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Modern methods of acne treatment in children

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The article is dedicated to one of the relevant issues of childhood and adolescence – acne. It describes modern approaches to acne treatment, including local, systemic and combined therapy and physiotherapeutic treatment methods. The article also presents foreign and Russian data on the use of different groups of drugs for acne therapy and peculiarities of acne treatment in pediatric practice.
Keywords: *acne, treatment, children, adolescents.*

Acne was first described in 542 AD by a Roman Etius Amidenus, personal physician of Emperor Justinian I. However, the disease continues to attract great interest both among Russian and foreign dermatologists. This issue acquires special significance in pediatric practice due to a variety of forms, after-effects for the mental health and a limited range of the means that may be used in children [1].
Acne is the most widespread variant of skin affection among children and adolescents. Thus, according to a retrospective cohort trial, which aimed at assessing contribution of various skin diseases into the general disease incidence, acne spread was 28.6% - more widespread that dermatitis (19.4%) and warts (16.2%) [2]. According to some reports, comedones are observed in all adolescents at least one [3]; acne spread in this age group reaches 70-90% [4, 5].
For many years, physicians have been trying to understand acne pathogenesis: different options are being discussed, including microbial aspects and *Propionibacterum acnes* colonization, excessive sebum production, follicular hyperkeratosis and transitory endocrine profile alterations, including the alterations connected with emotional reactions. An important role among the factors promoting development of acne and affecting its course is given to various gastrointestinal tract disorders [6].
This determines approaches to acne treatment, which include local and systemic therapy, combined therapy and physiotherapeutic treatment methods.

Local acne therapy

The drugs containing an antibacterial or antiseptic agent have traditionally been used for acne treatment, including their combinations with other components.

- **Benzoyl peroxide (Baziron AC)**: the reactant is represented by an antiseptic with antimicrobial activity against *P. acnes* and *Staphylococcus epidermidis*. The drug is allowed for use in children over 12 years of age.
- **Topical antibiotic Zineryt**: a drug combining erythromycin and zinc acetate. Erythromycin has bacteriostatic effect against *P. acnes* and *S. epidermidis*, while zinc reduces production of sebaceous glands' secretion and acts as an astringent. The drug is allowed for use in children over 8 years of age.

- **Azelaic acid (Skinoren)** has keratolytic and antibacterial effect against P. acnes and S. epidermidis; it has antibacterial action, suppresses growth and viability of abnormal melanocytes and prevents post-inflammatory pigmentation. The drug is officially allowed for use in children over 12 years of age.
- **Salicylic acid** has keratolytic, mild anti-inflammatory and antiseptic action. The use of salicylic acid at acne is justified in order to suppress the process of follicular keratinization and comedone detritis loosening. It is used as an alternative remedy for mild acne. Official topical pharmacological remedies and prescription medicines may contain salicylic acid. The drug is allowed for use in children; contraindication – infancy.
- **Topical retinoid Differin** contains a metabolite of retinoid adapalene, which has anti-inflammatory and pronounced comedonolytic action. The drug is officially allowed for use in children over 14 years of age; there is international practice of using the drug in children of 10 years of age.
- **Combination of a topical retinoid and a topical antibiotic (Klenzit-C):** a drug combining adapalene and clindamycin – a multipurpose bacteriostatic antibiotic (lincosamides). The drug is allowed for use in children over 14 years of age.
- **Topical antiseptic Kvotlan** contains cetylpyridinium chloride, which has antimicrobial effect against gram-positive and, to a lesser extent, gram-negative bacteria. It has variable antifungal effect; effective against some viruses; allowed for use in children.

Systemic acne therapy

- **Systemic antibiotics, e.g. Unidox Solutab**; its reactant is represented by doxycycline – a multipurpose antibiotic (tetracyclines). The drug is contraindicated for children under 8 years of age due to a range of side effects. In the real dermatological practice, it is usually prescribed to children from 14 years of age. Another representative of this group is **minocycline hydrochloride**; however, the experience of using this drug in patients with acne is rather limited.
- **Systemic isotretinoin (Roaccutane, Acnecutan)**: reactant – isotretinoin. The drugs' action is connected with suppressed activity of sebaceous glands and histologically confirmed reduction in size. Moreover, isotretinoin has a confirmed anti-inflammatory effect on skin. Indications to use are severe forms of acne (nodulocystic acne, acne conglobata or acne with risk of scar formation) and the acne that do not yield to other types of therapy. Contraindications to the use of isotretinoin are hepatic failure, hypervitaminosis A, pronounced hyperlipidemia, concurrent tetracycline therapy, pregnancy, breast feeding period, age under 12 years and increased sensitivity to the drug or its components.

A widespread additional method of treatment is phototherapy. Polarized light is allowed for use at any age; blue and red light phototherapy is contraindicated to children under 14 years of age. One of the trials demonstrated a higher efficacy of blue light against inflammatory elements than topical 1% clindamycin, while a combination of blue and red light was more effective that benzoyl peroxide therapy and blue light phototherapy [7].

An algorithm of acne treatment on the basis of disease severity is given in the tb. [8].

Peculiarities of acne treatment in pediatric practice

Therapy including antibacterial local and systemic drugs

Usually, local drugs are prescribed at mild acne with inflammatory elements. Topical antibiotic erythromycin has less side effects; however, given the altered sensitivity profile, it is reasonable to prescribe clindamycin; its efficacy and safety have also been demonstrated by a range of randomized controlled trials [9, 10]. There are data on the use of these drugs in children of 0-1 years of age with mild acne [11].

The main problem in case of local treatment with macrolides is high resistance of *P. acnes* strains to antibacterial drugs. At the same time, most strains are sensitive to the combined therapy with an antibiotic and benzoyl peroxide [12].

In one of the recent trials, L.F. Eichenfield et al. demonstrated high efficacy and safety of a local combined drug – 1.2% clindamycin phosphate and 3% benzoyl peroxide [13]. The trial involved 1,319 patients from 12 years of age. The authors compared monotherapy with each drug to combined treatment in the fixed dosages. Efficacy and safety were assessed in treatment weeks 2, 4, 8 and 12. Along with higher efficacy and considerable inflammation reduction, according to the common scale of statistical appraisal (Investigator's Static Global Assessment, ISGA), safety of using combined therapy was the same as the safety of benzoyl peroxide monotherapy.

In their trial, A. Langner et al. compared efficacy of combined local therapy at mild and moderate face acne; in the first case it involved 1% clindamycin and 5% benzoyl peroxide, in the second – 4% erythromycin and 1.2% zinc acetate [14]. 72 patients had been receiving treatment with the first combination of drugs OD for 3 months; 75 patients – with the second combination of drugs BID for 3 months. Efficacy was assessed in weeks 1, 2, 4, 8 and 12. This trial demonstrated a range of advantages of combined treatment with clindamycin and benzoyl peroxide over erythromycin and zinc acetate. Thus, the authors observed the effect of the first combination of drugs in the first week of treatment; tendency to the higher efficacy of clindamycin and benzoyl peroxide was observed at all stages of the clinical trial. Moreover, single application of the drug a day was more convenient for patients and promoted better adherence to the treatment. Both variants of therapy demonstrated high level of safety [14].

Systemic antibacterial therapy remains the main method of treating moderate and severe acne in children. At the same time, the use of certain drugs may be restricted due to the patients' age. Thus, tetracycline may only be prescribed to children over 8 years of age due to high risk of teeth color alteration and enamel hypoplasia in the setting of the drugs' use in younger children.

Analysis of prescriptions of dermatologists and pediatricians revealed that dermatologists prefer doxycycline and minocycline as a systemic antibiotic for treating children over 8 years of age, while pediatricians use tetracycline more often [15]. Advantages of doxycycline and minocycline for pediatric practice are smaller number of uses per day (OD-BID; tetracycline – QID), which promotes better adherence to the treatment of the problem adolescent group of patients, higher sensitivity of *P. acnes* to them and lower risk of development of gastrointestinal tract's side effects. When selecting a therapy, it should be considered that high antibiotic resistance to tetracyclines has formed in recent years [15].

S. Babaeinejad et al. compared efficacy and safety of systemic therapy with doxycycline and azithromycin in patients of different age groups [16]. The randomized double-blind clinical trial involved 100 patients with moderate acne; 50 people of the first group had been receiving daily 500 mg of azithromycin for 4 days a month for 3 months; 50 patients of the second group were treated with 100 mg of doxycycline per day on the basis of the same scheme. Efficacy and safety had been being assessed every treatment month and for 3 months after the therapy course was finished. According to the obtained results, both antibiotics were effective in the group of patients under 18 years of age; no considerable side effects were registered in any of the groups. It should be mentioned that doxycycline demonstrated a much higher efficacy in the group of patients over 18 years of age [16].

Apart from tetracyclines, macrolides are also used to treat acne. Erythromycin is a drug of choice for patients with contraindications to tetracycline antibiotics; it is widely used even in pregnant women and children under 8 years of age. Restricted application of this antibacterial drug among other groups of patients is caused by the development of the *P. acnes* strains resistant to it. According to C.G. Burkhart et al., resistance to erythromycin is registered in 42% of cases [17]. The daily dose of the drug both for children and adult is 1,000 mg (500 mg BID).

Another drug of this group of antibiotics is azithromycin; its safety and efficacy have also been confirmed in the group of children and adolescents. Thus, the trial by F. Bardazzi involved 52 adolescents with moderate and severe papulopustular acne. All patients have been receiving

treatment with azithromycin only in the dose of 500 mg per day 3 days a week for 2 months. Efficacy and safety were assessed every 2 weeks and 4 months after the therapy course was finished. The author observed a more than 20% reduction in skin manifestations in 47 adolescents within the first month of treatment. Azithromycin had the best efficacy in the form of almost complete regression of skin manifestations in 32 patients, the least – in 6. The drug's side effects included pyrosis and nausea (in 3). The therapy effect was intact 4 months after the treatment course was finished. Low azithromycin efficacy in 6 adolescents was probably caused by low adherence to the treatment [18].

Thus, despite high resistance of *P. acnes* strains, macrolides remain one of the main antibacterial drugs for acne due to their high safety, especially in the groups of children and pregnant women.

Therapy with local and systemic retinoids

Topical retinoids remain highly effective remedies for acne with mild inflammation and are prescribed by dermatologists to every second adult patient. At the same time, their prescription in the modern pediatric dermatological practice is restricted. According to B.A. Yentzer et al., pediatricians resort to this group of drugs only in 12% with acne manifestations [15].

Restricted experience of use and few trials of efficacy and safety of local retinoids in children are caused primarily by fear of development of side effects. One of the works demonstrated efficacy and safety of 0.04% tretinoin gel for mild and moderate acne in 40 children of 8-12 years of age. Local therapy had been conducted for 3 months; treatment efficacy was assessed in weeks 3, 6 and 12. Significant reduction in acne manifestations was observed by the end of the trial, according to the Evaluator's Global Severity Score and Alternative Evaluator's Global Severity Score. The only side effect observed by the authors was insignificant skin irritation, which did not require the drug's withdrawal [19].

Similar results were obtained by a different group of scientists (J. Jorizzo et al.) as well, who studied efficacy and safety of 0.04% tretinoin gel at moderate face acne in a group of 245 patients of 11-16 years of age. The treatment had been conducted for 3 months; significant reduction in both inflammatory and non-inflammatory elements was observed in the end. Side effects in the form of skin irritation were observed in 30% of patients and did not require therapy withdrawal [20].

Despite the indicated age restriction (from 12 years of age), systemic retinoids (isotretinoin) are extremely rarely used in pediatric practice, largely due to the description of such side effects of this drug as depression, psychosis, suicidal ideation and attempts and teratogenic action by FDA in 1998.

Nevertheless, some authors still consider isotretinoin as a drug of choice for the severe acne resistant to the combined antibacterial and local therapy [21]. Given a wide range of indications to use, in children and adolescents as well, there has been a need in accurate evaluation of isotretinoin safety, which is why physicians of the University of California developed a rating scale of the possible side effects, including xerochilia, xerophthalmia, xeroderma, myalgiae, epistaxis, frequency of headaches, mood swings, depression, suicidal ideation, skin rash, aggravation of mesopic vision and increased photosensitivity.

The researchers conducted retrospective analysis of 123 medical records of patients of 11-21 years of age. These patients received isotretinoin therapy and filled in a questionnaire, where they listed all their complaints, during each visit. It should be mentioned that the side effects revealed in children were the same as the side effects in the group of adult patients: thus, e.g., xerochilia and xeroderma were observed in 94.25 and 72.13% of cases, respectively. Mental disturbances developed in 1.65% of patients in the setting of therapy; their spread was not significantly different from the spread in patients with mental disorders in anamnesis. Moreover, side effects were almost the same in patients of 11-15 years of age and 16-21 years of age; the only difference was that mesopic vision impairment, epistaxis and xerophthalmia were significantly more often observed in older patients. That trial demonstrated low spread of mental disorders in both the children and adolescents receiving isotretinoin therapy [21].

On the contrary, psychodermatological group of the French Dermatology Society proved an extremely high spread of mental disorders, including depression and suicide attempts, among adolescents. The indicated disorders were prevalent in patients with severe acne; isotretinoin did not aggravate mental pathology in that group of patients [22]. It should be mentioned that one of the trials demonstrated reduction in depression symptoms in adolescents with moderate and severe acne in the setting of systemic retinoid treatment [23].

A range of works analyzed cases of prescription not only of topical, but also of systemic retinoids to children of the first years of age. Thus, a retrospective trial per 1985-2007 conducted in France on the basis of several child centers involved 16 children under 24 months of age with both inflammatory (papules, pustules and nodules) and non-inflammatory (open and closed comedones) elements and disease duration of more than 2 months. Such an amount of patients is evidently caused by low spread of acne among small children. It should be mentioned that 3 children had not been receiving any treatment; skin manifestations regressed in them unassisted. Other children were prescribed drugs; 8 of them received combined treatment. 4 patients received local benzoyl peroxide therapy, 5 – antibiotic therapy, 7 – retinoid therapy. 4 children were prescribed systemic treatment with zinc salts, 2 – with macrolides; 2 children had been receiving isotretinoin. No side effects of the conducted therapy were registered in that trial; however, such a small sample does not allow us to widely extrapolate the obtained results on a different group of patients [24].

Several other trials confirmed efficacy and safety of retinoid treatment of children of 0-1 years of age. Thus, C.J. Barnes et al. described 2 cases of isotretinoin use in children of 0-1 years of age with the cystic acne resistant to treatment with other drugs. Isotretinoin dosage varied from 0.2-1.5 mg/kg per day. Treatment duration was 5 and 14 months. Isotretinoin treatment demonstrated high efficacy and did not result in the development of significant side effects in these children [25].

In whole, results of the conducted trials do not allow speaking of a possibility of wide use of systemic retinoids in children. These drugs should only be prescribed in case there are considerable indications in the form of the severe acne resistant to the combined therapy. At the same, it is necessary to accurately count all pros and contras in each case and inform adolescents and their parents of the possibility of undesirable effects, need in contraception and importance of follow-up observation by a doctor.

Peculiarities of the use of different forms of drugs

An important role in the modern acne pharmacotherapy in children and adolescents is given to the development of combined drugs. On the one hand, this is caused by the fixed content of components, on the other – by a smaller number of uses per day; this increases adherence to the treatment. The most interesting among the new fixed combinations are an antibiotic and benzoyl peroxide, an antibiotic and a retinoid, benzoyl peroxide and a retinoid [26].

Another important aspect determining efficacy and adherent to treatment, along with the selection of a drug itself, is the drug's pharmaceutical form. Thus, ointments, creams, gels and solutions are convenient and are more willingly used by children and adolescents. New topical forms of drugs, such as foam and hydrogel, have been recently introduced into clinical practice; their main advantages are easy putting, including putting on a large skin surface area, and the possibility of use on pilary skin segments. Several drugs are manufactured in this form: clindamycin in the form of aqueous-alcoholic foam and a combined drug of 0.025% tretinoin and 1.2% clindamycin in the form hydrogel.

Physiotherapeutic methods of acne treatment

Data on successful use of non-medicated methods of acne treatment have been being published more often recently due to, on the hand, appearance of the antibiotic-resistant *P. acnes* strains, on

the other – an attempt to reduce drug dosage, thus reducing the possibility of development of side effects.

It has long been known that natural light allows reducing acne intensity: firstly, ultraviolet radiation has bactericidal effect; secondly, it suppresses skin inflammatory processes [27, 28]. Data of these trials stimulated development of new methods of acne treatment with lasers and other light sources. Physically speaking, the therapeutic mechanism may be explained as follows: *P. acnes* produce porphyrins, which result in the production of singlet oxygen, which has a bactericidal effect, and an anti-inflammatory radiation effect at light absorption [29]. Depending on the wave length, this mechanism may target either bacteria or sebaceous glands.

Phototherapy and photodynamic therapy are distinguished; the latter requires putting the drug, which is activated by light. Such substances include methyl aminolevulinate and 5-aminolevulinic acid [30]. Analysis of the trials using physiotherapeutic methods of acne treatment showed that the exclusion criteria almost always involved the age under 18 years [30-36].

One of the trials aiming at comparing phototherapy efficacy in the blue light range and local clindamycin therapy involved patients over 13 years of age [37]. The trial involved 25 patients of 13-55 years of age with mild and moderate acne. 13 patients had been receiving locally 1% clindamycin BID for a month, 12 patients – phototherapy with a 417 nm-long wave twice a week. Reduction in inflammatory manifestations was observed in 36% of patients in the setting of physiotherapeutic treatment in comparison with 14% of patients from the control group. At the same time, the authors did not reveal significant difference using the Evaluator's Global Severity Score and the Alternative Evaluator's Global Severity Score.

It should be mentioned that efficacy of physiotherapeutic methods of treatment had been being studied on a small sample of patients (10-46 people) for a short period of time (4-12 weeks). The study of efficacy of phototherapy involved both placebo [38, 39] and different variants of local therapy [36, 37] as a method of control. Moreover, the authors assessed treatment efficacy on the basis of the wave length [7]. They observed slight advantage of light exposure in blue and red light range in comparison with local treatment with 5% benzoyl peroxide [7], though phototherapy used as the only method of treatment did not show significant efficacy in whole.

The trial revealed some advantages of photodynamic therapy, especially in the setting of combined treatment and lack of an inflammatory component. However, according to C.K. Yeung et al., local therapy with 1% adapalene was more effective than physiotherapeutic methods of treatment [33]. That group of scientists involved 30 people of 18-41 years of age with moderate face acne in their trial. All participants had been receiving 1% adapalene gel. All patients were divided into 3 groups: the first group had been receiving photodynamic therapy with a 530-750 nm-long wave and methyl aminolevulinate, the second – phototherapy, the third – only adapalene. Efficacy was assessed every 3 weeks and 4 and 12 weeks after the treatment was finished. According to the obtained results, inflammation was significantly reduced only in the control group: efficacy was confirmed in 53 and 65% of cases in the first group in weeks 4 and 12, respectively, in the group – in 22 and 23%, in the third – 72 and 88% of cases.

Moreover, side effects of the photodynamic therapy, such as painful sensations during the procedure, risk of erythema development, aggravation of the disease and epithelium detachment in the initial treatment period should be carefully observed [31, 34, 40]/

We consider therapy with polarized light one of the prospective methods of acne treatment. The method is based on the exposure to light with a wide wave length range (480-3,400 nm); this ensures different penetrability of the radiation, simultaneous influence on several "targets" and specificity of photoreactions. Integral visible and infrared radiation cause heat evolution in skin, which alters impulse activity of thermomechanical-sensitive skin fibers, activates reflexosegmental and local microvascular reactions, which result in intensification of local blood flow and lymph drainage, stimulates lipid and carbohydrate metabolism and increases myotility [41].

Penetrating tissues at a depth of down to 2.5 mm, this light has a stimulatory action on regenerative processes and normalizes blood circulation. When treating acne, the patient is to be exposed to polarized light 1-2 times every day for 8-10 minutes per site. The light is directed at a straight angle to the treated surface of the previously cleaned skin. The treatment duration is to be at least 2 weeks, with a break of 2-3 weeks; according to the authors, the total duration of the polarized light therapy course is to be at least 6 weeks [41].

Thus, physiotherapeutic methods are becoming gradually implanted into clinical practice of both Russian and foreign dermatologists. Further development of this prospective sphere of medicine will allow minimizing risk of development of side effects, vividly confirmed by Russian authors through the example of polarized light therapy. However, small sample and young age of the patients, lack of long-term results and short-term side effects do not allow speaking about using physiotherapeutic methods as monotherapy and introducing them into recommendations on acne treatment in children.

Practical difficulties of managing children with acne

Low adherence of children and adolescents with acne to treatment can be explained by characterological peculiarities of patients of this age group and need in a long-term systemic multiple use of drugs within a day [42]. Thus, according to H.L. Richards et al., only 50% of children and adolescents with chronic skin diseases adhere to the intended treatment plan [43].

Methods of overcoming such “resistance” include the use of questionnaires for the parents of children with acne aimed at determining the main treatment-hindering factors [44]. One of the trials revealed that most parents are concerned about the price of drugs and safety of their use and see no reason for daily treatment [45]. Thus, the importance of founding special school for the parents of children with chronic skin diseases has been shown.

Another work studied different methods of increasing adherence to treatment in the group of adolescents directly. Interestingly, the highest adherence to treatment had those adolescents, who often visited doctors themselves (82%), the lowest – those children, who had to be reminded to take the drug by parents (36%) [42]. It is also important to develop combined drugs with fixed doses and simpler schemes of application [26].

Conclusion

Nowadays, high acne spread in children and adolescents sets several difficult problems connected with the selection of a safe, effective and timely therapy with a simple dosage scheme and a child-friendly method of application for pediatricians and dermatologists. It should also be considered that it is important to conduct active acne treatment for children of different age groups, especially for adolescents, whereas the refusal of therapy motivated by doctors’ or parents’ fears or children’s unwillingness may result in irreversible alterations of the patients’ skin and, furthermore, emotional sphere.

Moreover, it is extremely important to conduct randomized controlled clinical trials of efficacy and safety of the drugs used to treat acne; this process is in most cases hindered by the need in involving children and adolescents in it.

Further introduction of physiotherapeutic methods within combined therapy into clinical practice is prospective; it will allow reducing drug dosages and minimizing risk of development of side effects.

Table. Acne treatment algorithm

Severity	**Mild**		**Moderate**		**Severe**
Treatment variant	**Comedones**	**Papulopustular elements**	**Papulopustular elements**	**Nodular elements**	**Nodular elements**

					and acne conglobata
First line drugs	Topical retinoid	Topical retinoid + topical antibiotic	Systemic antibiotic + topical retinoid +/- benzoyl peroxide	Systemic antibiotic + topical retinoid + benzoyl peroxide	Systemic isotretinoin
Alternative treatment	Alternative topical retinoid or azelaic acid or salicylic acid	Alternative topical retinoid or antibiotic + alternative topical retinoid or azelaic acid	Alternative systemic antibiotic + alternative topical retinoid +/- benzoyl peroxide	Systemic isotretinoin or alternative systemic antibiotic + alternative topical retinoid +/- benzoyl peroxide / azelaic acid	Systemic antibiotic (high dosage) + topical retinoid + benzoyl peroxide
Supporting therapy	**Topical retinoid**		**Topical retinoid +/- benzoyl peroxide**		

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