Retinoids are known to play an important role in acne therapy. The formation of acne elements begins with the microcomedone, a nonclinical element formed when excess sebum accumulates in the pilosebaceous follicle and abnormal keratinocyte keratinization (follicular hyperkeratosis) occurs along with proliferation (multiplication) of *Propionibacterium/C. acnes*. Microcomedones are the precursors of all visible acne lesions (comedones, papules, and pustules). Retinoids have comedolytic and anticomedogenic effects and reduce the formation of microcomedones and comedones. Therapy targeting microcomedones minimizes the visible manifestations of acne. Furthermore, retinoids have been shown to have anti-inflammatory effects and restore normal keratinization [22]. When applied to the skin, retinoid penetrates the pilosebaceous follicle and the site of microcomedone formation, is transported to epithelial cells, binds to retinoic acid receptors (RARs) in their nuclei, and causes the activation of genes that alter follicular keratinization, cell proliferation, and inflammation. These processes are pivotal in the pathogenesis of acne; thus, their normalization is beneficial for the treatment of acne and the prevention of new lesions [23, 24]. As demonstrated by Thielitz et al. [25], the cessation of active retinoid treatment results in the immediate formation of new microcomedones (Figure 2).

Adapalene is a well-studied and widely used retinoid in clinical practice. It belongs to the third generation of this group of drugs, which are retinoic acid antagonists by chemical origin [24, 26]. Furthermore, adapalene's anti-inflammatory efficacy in acne therapy is achieved through multiple mechanisms of action, including the inhibition of neutrophil migration (chemotaxis) at the inflammation site, lipoxygenase (which impedes the metabolism of arachidonic acid), and the release of proinflammatory cytokines (which are inflammatory mediators). Furthermore, binding of epithelial cells to TLR-2 (type 2 toll-like receptor) and blocking of activator protein-1 (AP-1), a crucial factor in inflammatory

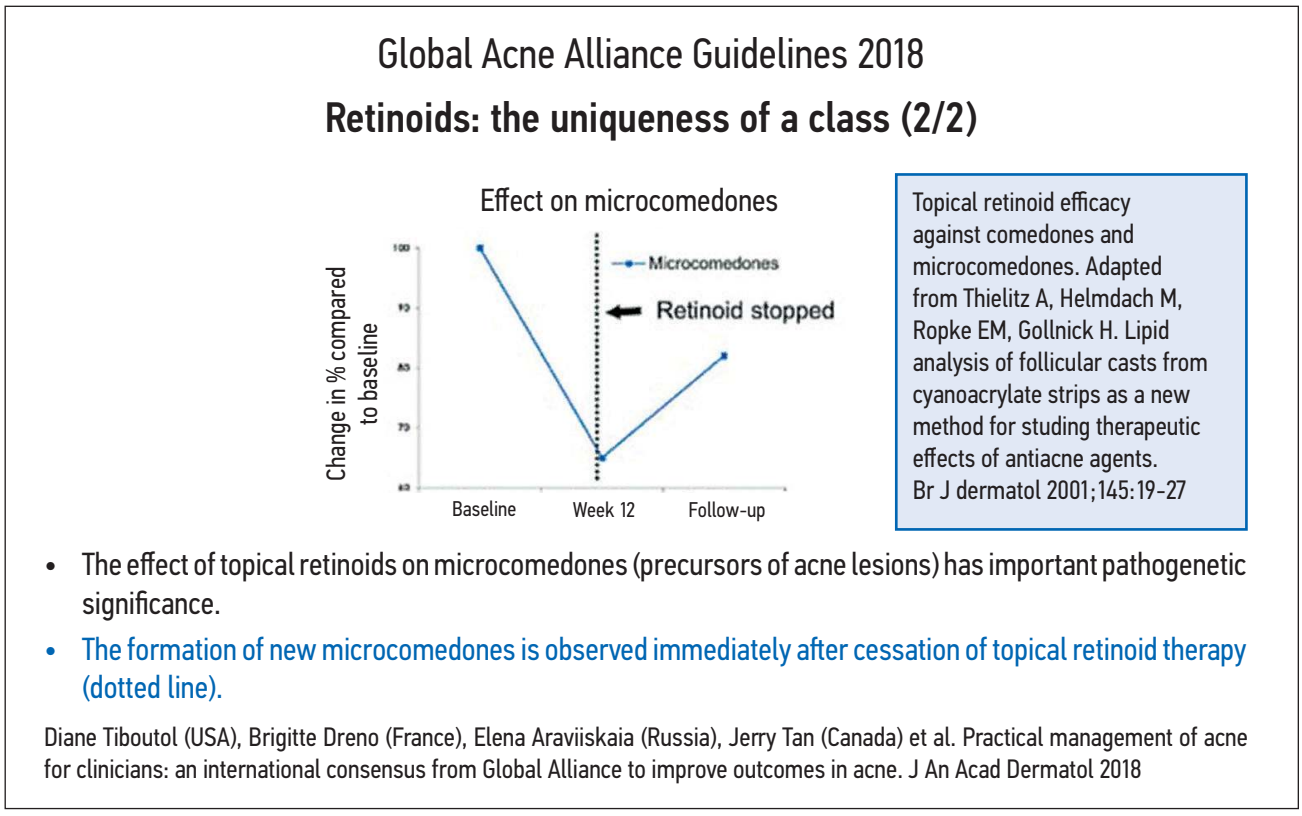



**Fig. 2.** Global Alliance to Improve Outcomes in Acne recommendations to improve acne treatment outcomes (2018).

responses in skin cells, results in a reduction in the release of proinflammatory cytokines (IL, etc.)[3] [27].

In a 12-month multicenter, open-label study of the fixed combination of adapalene/benzoyl peroxide in the daily treatment of moderate acne at bedtime in 452 patients, a reduction in the number of inflammatory lesions was observed as early as the first week. After 12 months, a mean reduction of 76.0% in the number of inflammatory lesions was noted. The mean rates of local adverse events (erythema, dryness, peeling, tingling/burning) were mild to moderate, occurred at baseline, and decreased thereafter, confirming the safe and effective use of the fixed combination of adapalene and benzoyl peroxide over a prolonged treatment period. Additionally, the low rate of drug withdrawal due to adverse events (mean 2.0%) during 12 months of daily use [28] was noted.

The application of a fixed combination of adapalene 0.1% and benzoyl peroxide 2.5% resulted in an improvement in the quality of life of patients with acne. After nine months, the average quality of life according to the CADI (Cardiff Acne Disability Index) questionnaire improved from 5.9 ± 3.0 to 2.4 ± 2.7 points. Long-term adherence to treatment was observed in 83.9% of patients. Most patients (84.8%) were satisfied with the results of using the fixed combination by the end of the follow-up period [29].

A total of 40 patients (28 women and 12 men, aged 14 to 23 years) with grade I–II acne were treated with a gel containing a fixed combination of adapalene 0.1% and benzoyl peroxide 2.5% once a day for 4 to 6 weeks under the supervision of Y.A. Sinozatskaya [30]. A reduction in inflammatory processes and the resolution of comedones were observed after three weeks, while the complete disappearance of clinical signs of acne was noted after four to six weeks. No adverse effects were observed, and no complications were present.

The fixed combination of adapalene 0.1% and benzoyl peroxide 2.5% demonstrated clinically significant efficacy against moderate-to-severe acne with atrophic postacne scars, both as monotherapy and in combination with doxycycline 100 mg/day, for the treatment of severe papulopustular acne during the initial four weeks of the therapy. The use of a fixed combination of adapalene 0.1% and benzoyl peroxide 2.5% in an intermittent mode for six months following a course of systemic retinoid therapy has been demonstrated to result in the preservation and improvement of the achieved effect [31].

The fixed combination of adapalene and benzoyl peroxide is indicated for the treatment of children aged 9 years and older, representing the only drug registered in Russia for acne therapy in this age group [32–34]. Moreover, the drug is indicated for the prevention of post-acne scar formation. Administration of the drug once daily for six months has been demonstrated to reduce the risk of new atrophic scars and to improve the overall severity of acne scars [35, 36].

The Global Alliance to Improve Outcomes in Acne recommends a topical retinoid in combination with benzoyl peroxide as supportive therapy in patients who have received systemic retinoids for the treatment of severe forms of the disease. The efficacy of a 12-month regimen of a fixed combination of adapalene and benzoyl peroxide, administered once daily, was investigated in 68 patients who had undergone a course of therapy with oral isotretinoin. Only two patients (2.94%) exhibited an exacerbation of moderate-to-severe acne during the supportive therapy phase [35]. In accordance with the RSDC guidelines, supportive therapy of acne is defined as the prolonged use of appropriate therapeutic agents (up to 12 months) in an intermittent regimen [10].

An important point should also be noted regarding antibiotic resistance, which has become a serious problem since the 1980s, when topical and systemic antibiotics of different classes were widely used for the treatment of various dermatoses, including acne. Thus, according to Karadag et al. [37], the global antibiotic resistance was 50%–60% in the 1990s and reached a peak of 75% in the early 2000s. Over the past decade, there has been a notable decline in antibiotic resistance rates, largely due to the implementation of preventive measures by the World Health Organization[4] and national programs designed to combat antibiotic resistance. However, the COVID-19 pandemic has led to a resurgence of antibiotic resistance globally[5] [38] (Figure 3).

All international and national clinical guidelines for the management of patients with acne, including the RSDC Acne Clinical Guidelines, impose restrictions on the choice, frequency, and duration of antibacterial agents. In contrast, treatment with benzoyl peroxide and its fixed combination with adapalene does not result in bacterial resistance, rendering the drugs effective in acne caused by antibiotic-resistant strains *of C. acnes*.

Topical antibacterials are not recommended as supportive therapy to minimize antibiotic resistance and following the completion of the primary course of acne treatment. The drug of choice for maintenance therapy is adapalene, with azelaic acid as an alternative. If antimicrobial therapy is necessary, a combination of adapalene and benzoyl peroxide is the optimal choice [10, 22].

## Results of preventing exacerbations and scarring based on personal experience

The Clinic for Skin and Venereal Diseases of the Sechenov University Clinical Hospital No. 2 has gained

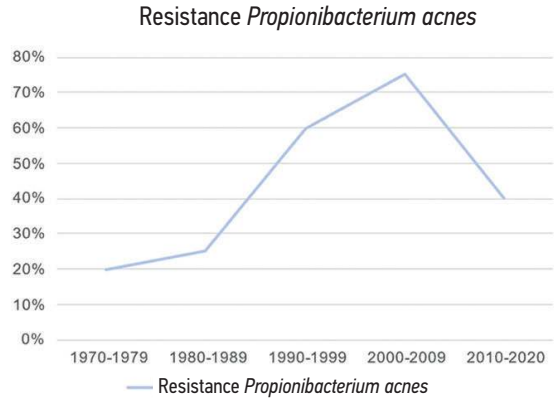
[3] Instructions for medical use of Effezel, authorization number: LP-000738. Available at http://galderma.tmweb.ru/uploads/file/effezel_instrukciya_(1).pdf.

[4] WHO. Global action plan on antimicrobial resistance [2016 Jan 1]. Available at https://www.who.int/publications/i/item/9789241509763.

[5] CDC. COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2022. Available at https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf.

## Karadag A.S. et al., Antibiotic resistance in acne: Changes, implications, and questions, JEADV, 2021

- AB resistance rates for R./C.acnes have gradually increased over the years, from 20% to 25% in the 70s and 80s to 50% to 60% in the 90s, peaking at 75% in the early 2000s[1]
- Over the past decade, AB resistance has decreased to 30%–40%[1]
- *In the context of preventive measures initiated by the WHO and national ABR programs*[2]
- But the COVID-19 epidemic has increased AB resistance rates in every country worldwide![3]




1. Karadag A.S. et al, Antibiotic resistance in acne: changes, consequences and concems, JEADV, 2021
2. WHO. Global Action Plan to Combat Antimicrobial Resistance, January 1, 2016.
3. CDC. COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2022. Available at https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf.

**Fig. 3.** Antibiotic resistance rates globally for the period 1970–2020.

extensive experience in the treatment of acne. In the Treatment and Diagnostic Department, patients with mild to moderate acne are consulted and treated almost daily. As a rule, these are young patients, but 10%–15% of patients are diagnosed with late acne. Dermatological examination is performed visually with simple counting of rashes (papules, pustules, and nodules), which is used to determine the severity. In accordance with the guidelines, external therapy is the primary course of treatment for cases of mild acne. For moderate acne, topical agents are used along with antibiotics (doxycycline or minocycline) or hormonal preparations (as indicated). Patients with severe forms of acne receive systemic retinoids in conjunction with corrective therapy until a specified cumulative dose is reached, after which they are treated with external supportive therapy on an intermittent schedule for 12 months. This helps to prevent aggravation and scarring in post-acne conditions and smooth the skin surface with existing atrophic scars. The results of our own observations are illustrated (Figures 4–9).

## DISCUSSION

Acne treatment may frequently be a challenging issue. Despite the developed effective methods of treatment of dermatosis, the compliance of patients with the treatment remains low, which is mainly due to the duration of treatment, not always quick achievement of the expected result, and the development of psycho-emotional disorders in patients. In accordance with Federal Law No. 323-FZ,[6] medical care in the Russian Federation is structured and delivered based on the guidelines. Additionally, standards of medical care are formulated on this basis.

The most recent version of the RSDC guidelines recommends benzoyl peroxide and a fixed combination of adapalene and benzoyl peroxide for the treatment of mild to moderate acne with a high level of evidence (A1). In our experience, benzoyl peroxide (Basiron AC) yielded the best results in clearing skin in the presence of few papulopustular elements due to the triple action of the drug — namely, antimicrobial, keratolytic, and sebostatic. Clinical remission is typically achieved within four to six weeks, with no instances of bacterial resistance observed during the course of treatment. Remarkably, each case of acne is treated on an individual basis, with consideration given to a number of factors, including the severity of the condition, the presence of comorbidities, the patient's allergic history, their hormonal profile, previous treatments and responses, and other relevant factors. In terms of efficacy, benzoyl peroxide has been shown to be more effective than certain other topical

[6] Federal Law of November 21, 2011, N 323-FZ "On the Fundamentals of Health Protection of Citizens in the Russian Federation" (as amended and supplemented). Available at https://base.garant.ru/12191967/?ysclid=ls4jgpmxpo115716564.

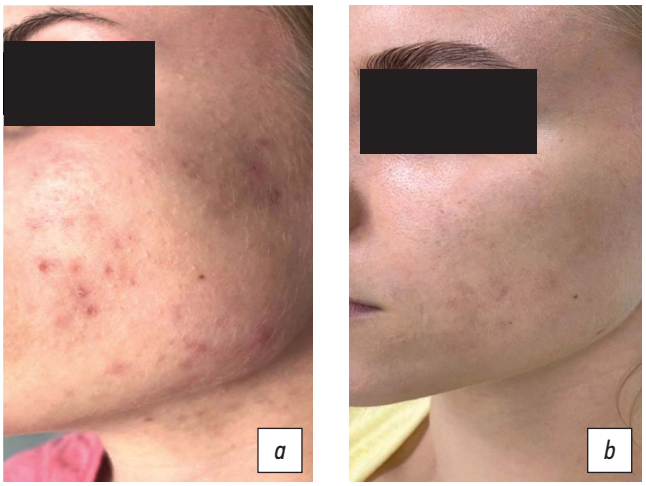



**Fig. 4.** Mild papulopustular acne (few papulopustular elements) in a 19-year-old female patient before (*a*) and after (*b*) treatment with benzoyl peroxide for 6 weeks 1–2 times a day: Clinical remission.

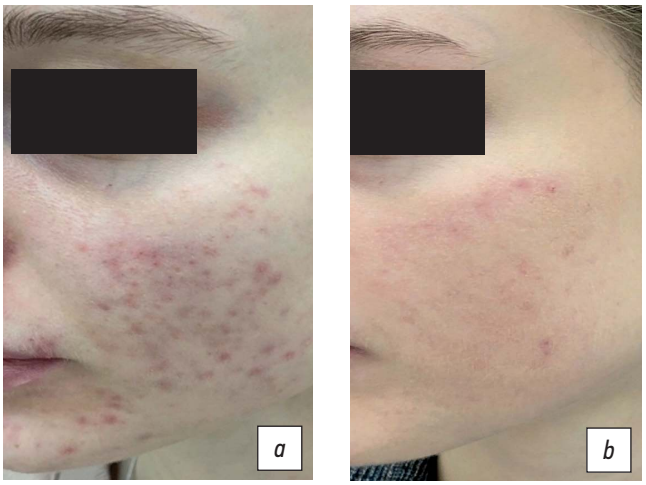



**Fig. 5.** Moderate papulopustular acne (moderate number of papules and pustules, open comedones) in a 20-year-old female patient before (*a*) and after (*b*) treatment with a fixed combination of adapalene and benzoyl peroxide (Effezel) for 9 weeks daily once a day in the evening: Clinical remission.

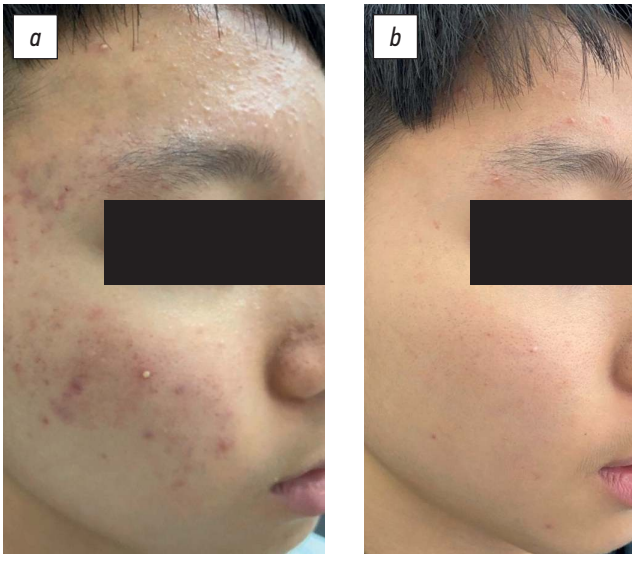



**Fig. 6.** Mild papulopustular acne (single papulopustular elements) in a 14-year-old patient before (*a*) and after (*b*) treatment with benzoyl peroxide for 8 weeks 1–2 times a day: Clinical remission.

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**Fig. 7.** Moderate papulopustular acne (moderate number of papules and pustules, open comedones) in an 18-year-old female patient before (*a, b*) and after treatment (*c, d*) treatment with a fixed combination of adapalene and benzoyl peroxide for 7 weeks daily once a day in the evening: Clinical remission.

agents. The same data was obtained by one of the leading experts in acne, J. Leyden [36], who demonstrated that the antimicrobial drug provides for a greater than twofold reduction *in the number of C. acnes* compared to other external monodrugs, including clindamycin, erythromycin, and azelaic acid.

In moderately widespread papulopustular rashes of moderate acne, as well as in cases of severe forms of the disease, when for any reason it is impossible to prescribe systemic isotretinoin or there is a tendency to scarring of the primary elements, we used a fixed combination of adapalene 0.1% and benzoyl peroxide 2.5%, both as monotherapy for moderate papulopustular acne and in combination with a systemic antibiotic (doxycycline or minocycline) for severe acne. The fixed combination of adapalene and benzoyl peroxide has anti-inflammatory, antimicrobial, keratolytic, sebostatic, comedonal, and anti-comedogenic effects, which synergistically affect the key pathogenic mechanisms of acne. This lends a pathogenetic rationale to the use of this topical agent in the management of acne. A noticeable regression of inflammatory and non-inflammatory elements of acne was observed as early as the first week of treatment. This finding aligns with the results reported by Gollnick et al. [20], who demonstrated a reduction in the number of acne lesions in 1670 patients from diverse geographical regions as early as the first week of therapy.

According to the Global Acne Alliance Expert Consensus, the fixed combination of adapalene 0.1% and benzoyl peroxide 2.5% (Epiduo/Effezel) is recommended as a first-line therapy

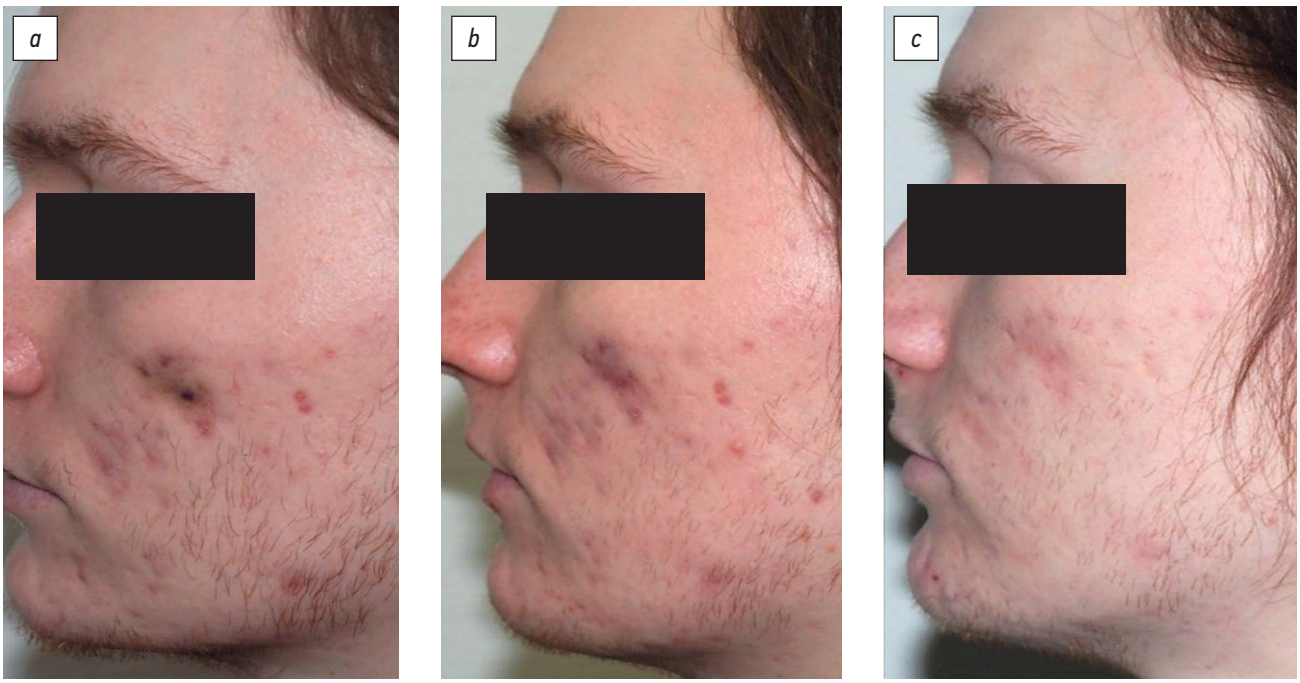


**Fig. 8.** Moderate papulopustular acne (grade IV post-acne scars, 27 points) in a 20-year-old patient (*a*). He was treated with systemic isotretinoin for 9 months (*b*), at the end of the course Longidaza 3000 units intramuscularly (№ 15) and gel with a fixed combination of adapalene 0.1% and benzoyl peroxide 2.5% daily for 4 months, once a day in the evening: Clinical remission (postacne scars grade III, 10 points) (*c*).


**Fig. 9.** Severe acne (papules, pustules, isolated nodules, grade IV post-acne scars, 25 points) in a 21-year-old patient (*a*). He was treated with systemic isotretinoin, followed by a fixed combination of adapalene 0,1% and benzoyl peroxide 2,5% daily once a day in the evening for 6 months: Clinical remission (absence of inflammatory elements, post-acne scars of III degree; 12 points, smoothing of facial skin relief) (*b*).

[38]. Side effects such as redness, burning and itching that may occur at the beginning of treatment can be compensated by using moisturizers and switching to a short period of intermittent application of the drug (every other day) until the skin adapts to the drug.

## CONCLUSIONS

Thus, dermatologists and cosmetologists have a range of external treatments for mild and moderate papulopustular acne with a high level of evidence. In cases of papulopustular acne

with minimal inflammatory lesions (papules and pustules), benzoyl peroxide gel may be a suitable option. For instances of moderately widespread papulopustular acne with comedones (medium severity), a fixed combination of adapalene and benzoyl peroxide may be recommended as a first-line therapy. Furthermore, the drug has been shown to be an effective long-term supportive therapy following a course of systemic isotretinoin. This allows for the maintenance of the therapeutic effect, the prevention of post-acne symptoms, and the equalization of existing atrophic scars. It can also be used in the treatment of severe acne as part of combination therapy with systemic antibiotics when systemic isotretinoin is not an option.

## ADDITIONAL INFORMATION

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**Authors contribution.** Author made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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