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CANDIDA ALBICANS AND STAPHYLOCOCCUS AUREUS CO-INFECTION IN MICE AFTER ANTIBIOTIC-INDUCED DYSBIOSIS

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Microbial interactions in Staphylococcus aureus–Candida albicans dual-species biofilms is a relevant research topic given the significant contribution of these microorganisms to hospital-acquired infections. Therefore, the purpose of our investigation was to study the interaction of opportunistic C. albicans and S. aureus in vivo and in vitro, both with the participation of normal microflora and in mice with antibacterial dysbiosis. The study of mentioned interactions was carried out on 100 white male mice weighing approximately 18 grams in vivo and using smears prepared from the grown mixed cultures of C. albicans and S. aureus and the Japan JEM 1400 transmission electron microscope for the purpose of electron microscopic study of microorganisms in vitro. Healthy mice forming control groups and mice with antibiotic-induced dysbiosis (after introduction of vancomycin, gentamicin, ampicillin) were divided into groups to create a mono- and associative infection: I group was given 1×10^7 CFU of C. albicans, II group – 1×10^8 CFU of S. aureus, and III group – a mixture of specified concentrations of C. albicans and S. aureus in the same proportion. Microorganisms causing monoinfection were being isolated from the body of animals treated with antibiotics till the end of the experiments in large quantities unlike in case of the healthy mice. Co-inoculation of these microbes in the same dose to animals (co-infection), which were injected with antibiotics, turned out to be fatal for them, whereas an adhesive bond was seen between the cells of C. albicans vs. S. aureus in vitro.

As can be seen, such bacterial-fungal co-infection reduce substantially the effectiveness of antibiotic therapy and the likelihood of successful treatment and can not be ignored when choosing the appropriate treatment.

KEY WORDS: C. albicans, S. aureus, colonization, interaction

CANDIDA ALBICANS ТА STAPHYLOCOCCUS AUREUS КО-ІНФЕКЦІЯ У МИШЕЙ ПІСЛЯ АНТИБІОТИКО-ІНДУКОВАНОГО ДИСБІОЗУ

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Мікробні взаємодії в біоплівках двох видів мікроорганізмів, Staphylococcus aureus і Candida albicans, є актуальною темою дослідження, враховуючи значний внесок останніх у розвиток внутрішньолікарняних інфекцій. Тому метою нашого дослідження стало вивчення взаємодії опортуністичних C. albicans і S. aureus in vivo та in vitro як за участю нормальної мікрофлори, так і у мишей з антибактеріальним дисбіозом. Вивчення вищенаведених взаємодій проводили на 100 білих самцях мишей вагою близько 18 г in vivo і in vitro з використанням мазків, отриманих з вирощуваних змішаних культур C. albicans і S. aureus, і японського трансмісійного електронного мікроскопа JEM 1400 з метою електронно-мікроскопічного дослідження мікроорганізмів. Здорові миші, якы сформулювали контрольні групи, і миші з викликаним антибіотиками дисбіозом (після введення ванкоміцину, гентаміцину, ампіциліну) були розділені на групи для створення моно- і асоціативної інфекції: групі I вводили 1×10^7 КУО C. albicans, II групі – 1×10^8 КУО S. aureus і III групі – суміш зазначених концентрацій C. albicans і S. aureus в тій же пропорції. Мікроорганізми, що спричиняли моноінфекцію, виділялися з організму тварин, які отримували антибіотики до кінця експерименту в великих кількостях, на відміну від таких у здорових мишей. Спільна інокуляція цих мікробів в тій же дозі тваринам (коінфекція), яким вводили антибіотики, виявилася для них фатальною, тоді як in vitro був помітний клітинний зв'язок між клітинами C. albicans vs. S. aureus.

Як бачимо, така бактеріально-грибкова коінфекция істотно знижує ефективність антибактеріальної терапії і ймовірність успішного лікування, та не може бути проігнорована при виборі відповідного лікування.

КЛЮЧОВІ СЛОВА: C. albicans, S. aureus, колонізація, взаємодія

CANDIDA ALBICANS И STAPHYLOCOCCUS AUREUS КО-ИНФЕКЦИЯ У МЫШЕЙ ПОСЛЕ АНТИБИОТИКО-ИНДУЦИРОВАННОГО ДИСБИОЗА

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Микробные взаимодействия в биопленках двух видов микроорганизмов, Staphylococcus aureus и Candida albicans, являются актуальной темой исследования, учитывая значительный вклад последних в развитие внутрибольничных инфекций. Поэтому, целью нашего исследования стало изучение взаимодействия оппортунистических C. albicans и S. aureus in vivo и in vitro как с участием нормальной микрофлоры, так и у мышей с дисбиозом. Изучение упомянутых взаимодействий проводили на 100 белых самцах мышей весом около 18 г in vivo и in vitro с использованием мазков, полученных из смешанных культур C. albicans и S. aureus. Приготовленные препараты изучали под трансмиссионным электронным микроскопом JEM 1400 производства Японии. Здоровые мыши контрольных групп, и мыши с вызванным антибиотиками дисбиозом (после введения ванкомицина, гентамицина, ампициллина) были разделены на группы для создания моно- и ассоциативной инфекции: группе I вводили 1×10^7 КОЕ C. albicans, II группе – 1×10^8 КОЕ S. aureus и III группе – смесь указанных концентраций C. albicans и S. aureus в той же пропорции. Микроорганизмы, вызывающие моноинфекцию, выделялись из организма животных, получавших антибиотики до конца эксперимента в больших количествах, в отличие от таковых у здоровых мышей. Совместная инокуляция этих микробов (коинфекция) в той же дозе животным, которым вводили антибиотики, оказалась для них фатальной, тогда как in vitro была замечена клеточная связь между клетками C. albicans vs. S. aureus.

Такая бактериально-грибковая коинфекция существенно снижает эффективность антибактериальной терапии и вероятность успешного лечения, и не может быть проигнорирована при выборе соответствующего лечения.

КЛЮЧЕВЫЕ СЛОВА: C. albicans, S. aureus, колонизация, коинфекция

INTRODUCTION

Beneficial or harmful interactions between C. albicans i S. aureus for the host can both develop in a healthy organism and in the case of illness [1–3]. Microbial communities are known to be functionally diverse microorganisms localized in certain places and long-lastingly interacting with each other. The microorganisms included in these communities are in certain symbiotic relationships, influencing the biological properties of each other, stimulating and/or inhibiting growth and reproduction [4–6]. Such relationships contribute to the worsening of the course of the disease by strengthening the virulence of the causative agents of the disease in the human body [7–9]. Specifically, exometabolites of S. aureus affect the phospholipase activity of C. albicans, thereby increasing their aggressiveness, contribute to the development of antibiotic resistance and activation of other features [10–13]. At the same time, C. albicans also stimulate some bacterial infections [9, 14]. There is the scientific evidence of the diverse influence of C. albicans on the structural mechanism of the population of the main causative agents of nosocomial infections. In case of immunosuppressive animals, C. albicans can cause an increase and reproduction of highly virulent strains in populations of E. coli, S. aureus that are resistant to antibacterial drugs and their anti-lactoferrin and antilysocyme activity [15–16].

Thus, microbial associates play a certain role in the pathogenesis of infectious diseases: the dynamics of the isolation of associates may change, their prolonged stay in the body (in chronic form or as carriage) may also affect the ineffectiveness of antibiotic therapy. All these issues have not been studied enough, and their study is of practical importance, since they have been of significance in the diagnosis and treatment of associative infections.

OBJECTIVE

Purpose of the study was to research on the interaction of opportunistic C. albicans and S. aureus most frequently encountered in infectious pathologies in vivo and in vitro conditions, both with the participation of normal microflora, and in mice with antibiotic-induced dysbacteriosis, and to study their electron microscopic features.

MATERIALS AND METHODS

The strains of C. albicans and S. aureus used in the experiments were isolated from patients who applied to the private laboratory of the Department of Microbiology and Immunology of the Azerbaijan Medical University, and then were identified by morphological, cultural, and enzymatic features. Suspensions of 48-h culture of C. albicans in the amount of 1×10^7 CFU/ml and 1×10^5 CFU/ml, and prepared from the 24-h culture of S. aureus in the amount of 1×10^8 CFU/ml and 1×10^5 CFU/ml were used in the experiments.

In vivo experiments were carried out on 100 white male mice weighing approximately 18 grams. 0.20 t mg/ml vancomycin, 0.40 t mg/ml gentamicin, 0.50 t mg/ml ampicillin per 100 grams of weight were administered to mice orally in a dose of 0.1 ml for 5 days. They were used in order to prevent the possible influence of normal microbiota of mice on C. albicans and S. aureus. Healthy animals and mice with antibiotic-induced dysbacteriosis were divided into groups to create a mono- and associative infection: I group was given 1×10^7 CFU of C. albicans, II group –1×10^8 CFU of S. aureus, and III group – a mixture of specified concentrations of C. albicans and S .aureus in the same proportion. C. albicans were administered in the same amounts in the first control group of healthy mice, S. aureus – in another.

Infected mice were opened after 1, 3, 7, and 10 days according to generally accepted rules by preparing a homogenate from visceral organs (stomach, small and large intestine, liver, spleen, kidney) and cultured on Saburo's medium with gentamicin and egg-yolk salt agar. The resulting colonies were counted based on the weight of 1 gram.

The obtained figures were subjected to a variation row, the average number of each row (M) and the error (m) were calculated and indicated in log10. The difference between the indicators of the groups was established by means of Mann-Whitney statistical accuracy ($p \leq 0.05$).

The in vitro experiments were carried out in test tubes with sugar broth, where 0.1 ml from a concentration of 1×10^5 CFU of C. albicans and S. aureus were transferred and incubated at 37°C. Smears were prepared from the suspension on the 1, 3, 5. 7, 11, and 15 days of the experiment, and inoculated on solid nutrient media with sugar agar, Saburo medium. Smears were prepared from the grown mixed cultures, and then stained using the Gram method.

Concentrations of 1×10^7 and 10^8 CFU/ml were used for the purpose of electron microscopic study of microorganisms. The mixture of microorganisms was kept at 37°C for 48 hours, then centrifuged, and the blocks of microorganisms were prepared using accepted protocols. The obtained materials were then cut with diamond knives in an EM UC 7 -LEİCA microtome into plates with a thickness of 60 nm. Sections were stained with uranyl acetate and mercuric citrate. Ready-made preparations were studied using the Japan JEM 1400 transmission electron microscope.

The studies were conducted in the Electron Microscope Laboratory under the AMU headed by Professor E. Gasymov (with financial support from the Science Development Foundation under the President of the Republic of Azerbaijan. Grant No. EIF-2011-1 (3) -82 / 44/3-M-6).

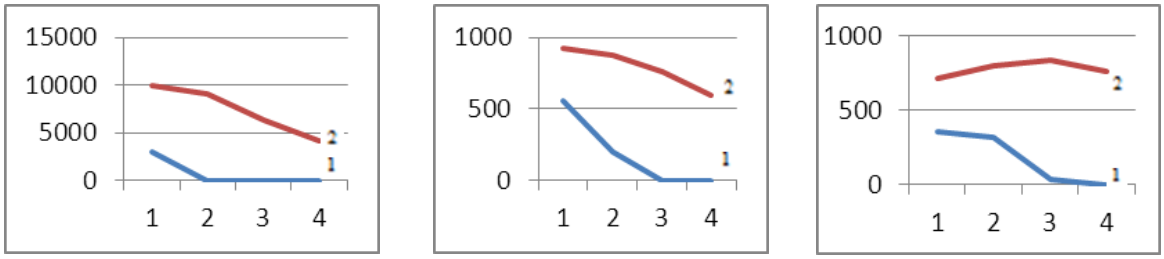
RESULTS AND DISCUSSION

C. albicans and S. aureus were isolated only from the digestive tract of both groups of animals, injected with cultures of these microorganisms. C. albicans was isolated from the stomach of healthy mice in the amount of 2.81 ± 0.19 CFU on the first day of the experiment, on the second day – in the amount of 2.40 ± 0.98 CFU; 2.92 ± 0.80 CFU were isolated from animals that were given antibiotics on the first day of the experiment, 2.83 ± 0.54 CFU – on the third day, 2.72 ± 0.27 CFU – on the seventh day, and $2.64 \pm 0{,}45$ CFU – on the tenth day (fig. 1 (1)).

C. albicans was found in the small intestine of healthy animals only on the first day and on the second day of the experiment in the amount of 2.75 ± 0.03 CFU and 2.3 ± 0.45 CFU, respectively. C. albicans isolated from the small intestine of animals that were given antibiotics in an amount of 2.96 ± 0.27 CFU on the first day, 2.94 ± 0.80 CFU on the third day, , 2.88 ± 0.15 CFU on the seventh day, and in the amount of 2.78 ± 0.35 CFU on the tenth day (fig. 1 (2)).

C. albicans was found in the large intestine of healthy mice on the first day in an amount of 2.56 ± 0.71 CFU, on the third day in an amount of 2.51 ± 0.15 CFU, on the seventh day it was detected only in the colon in an insignificant amount ($1,6 \pm 0.45$ CFU), and on the tenth day

microbes were not detected at all. Fungi were isolated from the colon in animals receiving antibiotics on the first day of observation in the amount of 2.86 ± 0.54 CFU, on the third day – 2.90 ± 0.05 CFU, on the seventh day – 2.92 ± 0.18 CFU and on tenth day – in the amount of 2.88 ± 0.06 CFU.



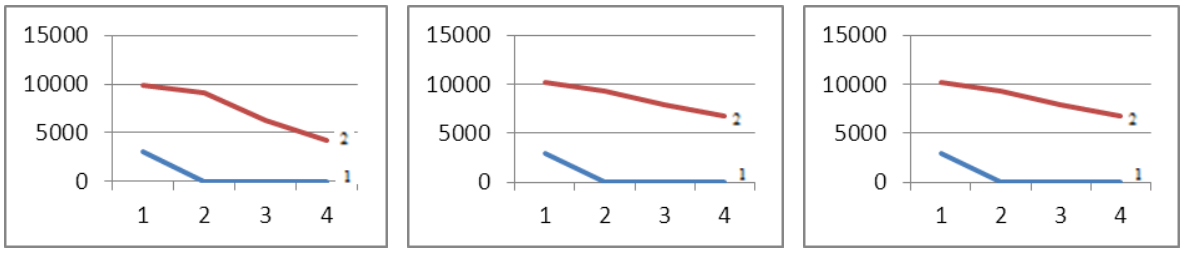
Stomach Small intestine Colon

Fig. 1. Detection of C. albicans (CFU) in case of mono-infection in healthy mice (1) and in animals that were administered antibiotics (2) in the stomach, small and large intestines
Abscissa: 1 – the first day, 2 – the third day, 3 – the seventh day, 4 – the tenth day. *Ordinate*: indicates CFU

S. aureus was found in the stomach of healthy animals only on the first day of the experiment (3.48 ± 0.43 CFU). In contrast, microbes were excreted from animals that were given antibiotics until the end of the experiment (3.99 ± 0.88 CFU on the first day, 3.96 ± 0.71 CFU on the third day, 3.80 ± 0.55 CFU on the seventh day, 3.62 ± 0.25 CFU on the tenth day) (fig. 2 (1)).

S. aureus was isolated from the small intestine of healthy animals only on the first day of the experiment (3.47 ± 0.25 CFU), whereas it was found in animals that were given antibiotics, on the first day in an amount of 4.1 ± 0.71 CFU, on the third day – 3.97 ± 1.12 CFU, on the seventh day – 3.90 ± 0.83 CFU, and on the tenth day – 3.83 ± 0.35 CFU (fig. 2 (2)).

Staphylococci were detected in the large intestine of healthy animals only on the first and second days of the experiment (2.92 ± 0.05 CFU). In contrast, they were found in animals that were given antibiotics, in an amount of 4.02 ± 0.84 CFU on the first day, 4.01 ± 0.88 CFU on the third day, 3.92 ± 0.91 CFU on the seventh day, and in the amount of 3.87 ± 0.81 CFU on the tenth day (fig.2 (3)).



Stomach Small intestine Colon

Fig. 2. Detection of S. aureus (CFU) in case of mono-infection in healthy mice (1) and in animals that were administered antibiotics (2) in the stomach, small and large intestines
Abscissa: 1 – the first day, 2 – the third day, 3 – the seventh day, 4 – the tenth day. *Ordinate*: indicates CFU

Oral administration with intervals of C. albicans and S. aureus simultaneously to animals that were given antibiotics in the first 24 and 48 hours caused the death of 60 % and 100 % of the animals, respectively. The microbial load of both types of microorganisms in the organs of dead animals exceeded to a significant degree such load in the control groups ($p \leq 0.05$). Microbes were found not only in the gastrointestinal tract of animals, they also colonized the liver, spleen and kidneys. The results of the experiments are shown in table.

Table

Microbial load in case of co-infection, caused by C. albicans and S. aureus of white antibiotic-treated mice (log10)

	I day		II day	
	C. albicans (CFU/gr)	S. aureus (CFU/gr)	C. albicans (CFU/gr)	S. aureus (CFU/gr)
Stomach	3,03 ± 0,25	4,2 ± 0,55	3,12 ± 0,13	4,29 ± 0,80
Small intestine	3,06 ± 0,17	4,06 ± 0,69	3,08 ± 0,05	4,26 ± 0,76
Colon	3 ± 0,13	4,07 ± 0,88	3,03 ± 0,13	4,19 ± 0,65
Liver	2,55 ± 0,15	3,61 ± 0,43	2,75 ± 0,65	3,74 ± 0,59
Spleen	2,51 ± 0,17	3,48 ± 0,35	2,68 ± 0,05	3,59 ± 0,25
Kidney	2,61 ± 0,35	3,62 ± 0,65	2,83 ± 0,07	3,60 ± 0,35

The study of the relationship between C. albicans vs. S. aureus in vitro showed once again the existence of a relationship between these two microorganisms that can be seen in smears prepared at different times from a mixture of microbes (fig. 3), where there is an accumulation of staphylococci around Candida fungi (fig. 3, A). You can also observe that staphylococci are distributed in insignificant amounts in the field of view where there are no cells of fungi. And staphylococci are arranged in small clusters and chains in places where cells of fungi are not detected. (fig. 3, B). Thus, staphylococci are more intense and with large groups, forming a classical cluster of bunches, are located around the cells of Candida fungi (fig. 3, A–B).

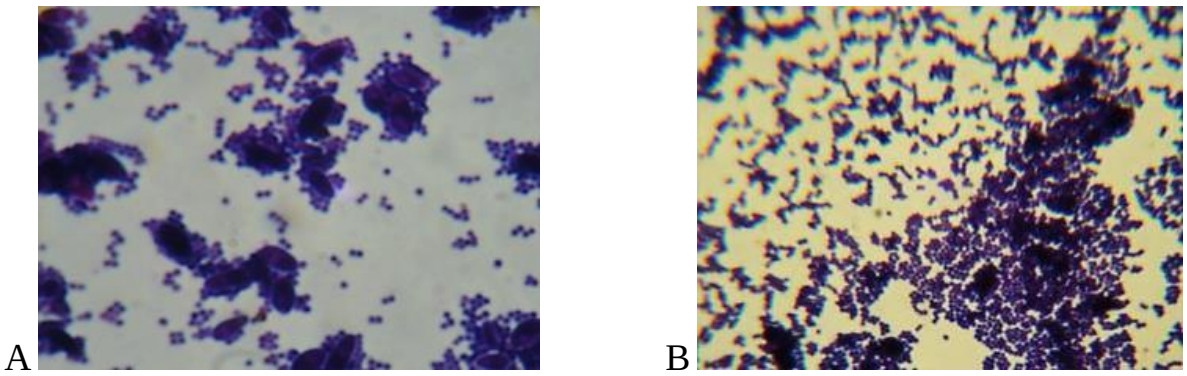


Fig. 3. Smears prepared from the mixed cultures of C. albicans and S. aureus (Gram stain)

We provide electron microscopic images for the purpose of introducing some clarity on the relationship between these microorganisms.

One can notice the attraction between the cells of staphylococci and fungi in the figure 4, these attractions are hardly noticeable (indicated by the arrow in figure 4.A) at the beginning of the experiments, and more clearly visible (fig. 4 B–C) as the cells approach each other; the formation of bridges between the cells (fig. 4 D–F) is also noticeable. Thus, an adhesive bond is formed between the cells of C. albicans vs. S. aureus. Reproduction of staphylococci adhered to the surface of fungal cells can also be viewed (fig. 4 C). 2–3 cells of staphylococci can accumulate on the surface of a single cell of the fungus (fig. 4 F).

Normal microflora of healthy organism contributes to the elimination of pathogens immediately after their introduction to the large extent along with other protection mechanisms. That is why, cultures of C. albicans and S. aureus, orally administered to healthy mice, were isolated from the digestive tract only in the initial days of the experiment. These microorganisms were also isolated mainly from the digestive tract, where the amount of host-gut microbiota was gradually decreased, in animals with antibiotic-induced dysbacteriosis. But the

studied microorganisms in the body of these mice were isolated in larger quantities unlike the body of healthy animals, and moreover, until the end of the experiment. However their number gradually decreased by the tenth day. Signs of the disease were observed from the first days of the experiment in animals that were injected with antibiotics.

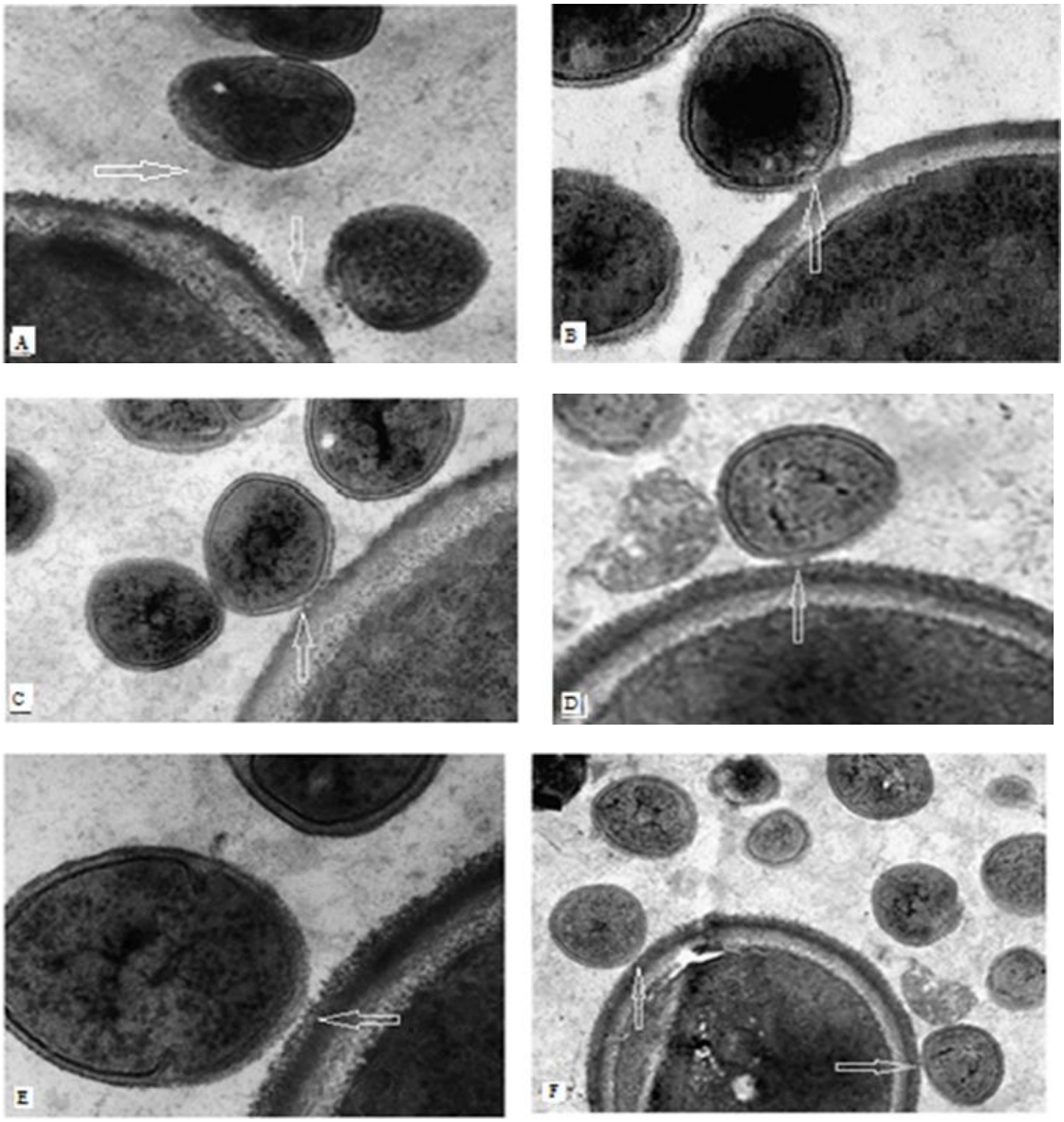


Fig. 4. Electron-microscopic image of the relationship between cells of C. albicans and S. aureus (arrows indicate adhesion)

Despite the significant decrease in normal microflora that was observed in animals administered with antibiotics, there was a gradual restoration of the composition of the microflora after cessation of the introduction of antibiotics. Detection of C. albicans and S. aureus for a long time (throughout the experiment) in the digestive tract of animals that were injected with antibiotics, in large quantities (CFU), was due to a decrease in the number of native microflora. The gradual restoration of normal microflora was accompanied by a gradual decrease in these microorganisms. Thus, signs of the disease were observed in mono-infections caused by C. albicans and S. aureus, both in healthy animals and in those who were given antibiotics, but no deaths were observed. There were no signs of major changes in the internal organs. However, co-infection induced by the Candida-Staphylococcus association in animals with dysbiosis caused

by antibiotics was the most difficult – accompanied by high rates of development and a high degree of mortality. Namely, 100 % of the animals died within the first 48 hours during co-infection. An autopsy of the dead animals showed an increase in the quantity of both microorganisms in the digestive tract, liver, kidney and spleen. Such results show the marked synergistic effect between C. albicans and S. aureus. Namely, when staphylococci are the only source of infection, a low percentage of dead animals are present, and co-infection with C. albicans at the same time increases the percentage of dead animals and the microbial burden in the internal organs, which coincides with the results of similar studies [9, 17]. On the basis of the data obtained, the causes of death of the mice are the mutual reinforcement of the physiological properties of the associates and reduction of the nonspecific protective system of the microorganism through the developed dysbacteriosis on the other hand. Microbial products have a synergistic effect in association, influencing on the growth and reproduction of bacteria, on the expression of pathogenicity factors [18]. The main factor ensuring the microbial pathogen's ability to cause an infection with severe flow is the amplification of the bacteria virulence under the influence of fungi.

In vitro studies also allowed establishing the dependence of staphylococci on Candida fungi. The results obtained and electron-microscopic images confirm the adhesive interaction between the cells of C. albicans and S. aureus, which led to an intensive multiplication of staphylococci on the surface of the fungi and formation of a multilayer film. As can be seen, S. aureus forms a film with the participation of C. albicans in the absence of the ability to form separately a film in the serum, and reproduce in the form of microcolonies based on the biofilm of C. albicans.

The complex interaction between fungi and staphylococci that arose under certain conditions is due to the presence of certain receptors [19–20]. The C. albicans agglutinin-like sequences (ALS) and specific surface glycoproteins in mixed microbial associations are important for co-adhesion [21].

CONCLUSIONS

The obtained results showed that the relationship between these microorganisms is ambiguous. Polymicrobial infection even nowadays remains a significant predictor of the patient's prognosis deterioration, reducing the effectiveness of antibiotic therapy and likelihood of successful treatment [22–23]. Various interactions arise under conditions of mutual enhancement of virulence in the animal organism, under conditions of quantity and time. Therefore it is especially important and necessary to take into account these data in case of the treatment of polymicrobial aetiology infections. The treatment strategy should not only be directed against a single pathogen, but also aim to destroy the microbial association.

PROSPECTS FOR FUTURE STUDIES

It remains relevant to study the effect of various therapeutic approaches in order to improve the effect on the fungus-bacterium association depending on the localization of the infection. Given the antibiotic resistance of individual bacteria, which significantly increases with cooperation with various representatives of the fungal flora, it makes sense to search for new methods of exposure, along with medical management. Further exploration of changes in the activity of various pathogens during the co-infection can make a significant contribution in this direction.

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