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Resistant Forms of Acne

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Abstract

The global problem of increasing cases of antibiotic resistance in patients with acne is mainly determined by the regional prescription practices and patient compliance with doctor's directions and genomic variability of *Propionibacterium acnes*.

The research was aimed at analyzing the causal profile and risk factors for development of resistant forms of acne.

Crosssectional study of the causal profile was conducted and risk factors for development of resistant forms of acne were studied on the basis of dermatological clinics of the city in Kazan, Republic of Tatarstan, among 983 patients with acne of both genders aged 18 to 41 years. Bacteria were isolated using the bacteriological method, sensitivity to antibiotics was determined by the Kirby-Bauer disk diffusion test, the risk factors were analyzed by calculating the odds ratio in the procedure of logistic regression.

Most often, the pathogens of the disease were *Propionibacterium acnes* (70.60%). The share of resistant strains was 91.66% with erythromycin, 91.25% with clindamycin, 96.64% with azithromycin, and 91.35% with laevomycetin ($p<0.001$). The highest sensitivity was observed for levofloxacin (96.74%) ($p<0.001$). Risk factors were smoking (OR=3.15; 95% CI: 0.57-2.61), disruptions of the hormonal-endocrine profile (OR=4.71; 95% CI: 2.43-5.12), being female (OR=1.41; 95% CI: 1.04-2.99), duration of disease over 5 years (OR=3.16; 95% CI: 1.67-4.03), and impractical antimicrobial therapy (OR=5.11; 95% CI: 3.17-6.15).

Reducing the frequency of resistant forms requires rational prescription of antibacterial preparations, prescription delivery of antibiotics, and reduction of individual risk factors.

Keywords: acne, Propionibacterium acnes, resistant strains.

INTRODUCTION

Acne (acne vulgaris) is a chronic inflammatory disease, the main clinical manifestations of which are open or closed comedones, as well as papule, pustule and node-like skin lesions. To date, an impressive number of studies showing the multiple nature of this pathology have been made [1].

Emergence of the inflammatory component of acne is promoted both by the presence of pathogenic bacteria and by the accumulation of sebaceous glands detritus, dead cells of the stratum corneum, free fatty acids that appear during the life cycle of microorganisms and are excreted as a result of sebaceous glands' walls laceration, in the peripheral areas of the concerned tissue. With that, it is assumed that the key triggers of the inflammatory reaction are free fatty acids [2].

The main etiological agents of acne are lipophilic anaerobic bacteria of species *Propionibacterium acnes (P. acnes)*, colonizing in the lower parts of the follicular channel. The fatty acids excreted by propionibacteria have high inflammatory reactogenicity. Given the fact that other pathogenic bacterial agents are mainly localized in the surface sections of excretory ducts of the sebaceous glands, their lipolytic activity does not become a direct pathogenic factor of skin inflammatory reaction and acne development [3; 4].

Many scientists from around the world have reported an increased number of cases of resistance to antibiotics during acne therapy, pointing out to the multifactor nature of the isolated strains resistance development, including the use of various methods of therapy, the patient's compliance with the doctor's prescriptions, concomitant treatment, etc. [5; 6; 7; 8; 9; 10].

The most important determinant of resistivity is the method of assessing the levels of minimum inhibitory concentration (MIC), which is not homogeneous in all studies [11; 12; 13; 14; 15; 16; 17].

Some authors believe that the role of the one of key acne etiological agents - *P. acnes* - may be overestimated [18], and propose to use predominantly retinoids, benzoyl peroxide (BPO) and other antiseptics (Zn, etc.) for treatment [19].

The pathogenesis of development of *P. acnes* resistance to antibiotics is mainly due to point mutations and acquiring new genetic sequences [20].

There is an evidence of resistance in more than half of the isolates of *P. acnes*, mainly to topical erythromycin and clindamycin, and especially to tetracyclines [20; 21].

Thus, despite certain success in the evolution of acne therapy with antibacterial agents, retinoids and other medications, the medical community increasingly more frequently faces the growth in the number of cases of acne forms that are resistant to antibiotic therapy; this greatly increases the relevance of research in this area.

The research was aimed at analyzing the causal profile and risk factors for development of resistant forms of acne.

MATERIALS AND METHODS

Patients

Crosssectional study of the causal profile was conducted and risk factors for development of resistant forms of acne were studied on the basis of dermatological clinics of the city in Kazan, Republic of Tatarstan, between May and December 2017. The total number of participants was 983 people of both sexes aged 18 to 41 years, the median age was 29 years (quartile 25: 21 years old; quartile 75: 35 years old). Most participants of the study were females, accounting for 61.04% (600 of 983) participants.

Methods

To determine the causal profile, the pathogens from affected skin of patients with acne were bacteriologically studied using the method of prints on the nutrient medium followed by cultivation and analysis of the susceptibility to antibacterial effects.

Sensitivity of pathogens isolated from the surface of the skin was determined using the disk diffusion method according to the EUCAST standard.

Acne severity was assessed using the global rating system [22].

Ethics

Before the research, all participants were informed and consented to be included with previous receipt of the approving decision of the local ethical commission. Personal data were entered into the shared database under a special code, access to which was only granted to the main researcher. Every patient volunteered to participate in the research, and received assurances of anonymity and confidentiality of their personal data.

Statistical analysis

The results of the research were analyzed using the methods of descriptive statistics. For categorical variables, the data were shown as absolute and relative numbers. For quantitative data, central tendencies were measured; for the data with the distribution that was different from normal (asymmetric), the result ws expressed as the median and the 25-75 percentile. For qualitative data, the significance of the difference in the groups was determined by calculating the Chi-square ($\chi 2$); to determine the degree of influence of each risk factor during the development *P. acnes* strains resistance, the procedure of logistic regression

was performed with determining the odds ratios (OR) and its 95% confidence interval (95% CI). The critical level of significance of differences in the groups was set at probability of first type errors $\alpha<0.05$. The procedure of the statistical analysis was performed using the SPSS 20 application for Windows.

RESULTS

Using the global system of assessing acne [22], most patients (58.1%) had acne of moderate severity, 20% of patients had acne of light severity, and 21.9% of the studied individuals had severe form of acne.

The most frequent etiological agents of acne development were bacteria of species *P. acnes*, whose share amounted to 70.60%. In terms of frequency of detection, the second place was taken by bacteria St. Epidermidis – 19.43%. Both types of pathogens were significantly different in terms of detection frequency from the pathogens of other species, the share of which was only 9.97% (χ^2=52.65; d.f.=1; p=0.01 and χ^2=3.92; d.f.=1; p=0.04) (Figure 1).

Given the fact that in terms of the frequency of etiological causes in patients with acne the leaders were bacteria of species *P. acnes*, the susceptibility of this agent to various antibiotics used in local hospitals was assessed (Table 1).

The greatest number of resistant strains of P. acnes was identified in relation to the effect of erythromycin (91.66%), clindamycin (91.25%), azithromycin (96.64%) and laevomycetin (91.35%) (p<0.001). The maximum activity in terms of suppressing the growth of P. acnes was detected in tetracycline (67.34%), doxycycline (47.61%) and levofloxacin (96.74%) (p<0.001) (Table 1).

Table 1 – Susceptibility of *P. acnes* to various antibiotics.

Antibiotic	Sensitive strains, abs.p. (%)	Resistant strains, abs.p. (%)	p-rating
Erythromycin	82 (8.34)	901 (91.66)	<0.001
Clindamycin	86 (8.75)	897 (91.25)	<0.001
Azithromycin	33 (3.36)	950 (96.64)	<0.001
Tetracycline	662 (67.34)	321 (32.66)	<0.001
Doxycycline	468 (47.61)	515 (52.39)	<0.001
Levofloxacin	951 (96.74)	32 (3.26)	<0.001
Laevomycetin	85 (8.76)	898 (91.35)	<0.001

To determine the degree of each risk factor's contribution to the development of *P acnes* resistance, the logit regression procedure was performed. OR exceeding 1.0 showed the presence of statistically significant contribution, and the coefficient itself showed how many times the chances of acne form resistant to antimicrobial treatment increased.

It has been found that the most important risk factors are smoking (OR=3.15; 95% CI: 0.57-2.61), disruptions of the hormonal-endocrine profile (OR=4.71; 95% CI: 2.43-5.12), being female (OR=1.41; 95% CI: 1.04-2.99), duration of disease over 5 years (OR=3.16; 95% CI: 1.67-4.03), and impractical antimicrobial therapy (OR=5.11; 95% CI: 3.17-6.15) (Figure 2).

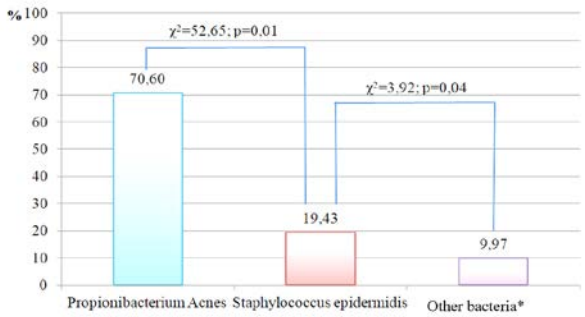

Figure 1 – The causal profile of acne causative agents among the study participants.

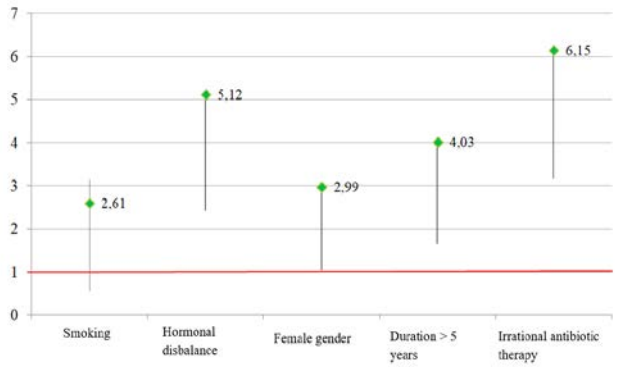

Figure 2 – Risk factors for development of a resistant form of acne.

DISCUSSION

The etiological profile and the risk factors for development of resistant forms of acne have been determined in the paper. The structure of the study meets the trend of modern scientific research. However, despite the numerous studies of resistance to antibiotics in acne therapy [5; 6; 7; 8; 9; 10; 11; 12; 13; 14; 15; 16; 17], there is a problem today of the lack of studies that compare various treatment groups, namely antibiotics and retinoids and/or benzoyl peroxide, in terms of the structure of resistance to antibiotics.

The use of antibiotics in acne therapy associated with development of *P acnes* resistance was mainly mediated by the appearance of point mutations [5]. Researchers from several countries in their works showed the presence of resistance in more than half of *P. acnes* isolates, mainly to topical erythromycin and clindamycin, and especially to tetracyclines [5; 6; 7; 8; 9; 10; 11; 12; 13; 14; 15; 16; 17].

It should be noted that clinical efficiency of topical erythromycin decreased from the 1970s to 2002 due to the growing resistance of bacteria to antibiotics [21].

Resistant strains of *P. acnes* can be identified on the skin of patients with acne before prescribing antibacterial treatment [21].

It is also reported that resistant *P. acnes* may cause severe infections, therefore the current practice of prescribing may be a risk for the contacts not treated before, especially for those who have the symptoms of reduced immune response to the bacterial infection [20].

The evolution of modern technology in treating acne is aimed at preventing the emergence of bacterial resistance and at the use of new efficient safe medications (topical and systemic), depending on the clinical form of the disease [23].

Bacterial antimicrobial resistance may be the result of chromosome mutation or acquisition of the corresponding gene by the bacteria. Resistance of *P. acnes* is mainly mediated by chromosome mutations. Cross-resistance between erythromycin and clindamycin is associated with point mutations in the genes encoding subunit 23S of the ribosomal RNA caused by resistance of macrolide-lincosamide (clindamycin)-streptogramin B (MLS) to antibiotics [24].

Resistance of *P. acnes* to tetracycline is often associated with a mutation in the 16S ribosomal riziform of the small ribosomal subunit in the equivalent base of E.coli 1058 (G-C). Resistance to MLS antibiotics in *P. acnes* may also be mediated by acquisition of transposone Tn5432, the gene that gives resistance to erythromycin (X). The transposone-mediated resistance of isolates to MLS is 8.9% [17].

The prevalence of antibiotic-resistant *P. acnes* increases worldwide with different rates in various parts of the world, showing the growth from 20% in 1979 to 64% in 2000. With that,

higher rates of resistance are observed to clindamycin and erythromycin, compared to tetracycline [21; 25].

The research mostly reflects the trend to the high resistance to macrolides and low level of resistance to levofloxacin worldwide [5].

During the research, it was found that among the studied group of patients, the main etiological agent of acne were bacteria of species *P. acnes* and St. Epidermidis. According to some scientists, resistance of *P. acnes* may be related to over-the-counter sales of antibacterial medications, as evidenced by lower levels of the incidence rate of resistance in countries with "state control" of antibiotics sales over the pharmaceutical network [26; 27].

Most frequently, resistant isolates of *P. acnes* were found in relation to the action of erythromycin, clindamycin, chloramphenicol and azithromycin. High levels of resistance to macrolides in this study may be explained by the wide use of this antibiotic group, the duration of their administration, patients' non-compliance with the prescriptions of doctors, and over-the-counter sales of antibiotics in our region. The maximum sensitivity in this work was observed in relation to levofloxacin.

In the study of J. K. Tan et al. it has been shown that female gender, mature age, and duration of the pathology over 5 years are additional risk factors in female patients with acne [28; 29]. A number of works confirm the role of tobacco in acne development and worsening its severity. It has been noted that smokers suffer from more severe forms of acne, compared to non-smoking patients [30; 31]. However, some other issues on resistance of *P. acnes* to treatment should be considered: some authors stated about the possible electromagnetic mechanisms for this process [32-35].

The procedure of logit regression in the analysis of risk factors showed that smoking women with hormonal and endocrine disorders, duration of the disease over 5 years, who irrationally used antibiotic therapy, were 2.61-of 6.15 times more likely to manifest resistant forms of acne.

CONCLUSIONS

Possible solutions to the problem of treating acne caused by resistant bacteria *P. acnes* consist in rational prescription of antibacterial medications from the group of macrolides, monitoring sales of antibiotics in the pharmaceutical network, and reducing individual risk factors, such as smoking and hormonal and endocrine disruptions.

Prospective studies of the genetic determinants of resistance of *P. acnes* bacteria in the region and consideration of effective schemes of combined therapy are required.

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