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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

**MODERN APPROACHES TO CLINICAL
AND LABORATORY DIAGNOSTICS, TREATMENT
AND PREVENTION OF MYCOSES OF EYES**

Specialty: 3202.01 – Epidemiology
3219.01 – Eye diseases

Field of science: Medicine

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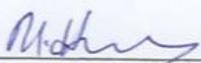
The work was performed at the on the basis of the Department of Epidemiology and Ophthalmology of Azerbaijan Medical University and the Educational and Surgical Clinic of Baku.

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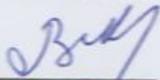
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RELEVANCE OF THE TOPIC AND DEGREE OF ITS DEVELOPMENT

Mycotic infections are still a pressing health problem. Even fifty years ago, ophthalmicosis were relatively rare. In the ophthalmological special literature, only isolated cases were described, when fungal etiology of the disease was established by cultural methods or simply the presence of the disease was assumed^{1, 2}. Such cases of observations are relatively less common compared to bacterial diseases; the frequency of eye mycosis is steadily increasing. At the same time, the pathological process involves both appendages of the eye: conjunctiva, eyelids, eye, tear organs, and all parts of the eyeball directly: sclera, cornea, retina, vascular shell of the eye, vitreous body and eye nerve.^{3,4} Mycotic keratitis, commonly known as fungal keratitis, is about 1-44% of all cases of microbial keratitis, depending on the geographical location. In general, it is more common in tropical and subtropical regions. The delivery, which usually causes corneal infection, includes *Fusarium*, *Aspergillus*, *Curvularia*, *Bipolaris* and *Candida*. Most of these species are saprophytes. They invade injured or immunologically weakened cornea. Rare fungal pathogens include *Fonsecaea pedrosoi*, *Lasiodiplodia theobromae*, *Cylindrocarpon* species, *Scedosporium prolificans*, *Metarhizium anisopliae*, *Paecilomyces* species and *Pythium insidiosum*. Most currently available antifungal

¹ Андреева, С.Э. Анализ изменений центральной зоны глазного дна при миопии по данным флюоресцентной ангиографии и оптической когерентной томографии // - Москва: Вестник офтальмологии, - 2015. № 4, - с.38-48

² Essman, T. Treatment outcomes in a 10-year study of endogenous fungal endophthalmitis / T.Essman, H.Flynn, W.J.Smiddy // *Ophthalmic Surg Lasers.*, - 2017. 3, p. 185-194.

Никольская, Г.М., Сидорова, М.В. Актиномикоз слезоотводящих путей // - Санкт-Петербург: Проблемы медицинской микологии, - 2017. №10, - с.42- 48.

³ Никольская, Г.М., Сидорова, М.В. Актиномикоз слезоотводящих путей // - Санкт-Петербург: Проблемы медицинской микологии, - 2017. №10, - с.42- 48.

⁴ Andersson, U. High mobility group 1 protein (HMG-1) stimulates proinflammatory cytokine synthesis in human monocytes / U.Andersson, H.Wang, K.Palmblad [et al] // *J Exp Med.*, - 2017. 4, -p.565–577.

drugs have limitations such as low bioavailability and limited eye penetration, especially in cases of deep lesions ^{5, 6}. These factors, especially in cases of severe fungal keratitis, explain the slow resolution of fungal infections, in most cases, therapeutic penetrating keratoplasty is required ^{7, 8, 9, 10}. PCR has become a sensitive and specific test for diagnosis of fungal eye damage. In different studies, PCR was compared with traditional diagnostic methods in cases of suspected fungal keratitis. PCR has the highest positive detection rate, especially in cases with negative results of the cultural method or microscopy of smear. PCR has become a sensitive and specific test for diagnosis of fungal eye damage. In different studies, PCR was compared with traditional diagnostic methods in cases of suspected fungal keratitis. PCR has the highest positive detection rate, especially in cases with negative results of the cultural method or microscopy of smear ^{11, 12, 13, 14}.

⁵ Южаков, А.М. Основные направления в ликвидации устранимой слепоты в РФ // - Москва: Окулист, - 2016. № 4, - с.6-9.

⁶ Gimbel, H.V. Intracameral vancomycin rationale and experience // J. Cataract Refract. Surg. Today, - 2017. 1, - p. 71-74.

⁷ Потекаев, Н.Н., Корсунская, И.М. Микотическая инфекция в России: заболеваемость, клинические характеристики, опыт терапии отечественными антимикотиками // - Москва: Клиническая дерматология и венерология, - 2016. № 3, - с. 92 – 95

⁸ Brod, R. Endogenous Candida endophthalmitis. Management without intravenous amphotericin B / R.Brod, H.Flynn, J.Clarkson [et al] // Ophthalmology, - 2017. 5, - p.666-672.

⁹ Donahue, S. Intraocular candidiasis in patients with candidemia. Clinical implications derived from a prospective multicenter study / S.Donahue, C.Greven, J. Zuravleff // Ophthalmology, - 2017. 7, - p.1302-1309.

¹⁰ Foster, C.S. Peripheral ulcerate keratitis: Differential diagnosis and therapy // Congress of the European society of ophthalmology, - 2017. 9, - p.139-143.

¹¹ Jaeger, E.E. Rapid detection and identification of Candida, Aspergillus, and Fusarium species in ocular samples using nested PCR / E.E.Jaeger, N.M. Carroll, S.A. Choudhury // J Clin Microbiol., - 2016. 9, - p.290-296.

¹² Nucci, M. Fusarium infections in immunocompromised patients / M.Nucci, E.Anaisie, K.A.Marr [et al] // Clin Microbiol Rev, - 2017. 2, - p.695-704.

¹³ Rosa, R.H. The changing spectrum of fungal keratitis in South Florida / R.H.Rosa, D. Miller, E.C.Alfonsa // Ophthalmology, - 2017. 8, - p.1005-1013..

¹⁴ Shah, C.. Ocular candidiasis: a review / C.Shah, J.McKey, M.Spirn [et al] // Br J Ophthalmol., - 2017. 4, - p. 466-468.

Pandemic incidence of tuberculosis, HIV / AIDS, chronic obstructive pulmonary disease, bronchial asthma and increased tumor incidence are the leading factors of pathogenic fungal infections worldwide¹⁵. But the main reason for the increased increase in the number of cases of mycoses of the eyes is the uncontrolled use of antibacterial broad spectrum action, corticosteroid drugs, immunodeficiency states, prolonged catheterization, infectious processes, iatrogenic diseases¹⁶. Some of the changes in endemic fungal infections can be attributed to climate change, expansion of human habitat, ease of movement and population displacement. Risk groups for opportunistic fungal infections or common endemic fungal infections include patients who have received transplants, prescribed immuno-depressants and chemotherapy agents, HIV-infected patients, premature infants, the elderly, and patients who have undergone major surgery. Although the epidemiology of fungal diseases has changed a lot over the past few decades, *Aspergillus*, *Candida*, *Cryptococcus* species, *Pneumo-cystis jirovecii*, endemic dimorphic fungi such as *Histoplasma capsulatum* and *Mucormycetes* remain the main fungal pathogens responsible for most cases of serious fungal disease. *Candida albicans* is the main agent responsible for mucosal disease, *Aspergillus fumigatus* for most allergic fungal diseases and *Trichophyton* species, especially *Trichophyton rubrum*, for skin infections

Thus, early diagnosis and properly administered treatment at the initial stages of the disease, regular, maintenance of the therapy in the distance will significantly improve the quality of life of such patients.

Object of study. The main group consisted of 135 patients aged 5 to 55 years with a diagnosis of ophthalmomycosis. The control group consisted of 50 practically healthy individuals.

The purpose of the study: The purpose of the study was to develop modern approaches to clinical-laboratory diagnosis, treatment and prevention of eye mycosis.

¹⁵Майчук Ю.Ф. Клинические формы и современная терапия грибковых кератитов // Материалы научно-практической конференции «Новые технологии в лечении заболеваний роговицы» - Москва: 2014, - с.596-603.

¹⁶ Ritterband, D.C. Fungal keratitis at the new york eye and ear invirmary / D.C.Ritterband, J.A. Sedor, M.K. Shah [et al] // Cornea, - 2016. 3, - p.264-267..

Research objectives:

1. To conduct clinical-laboratory and functional examination of patients with eye mycoses;
2. To identify and study the characteristic clinical and laboratory features of the flow of mycotic lesions of the eye organ;
3. To study the etiological structure of the main pathogens of ophthalmomycoza.
4. Establish the nature and frequency of the body of vision by the pathogens of eye mycoza and indicate significant leading factors contributing to exacerbation or increasing the intensity of ophthalmomycoza disease.
5. Develop an algorithm for complex therapy and prevention of ophthalmomycoza.

Research methods. In the work, instrumental, clinical and laboratory, biochemical, epidemiological, bacteriological and statistical research methods were used.

Main guidelines for defense:

1. Improvement of methods of early diagnosis of eye mycosis, taking into account pathogenesis of the disease, with the aim of identifying leading risk factors.
2. Timely diagnosis of eye mycosis helps to develop the necessary medical and preventive and anti-epidemic measures in patients with this pathology.
3. Analysis of clinical and laboratory features of the course of fungal pathology, with the purpose of development of a complex method of therapy of mycosis of the eyes.

Scientific novelty:

- For the first time in Baku conditions, clinical and functional studies of patients with mycotic eye lesions were carried out.
- A diagnostic algorithm for ophthalmomycosis has been developed, including a thorough collection of the history of the real disease, sampling for a complex mycological study.
- The etiological structure of the main pathogens of ophthalmomycoza has been established and dominant species of pathogenic fungi have been identified.
- For the first time, the nature and frequency of infection with

pathogenic fungi of all biotypes of the eye organ has been established and the main trigger factors that provoke exacerbation or increase the intensity of the disease by ophthalmics have been identified.

– A system of measures for the diagnosis, treatment and prevention of eye mycosis has been developed, based on a differentiated approach to the administration of antimicrotics, taking into account the localization of the process and the etiological structure of the disease.

The practical significance of the study. The revealed features of the clinic of mycotic eye lesions are of practical value for ophthalmologists in timely clinical diagnosis of a specific process in the eye. The developed algorithm of complex therapy of ophthalmomycosis, taking into account the localization of the process and the genus of fungi - the causative agents of mycosis of the eye, will reduce the number of relapses of the disease, shorten the time of treatment of patients with mycosis of the eye and the number of unsatisfactory results.

The proposed algorithm of diagnosis and treatment of ophthalmomycosis can be applied in outpatient and inpatient conditions. In the given data the possibility of clinical researches in ophthalmomycosis for improvement on this basis of diagnostics, treatment and prevention of disease is estimated.

Dissertation approbation and implementation. Thesis materials were discussed: at the scientific and practical conference dedicated to the 100th anniversary of the Azerbaijan Democratic Republic “Təbabətin aktual problemləri” at a scientific-practical conference (Baku, 2018); at the international scientific-practical conference dedicated to the 100th anniversary of the founding of the Faculty of Medicine (Baku, 2019), at the international scientific-practical conference dedicated to the 100th anniversary of the Department of Human Anatomy and Medical Terminology of the Azerbaijan Medical University (Baku, 2019), “Modern Medicine: New Approaches and current research” at the international scientific-practical conference (Moskva, 2019), Tbilisi International Ophthalmological Conference TIOC (Tbilisi, 2019). The materials of the dissertation were reported and discussed at the interdepartmental meeting held jointly by the specialized departments of the Azerbaijan Medical University (Baku, 2020, protocol No. 1), at the scientific seminar of the approbation

commission at the dissertation council of the Azerbaijan Medical University (Baku, 2021, protocol No 4). The dissertation materials are used in the educational process at the departments of epidemiology and ophthalmology of the AMU, the proposed practical recommendations are applied in practice.

Use of scientific research work. The work was performed at the on the basis of the Department of Epidemiology and Ophthalmology of Azerbaijan Medical University and the Educational and Surgical Clinic of Baku.

Publishing. 13 scientific works on the topic of dissertation were published.

Volume and structure of the thesis. The thesis is presented on 153 pages of computer text (172.800 characters) and consists of an introduction (8.800 characters), list of references (53.700 characters), research materials and methods (8.700 characters), 3-chapter research results and their discussion (16.900 + 26.000 + 23.000 characters), summary, conclusions, practical recommendations (35.700 characters), bibliography covering 201 sources. The thesis contains 24 tables and 21 graphics.

MATERIAL, METHODS AND SCOPE OF RESEARCH

The work was carried out in 2015-2018, within the framework of the scientific program of the Department of Ophthalmology and Epidemiology of AMU. Laboratory tests were carried out in clinical and bacteriological laboratories of the Department of Epidemiology of AMU. Under our supervision between 2015 and 2018, the main group was 135 patients aged 5 to 55 years with fungal eye diseases. Of these, 16 were males and 74 were females. According to the study, two groups of the examined were formulated: The main group - 135 patients from the ME and the control group of 50 practically healthy individuals.

The obtained clinical-laboratory results allowed the patients of the main group to form the appropriate clinical groups: 1 group (n = 86) - patients, from the ME having different eye diseases for the study period. 2 group (n = 49) - patients with ME, for the duration of the study

were without clinical manifestations of eye diseases. In the work were used instrumental, clinical-laboratory, biochemical, epidemiological, bacteriological and statics methods of research.

The formulation of the diagnosis was carried out on the basis of the International Classification of diseases of the 10th revision, adopted by the 43rd World Health Assembly from 01.01.99. Mycological examination of patients included microscopic examination of pathological material and cultural study. To identify the species of the selected fungi, PCR diagnostics were used. PCR analysis used in this study takes 4 hours to produce results much faster than 2 days to 2 weeks required by any method of fungal culture. While fungal smears can be analyzed with light microscopy in minutes, the effectiveness of this method is more variable, and the results are not final. The ability of PCR-based tests to detect or exclude the presence of fungi in less time will represent progress in the treatment of eye infections, and can also contribute to efforts to recognize and study fungal keratitis. Intra-cellular production in the peripheral blood of cytokines lymphocytes was carried out using whole blood with sodium heparin for anticoagulation.

Spontaneous and mitogen-induced production of ex vivo cytokines by whole blood cells was carried out using the reagents "CYTOKINE-INCENTIVE-BEST" produced by CJSC "Vector-Best" (Russia). Trombozitary hemostasis was investigated by the method of quantifying the willebrand factor (according to Osten and Evans, in the modification of B.F. Arkhipov, L.V. Maramzina, L. 3. Barkagan (1982). The mathematical processing was carried out directly from the common data matrix EXCEL 7.0 (Microsoft, USA) with the help of STATGRAPH 6 (Microsoft, USA) programs. All quantitative data was recorded as a spreadsheet. Statistical analysis was carried out by standard means of a package of analysis of a spreadsheet, with calculation of average, their errors, before the correct intervals, criterion U-Wilkokson, criterion Van der-Vardin, criterion χ^2 .

RESULTS OF THE RESEARCH AND THEIR DISCUSSIONS

The research has shown that the population of Baku is characterized by a global trend – high body of sight with pathogenic fungi: The incidence of men was 45,2%, women – 54,8% of cases. Another trend is characterized – as the age of the examined persons increases, the frequency of contamination of their visual organ with pathogenic fungi increases - from 8,9±2,5% to 32,6±4,0% of cases ($\chi^2=23,07$; $p<0.001$). The results of the survey are presented in Table 1.

Table 1
Infection with pathogenic fungi for patients of different age groups

Age-gender characteristics		The number of pathogenic fungi infected					
		Total (n=135)		1 group (n=86)		2 group (n=49)	
		Abs.	%	Abs.	%	Abs.	%
Age groups, years	5- 7	12	8,9±2,5	8	9,3±3,1	4	8,2±3,8
	8-12	19	14,1±2,9	13	15,1±3,9	6	12,3±4,6
	13- 18	26	19,3±3,4	16	18,6±4,2	10	20,4±5,8
	19- 35	34	25,1±3,7	21	24,4±4,8	13	26,5±6,3
	36 - 55	44	32,6±4,0	28	32,6±5,1	16	32,6±6,7
Gender	Муж.	61	45,2±4,3	39	45,4±5,4	22	44,9±7,1
	Женщ.	74	54,8±4,3	47	54,6±5,4	27	55,1±7,1

Although the parameters of the frequency of testing of the eye organ in the 1st group of all parameters, according to the Van der Warden criterion, are significantly higher than in the 2nd group ($X = 3,47$; $p<0,01$), we attach great importance to the hygienic factor, along with immunological factors. Thus, the incidence of the body of vision with pathogenic fungi among men is higher than women - respectively 64,5±3,1% and 53,1±2,9% ($\chi^2 =10,44$; $p<0.01$). It is true both for the surveyed 1st group – 79,1±3,3% to 63,5±3,6% ($\chi^2 = 9,67$; $p<0.01$), for the surveyed 2nd group – 40,2±5,1% and 35,8±4,6% ($\chi^2 =0,42$;

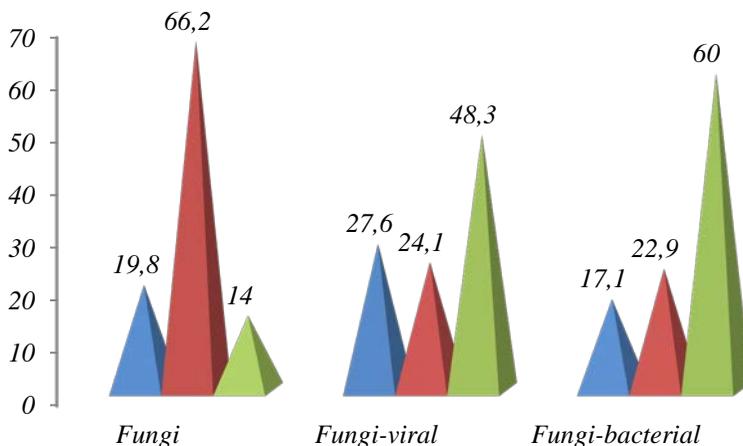
$p > 0.05$). The distribution by sex and age may reflect an increased impact on the environment of fungi. The predominant proportion of patients with mycoses of the eyes is represented by the affected in the age group of 36-55 years and 19-35 years: Respectively $32,6 \pm 4,0\%$ and $25,1 \pm 3,7\%$. For the first time detected patients of the disease were registered 91 people ($67,4 \pm 4,0\%$), with repeated recurrent diseases - 44 people ($32,6 \pm 4,0\%$). In the study of the symmetry of the process, depending on the age groups, it was established that the two-sided lesion, revealed in 87 patients (174 eyes, $66,4 \pm 4,1\%$), a one-sided lesion was detected in 48 patients (48 eyes, $35,6 \pm 4,1\%$). A total of 222 eyes were struck. In the study of infection with pathogenic fungi in different age groups, depending on the symmetry of the lesion, the greatest defeat in the unilateral process was noted in the age group of 36-55 years - 20 cases ($41,7 \pm 7,1\%$). In the other age groups, the distribution of patients was approximately the same: From $10,4 \pm 4,3\%$ in the age group of 5-7, to $14,6 \pm 5,2\%$ in the age groups of 8-12 and 13-18 years, respectively.

The age group of 19-35 years - $18,7 \pm 5,7\%$ - was slightly higher. In the bilateral process, the greatest lesion was noted in the age group of 19-35 years - 25 cases ($28,7 \pm 4,7\%$). Approximately the same was the distribution of patients in the age group of 36-55, and 13-18 years: $25,4 \pm 4,6\%$ and $24,1 \pm 4,6\%$, respectively.

The age group of 8-12 years - $13,8 \pm 3,7\%$ was slightly less affected and the lowest age group was 5-7 years - $8,0 \pm 2,9\%$. The reported distribution of the examined patients on the etiology of mycotic eye lesions allows them to be shown as follows: Fungal etiology was detected in 71 patients ($52,6 \pm 4,3\%$), fungal-viral etiology - in 29 patients ($21,5 \pm 3,6\%$; $\chi^2 = 28,02$; $p < 0,001$), fungal etiology - in 35 patients ($25,9 \pm 3,8\%$; $\chi^2 = 20,13$; $p < 0,001$). The data showed the prevalence of nonfungal eye damage in $52,6 \pm 4,3\%$ of patients (71 people) and mixed fungal- bacterial eye damage in $25,9 \pm 3,8\%$ of patients (35 people). A few of the following were noted mixed fungal-viral eye lesions in $21,5 \pm 3,6\%$ of patients (29 people). In the distribution of patients according to the symmetry of the lesion depending on etiology, it was revealed that in mono fungal etiology, a unilateral process was revealed in 29 eyes ($60,4 \pm 7,0\%$), a two-sided process was detected in 84

eyes (48,2±3,8%). In fungal-bacterial mixed etiology, the unilateral process is registered in 11 eyes (22,9±2,9%; $\chi^2=71,23$; $p<0,001$), the bilateral process is noted in 48 eyes (27,8±3,4%; $\chi^2=23,57$; $p<0,001$). With mixed fungal-viral etiology, the one-sided process was registered in 8 eyes, (16,7±5,4%; $\chi^2=11,51$; $p<0,01$) and the two-sided process is noted in 42 eyes (24,0±3,2%; $\chi^2=1,85$; $p>0,05$). In the distribution of patients according to the etiology of mycosis of the eyes, depending on the age groups, it was revealed that in the age group 5-7 years diseases of fungal - viral etiology (10,3±5,8%) and mono fungal (8,9±2,5%) etiology predominate. In the 8-12 age group, mono fungal etiology (16,9±4,5%) is noted in most cases, fungal etiology was encountered in 11,4±5,5% of cases, fungal etiology was found in 10,3±5,8% of cases. In the age group of 13-18 years, diseases of fungal-bacterial etiology (28,9±7,7%) prevailed, and mono fungal etiology was encountered in 18,3±4,6% of cases, fungal - viral etiology was encountered in 17.2±7,9% of cases. In the age group of 19-35 years, the prevalence of any form of disease was not observed. The occurrence was almost the same: Fungal-bacterial etiology - in 25,4±7,4%, mono fungal etiology - in 22,5±4,9% of cases, fungal - viral etiology - in 24.1±7,9% of cases. In the age group of 36-55 years, fungal- viral etiology (38,1±9,0%) prevailed, and mono-fungal etiology was found in 32,4±5,6% of cases, fungal - bacterial etiology was found in 28,6±7,7% of cases (graph 1).

In the study of the characteristics of different groups of patients in degrees of severity of the disease, it was established that in the first group of patients studied (with a slight current) the number of patients was 28 people (20,7±3,5%). In the second group with a moderate disease, the number of patients was 62 people (45,9±4,3%). In the third study group (with heavy current), 45 patients (33,4±4,1%; $p<0,01$) were admitted. An analysis of the distribution of the groups of patients studied by severity of the disease among 91 patients first identified with eye mycoses showed that the number of patients with light current was 20 (21,9±4,3%; $p<0,001$). In the group of patients studied with the course of an average disease, the number of patients was 43 people (47,3±5,2%; $p<0,001$).



Graph 1. Characteristics of groups of diseases studied on etiology depending on the severity of the current case.

In the third group of patients studied with heavy current, the number of patients was 28 people ($30,8 \pm 4,8\%$; $p < 0,001$). In 44 patients with recurrent eye mycosis, the number of patients with mild current was determined to be 8 ($18,2 \pm 5,8\%$). In the group of patients with an average course of disease, the number of patients was 19 people ($43,2 \pm 7,5\%$). In the third study group of patients with heavy current, the number of patients was 17 ($38,6 \pm 7,4\%$). The mild severity of the disease among the patients studied was as follows: For the first time detected cases of eye mycosis were 20 people ($71,4 \pm 8,5\%$), recurrent forms 8 people ($28,6 \pm 8,5\%$). The average severity of the disease among the patients studied was as follows: for the first time detected cases of mycosis of the eye were 43 people ($69,4 \pm 5,9\%$), recurrent forms - 19 people ($30,6 \pm 5,9\%$). The severity of the disease among the patients studied was as follows: for the first time detected cases of eye mycosis were 28 people ($62,2 \pm 7,2\%$), recurrent forms - 17 people ($37,8 \pm 7,2\%$). The distribution of patients according to the symmetry of the process, depending on the severity of the disease, revealed, with a unilateral process, the number of patients with a slight current was 7

people ($14,6\pm 5,1\%$). In the group of patients with an average course of disease, the number of patients was 18 people ($37,5\pm 6,2\%$). In the third clinical group of patients with severe current, the number of patients was 23 people ($47,9\pm 7,2\%$) ($\chi^2=7,265$; $p=0,026$). The distribution of patients according to the symmetry of the process, depending on the severity of the disease, showed that in the bilateral process, the number of patients with a slight current was 21 people ($24,1\pm 4,6\%$). In the group of patients with an average course of disease, the number of patients was 44 people ($50,6\pm 6,3\%$). In the third group of patients with severe current, the number of patients was 22 people ($25,3\pm 4,7\%$). The mild severity of the disease among the studied groups of patients was as follows: The one-sided process of disease of mycosis of the eye was 7 people ($25,0\pm 8,2\%$), the two-sided process - 21 people ($75,0\pm 8,2\%$). The average severity of the disease among the studied groups of patients was as follows: The one-sided process of disease of mycosis of the eye was 18 people ($29,0\pm 5,8\%$), the two-sided process - 44 people ($71,0\pm 5,8\%$). The severe severity of the disease among the studied groups of patients was distributed as follows: The unilateral process of disease of mycosis of the eye was 23 people ($51,1\pm 7,5\%$), two-way process - 22 people ($48,9\pm 7,5\%$). The distribution of patients according to the etiology of the disease, depending on the severity of the disease, showed that in fungal etiology, the number of patients with a slight current was 14 people ($19,8\pm 4,7\%$; $p<0,001$). In the group of patients with an average course of disease, the number of patients was 47 people ($66,2\pm 6,0\%$; $p<0,001$). In third patients with severe current, the number of patients was 10 ($14,0\pm 4,1\%$; $p<0,001$). In fungal- viral etiology, the number of patients with a slight current was 8 people ($27,6\pm 8,3\%$; $p<0,001$). In the group of patients with an average course of disease, the number of patients was 7 people ($24,1\pm 7,9\%$; $p<0,001$). In the third group of patients with severe current, the number of patients was 14 people ($48,3\pm 9,3\%$; $p<0,001$). At fungal - bacterial etiology the number of patients with a slight current was 6 people ($17,1\pm 6,3\%$; $p<0,001$). In the group of patients with an average course of disease, the number of patients was 8 people ($2,9\pm 7,1\%$; $p<0,001$). In the third group of patients with severe current, the number of patients was 21 people ($60,0\pm 8,3\%$; $p<0,001$). The

mild severity of the disease among the studied groups of patients was as follows: Fungal etiology of mycosis of the eye was 14 people (50,0±9,4%), fungal- viral etiology - 8 people (28,6±8,6%), fungal-bacterial etiology - 6 people (21,4±7,8%). The average severity of the disease among the studied groups of patients was as follows: fungal etiology of mycosis of the eyes was 47 people (75,8±5,4%), fungal-viral etiology - 7 people (11,3±3,9%), fungal-bacterial etiology - 8 people (12,9±4,3%). The severe severity of the disease among the studied groups of patients was as follows: fungal etiology of mycosis of the eye was 10 people (22,2±6,2%), fungal- viral etiology - 14 people (31,1±6,8%), fungal- bacterial etiology - 21 people (46,7±7,4%). In the first study group (with a slight flow), the number of patients was 28 ($\chi^2=31,617$; $p<0,001$). The number of patients with recurrent mycosis in this group was 8 people (28,6±8,5%), with the first detected mycosis - 20 people (71,4±8,5%). In 21 people (75,0±8,2%) the process was bilateral, in 7 people (25,0±8,2%) - one-sided. In etiology, patients were distributed as follows: Most of 14 people are found in diseases of mono fungal etiology (50,0±9,4%), fungal-viral etiology - 8 people (28,6±8,6%) and fungal-bacterial etiology - 6 people (21,4±7,8%). In the mean group, the number of patients was 62. Among them, 43 people were first diagnosed with disease (69,4±5,9%), 19 people (30,5±5,9%) had a recurrent character. The bilateral process was observed in 44 cases (71,0±5,8%), one-sided in 18 cases (29,0±5,8%). According to etiology, the following distribution was noted: Most (47 people) are accounted for by diseases of mono-fungal etiology (75,8±5,4%), fungal-viral etiology - 7 people (11,3±3,9%) and fungal-bacterial etiology - 8 people (12,9±4,3%). In the third group (with a heavy current), the number of patients was 45. Recurrent mycosis is registered in 17 people (37,8±7,2%), the first detected mycosis - in 28 people (62,2±7,2%). The two-sided process is marked in 22 cases (48,9±7,5%), one-sided in 23 cases (51,1±7,5%). Etiology in this group is distributed as follows: Most (21 people) are accounted for by diseases of fungal-bacterial etiology (46,7±7,4%), fungal-viral etiology - 14 people (31,1±6,8%) and mono fungal etiology - 10 people (22,2±6,2%) ($p<0,001$).

Analysis of background diseases in patients with fungal eye pathology showed that mainly diseases from the gastrointestinal tract (chronic gastritis, gastric ulcer) - in 32 (23,7±3,6%), in 39 (28,9±3,9%) patients in the history of lambliosis, in 45 (33,3±4,1%) varicose symptomatic complex. The results obtained are consistent with the results of ultrasound, hepato-biliary system. Changes in 95,4±3,8% have been detected; undoubtedly, determine the relationship between somatic pathology and fungal diseases of the eyes. The greatest specific weight in the transferred diseases is occupied by ARI, childhood infections, chronic tonsillitis. As the main trigger factors that provoke exacerbation or increase the intensity of the disease, most patients noted the psychogenic factor (99 patients, 73,3±3,8%) (the connection of the onset of another exacerbation with work stress, personal situations, over-fatigue), as well as seasonality (82 patients, 60,7±4,2%) - deterioration in the autumn-winter season of the year. In addition, 72 (53,3±4,3%) patients noted as a starting factor contact with the allergen (household chemistry, washing powders, domestic dust, plant pollen), 55 (40,7±4,2%) patients noted errors in diet (use of honey, citrus, eggs, chocolate, coffee, fish). Allergic reactions to drugs in the history were noted in 76 (56,3±4,3%) people. Analysis of questionnaires allowed evaluating the existing practice of treating eye mycosis in outpatient conditions. Previously, 83 (61,5±4,2%) patients received treatment from various fungal diseases, including 100% topical antimicrobics, and systemic - only 7 patients (5,2%). The absence of treatment effect and recurrence of the disease is registered in 29 (34,9±5,2%) patients previously treated with drugs from the azole group, 26 (31,3±5,1%) - allilamines, 11 (13,5±3,8%) - naphthylamine and 17 (20,3±4,5%) - drugs of other groups.

The study of the structure and dynamics of the registered fungal pathology of the eye organ in patients for the period 2015-2017 in Baku showed the prevalence of fungal conjunctivitis (74 cases, 54,8±4,3%) in comparison with fungal injuries (23 cases, 17,0±3,2%) and fungal keratitis (18 cases, 13,3±2,9%). The specific weight of fungal endophthalmitis and blepharitis did not exceed 4,4±1,8% (in cases each), mycosis of the tear organs was 5,9±2,0% (8 cases).

The study of the etiological spectrum of fungal diseases showed

the presence of a small specific weight *Coccidies immitis* (7,4±2,4%), *Actinomicetes* (8,9±2,6%), *Sporotrichum* (11,1±2,8%), in the rest of the cases the fungal process was caused by micromycetes - mold fungi (37,8±4,2%) (*spp.Penicillum* (13,4±2,9%), *Aspergillus* (24,4±3,7%)) and *Candida* (34,8%) are potentially dangerous fungi (BSL-biological safety levels are estimated as 1-2 groups).

The allocation of these pathogens in patients with fungal diseases as independent etiological agents is confirmed by the degree of dominance of mold fungi (37,8±4,2%) and fungi of the genus *Candida* (34,8±4,1%).

Studies have shown that there is a dynamic alteration of the etiological structure of fungal conjunctivitis of the eyes. Increasingly, such fungi as *C.albicans*, *Coccidioides immitis*, *Pennicillium viridans* are gaining etiological significance. Analysis of the presented data of 74 cases of fungal conjunctivitis of the eye showed that in patients with this form of disease is allocated mainly *C.albicans* - an average of 86,5±4,0% of cases, the detection of *Coccidioides immitis* was 8,1±3,2% of cases ($\chi^2=8,91$; $p<0,01$), *Pennicillium viridans* - 5,4±2,6% ($\chi^2=0,43$; $p>0,05$). As it turned out, the forms of the disease on the detection of *C.albicans* do not have an influence and it varies in different forms of the disease from 84,2±8,6 to 87,2±5,4% ($\chi^2 =0,15$; $p>0.05$). But it should be recognized that the level of excretion of *C.albicans* is highest in chronic form of the disease - 55,5±5,8% of cases, rather than acute form of the disease 25,7±5,1% ($\chi^2=0,57$; $p>0,05$) and especially in the form of carrier fungi - 18,9±4,6% ($\chi^2=0,97$; $p>0.05$). As *C.albicans* can be seen, it is not always the cause of the development of the clinical form of fungal conjunctivitis of the eyes and it does not show pathogenic, long being in the body of the affected persons, while in the overwhelming number of cases it is represented as a monoinfection.

In acute form of infection *C.albicans* is found in 16 patients (84,2±8,6%), *Coccidioides immitis* is found in 1 patient (5,2±3,2%) and *Pennicillium viridans* is found in 2 patients (10,5±7,2% of cases). With the carrier *C.albicans* is found in 12 patients (85,7±9,7%), *Coccidioides immitis* is found in 1 patient (7,1±6,2%) and *Pennicillium*

viridans is found in 1 patient ($7,1 \pm 6,2\%$ of cases). The role of *C.albicans* in the development and long-term maintenance of chronic recurrent form of fungal conjunctivitis of the eyes is quite obvious. Mycotic eye infections develop pathogenetically unfavorable reactions at both systemic and local levels. In general, patients with ME have a tendency to moderate increase in blood indicators of anti-infectious and pro-inflammatory cytokines: IL-2, Il-6 ($p < 0,05$), TNO- α , INF- α , INF- γ and Il-8 ($p < 0,05$), compared with the control group. Local and systemic synthesis Il-8 has the predominant importance in the development of intraocular inflammation, in particular angiogenesis.

In the examination of patients with ME, cytokine Il-8 appeared in the serum of blood in all patients, both having newly formed vessels in different shells of the eye, and not having. Anti-inflammatory cytokines Il-4 and Il--10 were found in patients with my less often than pro-inflammatory. The differences in the cytokos-new profile of patients with injuries are explained by many factors: Severity, activity and duration of the disease periods, use of test systems of various production, the nature of the treatment conducted. Statistically significant increase in sex was observed: An increase in the level of small-scale dialdehyde (MDA) to $6,8 \pm 0,2$ mcm/l ($p < 0,001$). The AOS indices in patients with ME had a tendency to decrease: The activity of the myeloperoxidase of leukocytes decreased to $1,5 \pm 0,3$ UE ($p < 0,001$), ceruloplasmine - to $14,2 \pm 0,2$ mq/% ($p < 0,001$).

As a result of the activation of the sex, which is confirmed by the accumulation of MDA patients in the blood, the permeability of cell membranes is significantly impaired, and conditions are created for the development of the pathological process. Changes in the pentosopathous cycle were estimated by the activity of the enzyme glucose - 6 - phosphate dehydrogenase (G-6-FDG). In patients with MI, the activity G-6-FDG in peripheral blood decreased to $2,4 \pm 0,3\%$ ($p < 0,001$). At the same time, the blood of the studied revealed a significant accumulation of structural components of glycosamino-glycanes - hexose to $4,2 \pm 0,3$ $g \times 10^{-2}/l$ ($p < 0,001$), syalic acids to $248,18 \pm 7,2$ units ($p < 0,001$) and uronic acids to $1,27 \pm 0,2$ $g \times 10^{-2}/l$ ($p < 0,001$)

Dynamic patient examination allowed establishing positive effect

of integrated treatment (IT) on AHC and sex. In the peripheral blood of patients, the activity of ceruloplasmin (Cp) – $17,6 \pm 0,3$ mq% and myeloperoxidase (MP) – $2,3 \pm 0,2$ units, as well as MDA – $5,1 \pm 0,3$ Mkm /l, respectively, in the control group – $15,8 \pm 0,3$ and $2,2 \pm 0,2$, and $4,2 \pm 0,3$ ($p < 0,001$). The increase in the activity G-6-FDG in patients of ME after the application of complex treatment (CT) was significant: from $2,4 \pm 0,3\%$ to $4,9 \pm 0,3\%$ ($p < 0,001$). The content in the peripheral blood of patients with glycosaminoglykans (HAG) decreased: hexose from $4,2 \pm 0,3 \text{ g} \times 10^{-2}/\text{l}$ to $2,8 \pm 0,2 \text{ g} \times 10^{-2}/\text{l}$ ($p < 0,001$) and uronic acids from $1,3 \pm 0,2 \text{ g} \times 10^{-2}/\text{l}$ to $0,8 \pm 0,1 \text{ g} \times 10^{-2}/\text{l}$ ($p < 0,001$).

As a result of the research we have proposed a new approach to treatment of the ME. Drug complexes have been developed, providing, along with basic therapy of the main disease (sedation, hyposensitizing, antimicrobial preparations, according to the indications of stimulators of endogenous glucocorticoids), the use of antibacterial and immunocorrective agents in various combinations, depending on the clinical-pathogenetic features of various forms of the disease.

Patients from ME were appointed traditional medical and complex treatment. The complex of measures developed by us (basic therapy) consists in a combination of systemic and local therapy and, if necessary, in severe forms of diseases of surgical intervention. Three groups of patients (135 patients in total), similar in sex-age composition, manifestations and severity of the process were studied.

The first group (A) consisted of patients receiving medical treatment (36 patients), the second group (B) patients receiving systemic basis-therapy (56 patients) and the third group (C) patients receiving medical treatment + systemic basis-therapy (43 patients). My treatment has a poor prognosis, as the available anti-fungal drugs are limited by poor penetration, limited spectrum and surface toxicity. To try to successfully treat those fungi that entered the anterior chamber, we tested the use of intrachamber amphotericin B an alternative to traditional methods of treatment. We suggested that amphotericin B can reach fungi in the cornea stroma, penetrating through the membrane and this study was aimed at assessing the positive role of intrachamber injection of amphotericin B in keratomycosis.

The design of the study was a prospective controlled clinical test.

A total of 36 eyes, 18 patients were divided into two groups, 11 in the intrachamber amphotericin B group (group a) and 7 in the control group - local amphotericin B group (group B). The average time of disappearance of the hypopyon was $9,6 \pm 9,2$ (range: 1-26) days in group A and $26,8 \pm 20,8$ (range: 14-62) days in group B ($p=0,03$). The average percentage reduction in keratic precipitates was significantly greater than in the day 21 control group ($p < 0,05$) measured by area and perimeter. More patients had complete repeat epithelization in group A ($n=11$) than in group B ($n=7$) ($p=0,272$). None of the patients reported any side effects or discomfort in any treatment. Intrachamber injection of amphotericin B results in faster healing of keratic precipitates and a reduction in the time to disappearance of the hypopyon compared to local use of amphotericin B.

Patients were thoroughly examined. At the initial presentation, most patients (80%) had a 3/60 visual acuity. The distribution of visual acuity between the two groups did not differ significantly. Patients in group A 6 received one injection, 5 received two injections at an interval of one week. Of the 18 patients, 77,8% ($n=14$) were cured of any therapy; 90,9% ($n=10/11$) in group A and 57,4% ($n=4/7$) in group B. The average time of disappearance of the hypopyon was $9,6 \pm 8,2$ (range 1 - 26) days in group A and $26,8 \pm 20,8$ (range 14-62) days in group B ($p=0,272$). The average closure time for epithelial defects was $20,2 \pm 10,6$ days in group A and $31,2 \pm 21,4$ days in group B ($p=0,160$). However, the percentage decrease in the size of the epithelial defect, measured in area and perimeter, was different in both groups, which is much larger in group A. After the course of treatment there were positive changes in the regulatory systems: Immune (increase in the number of general T-lymphocytes with restoration of balance of their main populations, decrease in B-lymphocytes and circulating immune complexes, increase in the content of immunoglobulins of class A and M, complement, bactericidal and phagocytic activity).

The basis for the purpose of drug treatment +systemic basis-therapy in the treatment of ME is the ability of this method to eliminate the deficiency of immunoregulatory T-suppressor subpopulation of lymphocytes, to increase phagocytic activity of leukocytes, the ability to stimulate non-specific resistance of the organism, bactericidal and

bacteriostatic effect. In the comparative analysis of the dynamics of the inflammatory process, a significantly greater effectiveness of therapy in patients of group C was noted.

During the treatment, the level of the 3rd component of the complement increased, bactericidal activity of blood serum and phagocytic activity of leukocytes. However, the effectiveness of therapy was different, since the level of improvement was different. During the treatment, immunological reactivity was restored. T-lymphocytes increased to $56,1\pm 2,2\%$ in group A, $59,0\pm 2,2\%$ in group B and $59,7\pm 2,2\%$ in group C (before treatment $40,1\pm 3,0\%$), T-helpers- $30,3\pm 3,5\%$ in group A, $31,8\pm 2,5\%$ in group B and $32,2\pm 2,5\%$ in group C (before treatment $20,4\pm 1,4\%$). T-suppressors – $17,0\pm 1,5\%$ in group A, $19,7\pm 1,5\%$ in group B and $19,1\pm 1,5\%$ in group C (before treatment $10,1\pm 1,0\%$). Reduced B-lymphocytes content to $11,1\pm 1,3\%$ in group A, $10,7\pm 1,3\%$ in group B and $9,8\pm 1,3\%$ in group C (before treatment $18,8\pm 1,0\%$) and circulating immune complexes to $41,1\pm 3,3$ maintain in group A, $38,9\pm 3,3$ U in group B and $36,0\pm 3,3$ U in group C (before treatment $75,5\pm 8,0$ U, $p<0,001$) and the concentration of IgA – $1,1\pm 0,15$ g/l in group A, $1,5\pm 0,15$ g/l in group B and $1,7\pm 0,08$ g/l in group C (before treatment $0,80\pm 0,15$ g/l, $p<0,001$) and IgM- $1,35\pm 0,08$ g/l in group A, $1,65\pm 0,08$ g/l in group B and $1,6\pm 0,15$ g/l in group C (before treatment $0,98\pm 0,06$ g/l).

In addition, the content of the 3 component of the complement increased by $50,1\pm 1,6$ standard unit in group A, $51,9\pm 1,6$ standard unit in group B and $52,6\pm 1,6$ conventional units in group C (before treatment $44,0\pm 1,1$ conventional units), bactericidal serum activity – $41,1\pm 1,9\%$ in group A, $52,1\pm 1,9\%$ in group B and $53,8\pm 1,9\%$ in group C (before treatment of $34,6\pm 1,6\%$), phagocytic activity of leukocytes - $22,8\pm 1,0$ units in group A, $30,2\pm 1,0$ units in group B and $35,2\pm 1,0$ units in group C (prior to treatment $12,6\pm 1,0$ units).

The functional state of neutrophil leukocytes was evaluated in a spontaneous NST test, which allowed revealing the presence of metabolic changes that occur in polynuclear leukocytes in various pathological conditions. The study showed a significant decrease in spontaneous NST activity in all groups of study ($p<0,05$ – $0,001$), but in

groups B and C treated with complex therapy, the average of spontaneous and stimulated NST test was less than in patients in group A treated with traditional treatment alone. In all cases of the pathology studied, in particular, ME, complex therapy influenced the dynamics of the parameters of specific cellular immunity. Included in the basic therapy, it contributed to earlier normalization of the absolute and percent content of T-lymphocytes, reduced the number of B-lymphocytes. The latter was accompanied by normalization or increase in the level of individual classes of immunoglobulins.

The application of this treatment led to the normalization or increase of non-specific humoral immunity, bactericidal activity of blood serum. The advantage of the offered complex techniques with application of complex treatment of the ME in comparison with traditional medical treatment has been established. The absence of side effects, the effectiveness and accessibility of treatment methods make it possible to recommend them for practical health care. The effectiveness of the developed methods of complex therapy supports the role of identified pathogenetic mechanisms in the development of the ME.

Thus, the results of our research show the increasing medical and social significance of the ME among the population. Therefore, it is necessary to provide specialized ophthalmic care to patients with my - accurate timely diagnosis, comprehensive clinical differentiation of forms of disease and degrees of severity, as well as complex therapy.

CONCLUSIONS

1. In the study of the structure and dynamics of the registered fungal pathology of the eye organ in patients in Baku, it was revealed that the leading positions were: Fungal conjunctivitis ($54,8 \pm 4,3\%$), fungal uveitis ($17,0 \pm 3,2\%$), fungal keratitis ($13,3 \pm 2,9\%$). The specific weight of fungal endophthalmitis and blefaritis did not exceed $4,4 \pm 1,8\%$, mycosis of the tear organs was $5,9 \pm 2,0\%$ [10].

2. The study of the spectrum of etiology of isolated pathogens in fungal pathologies indicated a small proportion of *Coccidies immitis* ($7,4 \pm 2,4\%$), *Actinomicetes* ($8,9 \pm 2,6\%$), *Sporotrichum* ($11,1 \pm 2,8\%$), a share in cases where micromycetes (otherwise mold

fungi) ($37,8 \pm 4,2\%$) (spp. *Penicillium* ($13,4 \pm 2,9\%$), *Aspergillus* ($24,4 \pm 3,7\%$)) and candida ($34,8 \pm 4,1\%$), polysurveyed which belong to the group of potentially dangerous fungi [13].

3. The population of Baku is characterized by a worldwide trend - as the age of the examined patients increases, the frequency of contamination of their visual organ with pathogenic fungi increases - from $8,9 \pm 2,5\%$ to $32,6 \pm 4,0\%$ of cases ($\chi^2=23,07$; $p<0,001$). The predominant proportion of patients with mycoses of the eyes is represented by the affected in the age group of 36-55 years and 19-35 years: Respectively $32,6 \pm 4,0\%$ and $25,1 \pm 3,7\%$. For the first time detected patients with my were registered 91 people ($67,4 \pm 4,0\%$), with repeated recurrent diseases - 44 people ($32,6 \pm 4,0\%$). In the study of the characteristics of different groups of patients in degrees of severity of the disease, it was established that the number of patients with a slight current was $20,7 \pm 3,5\%$, with a medium severity disease - $45,9 \pm 4,3\%$, with a heavy current - $33,3 \pm 4,1\%$ ($t = 4,12$; $p<0,01$) [11].

4. As the main trigger factors of risk, most patients noted the psychogenic factor ($73,3 \pm 3,8\%$), seasonality ($60,7 \pm 4,2\%$), contact with the allergen ($53,3 \pm 4,3\%$), errors in diet ($40,7 \pm 4,2\%$), allergic reactions to drugs ($56,3 \pm 4,3\%$). Previously, treatment from various fungal diseases was received by $61,5 \pm 4,2\%$ of patients, including 100% topical antimicrobitics, and systemic - $5,2\%$ of patients [9].

5. The developed complex of measures has an immunocorriting effect on the indicators of specific and non-specific cellular and humoral immunity at various degrees of severity of the disease, more affects the cellular link of immunity, especially polymorphonuclear leukocytes, T-lymphocytes, and also the content of the CEC. The system principle predisposes two complementary directions: Destruction of the fungus with antimicrobial agents and work with the immune system aimed at eliminating immunodeficiency and preventing (or eliminating) sensitization to fungi [1,5].

PRACTICAL RECOMMENDATIONS

1. The algorithm for diagnosis of patients with eye mycosis should include the evaluation of lipid peroxidation and antioxidant protection systems to correctly assess compensatory capabilities of the body in order to choose the method of correcting metabolic disorders.

2. The results of the study make it possible to recommend the definition of the parameters of the sex-AOS system for assessing the adequacy of management of patients with my.

3. It is recommended to include the most informative indicators characterizing the state of cellular immunity and FA neutrophils.

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List of abbreviations

AOD	– antioxidant defence
ARVI	– acute respiratory viral infections
CIC	– Circulating immune complexes
G-6-PDG	– glucose-6-phosphate dehydrogenase
HIV	– human immunodeficiency virus
IL	– interleukin
INF	– interferon
MDA	– Malonic dialdehyde
MG	– mycosis of the eyes
NST	– Nitrosinium tetrazolium
PCR	– polymerase chain reaction
TNF	– tumor necrosis factor
US	– ultrasonic examination

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