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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

ETIOLOGICAL, PATHOGENETIC, AND THERAPEUTIC FEATURES OF SECONDARY INFECTIONS IN PATIENTS WITH MALIGNANT SOLID TUMORS AND LYMPHOMAS

Specialty: 3224.01 – "Oncology"

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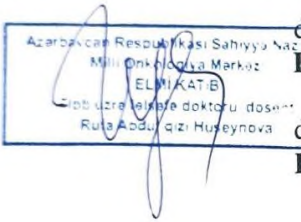

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THE RELEVANCE OF THE TOPIC

In recent years, new approaches in the treatment of oncology patients – including aggressive antitumor therapies and the use of intravenous catheters – have led to prolonged neutropenia and severe mucositis in cancer patients[1].As a result, both the presence of malignant tumors and the administration of cytoreductive chemotherapy and radiotherapy lead to reduced immune reactivity and immunosuppression, contributing to the development of severe secondary infections[2]. In oncology patients (OPs), intercurrent secondary infections are accompanied by a worsening of the clinical course of the disease, along with disruptions in structural and metabolic homeostasis. Additionally, antibiotic therapies in these patients contribute to the emergence of drug-resistant microbial strains[3].

In oncology patients, the causative agents of secondary infections (SIs) of bacterial, fungal, and viral etiology are widely distributed in nature and include pathogenic and opportunistic infectious agents, viruses, and fungi. SIs are common as intercurrent infections in oncology patients and remain one of the main causes of infectious complications and mortality in this group[4].

Therefore, at the current stage of development in clinical oncology, the timely detection of SIs in oncology patients is not only essential for their treatment and prevention but is also considered an integral part of the entire complex of therapeutic and preventive measures carried out in medical institutions.

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[4] Инфекционные болезни. Национальное руководство. Под ред. Н.Д.Ющука и Ю.А.Венгеров. Москва: ГЕОТАР-Медиа, 2019, с.616-664.

The clinical and pathogenetic significance of SIs in OPs should be regarded as a potential factor that can negatively affect their health, treatment course, and even prognosis. In oncology practice, this risk has been insufficiently studied, which hinders the improvement of the generally accepted algorithm for adaptive immunotherapy in OPs. Moreover, SIs limit the possibilities for adequate antitumor treatment, increase the frequency and severity of adverse and toxic effects of ongoing therapies, and reduce patients' quality of life. The full spectrum of these infections, their dependence on disease etiology, and effective prevention strategies have not yet been adequately explored or fully developed. At the same time, SIs hold greater clinical significance in patients with lymphomas compared to those with malignant solid tumors (MSTs), as immunodeficiency in lymphomas leads to an earlier manifestation of the clinical signs of SIs.

Moreover, the specific characteristics of this problem in Azerbaijan have not yet been fully identified. The prevalence of SIs, the species-taxonomic composition of the associated microflora, and its susceptibility to antibacterial and antifungal agents remain largely unknown. Although Azerbaijani oncologists have conducted separate observations on various aspects of SIs in oncology patients, the issue has not been comprehensively studied in the country. These factors underline the relevance, scientific and practical significance, as well as the objectives and aims of the present research.

The purpose of the research. To determine the prevalence and characteristics of the most common and subclinical secondary bacterial, fungal, and viral infections in patients with solid malignant tumors and lymphomas in Azerbaijan, as well as to assess the general clinical and pathogenetic features of these infections and their potential clinical significance in oncology patients.

Research Objectives:

In order to accomplish the outlined goal, the following tasks have been established:

1. To determine the spectrum and frequency of the most significant bacterial and fungal infections among patients with malignant solid tumors treated in the surgical and therapeutic departments of

the National Oncology Center; to characterize the features of their microbiota, and to assess the antimicrobial susceptibility of the isolated pathogens;

2. To determine the spectrum and frequency of bacterial and fungal infections observed in lymphomas, to characterize the features of the microbiota, and to assess the antibiotic susceptibility of the isolated pathogens;

3. To identify the characteristics of the hospital microflora detected in various clinical departments and auxiliary units of the National Oncology Center, and to determine the nature of the relationship between these indicators and the main features of the microbiota in oncology patients;

4. To study the hospital-acquired microflora that has developed over the past several years within the buildings and premises of the National Oncology Center;

5. To determine the prevalence of the most common viral infections worldwide (HBV and HCV) among patients with malignant solid tumors (MSTs) and lymphomas;

6. To evaluate the clinical significance of common bacterial, fungal, and viral infections as potential causes of complications in oncology patients.

Research Methods. The study employed bacteriological, microscopic, biochemical, and immunoenzymatic analysis methods.

Main Provisions Submitted for Defense

1. In oncology patients treated in the clinical departments of the National Oncology Center (NOC), a relative decrease in the number of bacteria detected after surgical procedures compared to preoperative results has been observed, which may be associated with perioperative antibacterial therapy. In contrast, following chemotherapy, a relative increase in the number of bacterial and fungal strains detected in oncology patients may be attributed to the immunosuppressive effects of cytostatic drugs.

2. The increased incidence of secondary infections in lymphomas is an indication of more severe immunodeficiency in these patients compared to those with malignant solid tumors.

3. The microbiological examination of patients in both the sur-

gical and therapeutic clinical departments at the National Oncology Center (NOC) showed that the species-taxonomic composition of the microbiota in all patients is significantly similar and represented by only a few bacterial genera. Most of these bacterial species belong to relatively low virulence gram-negative microorganisms.

4. The regular serological and microgenetic screening among existing oncology patients (OPs) allows for the identification of patient groups that pose a potential risk as sources of viral infections, such as hepatitis B and hepatitis C.

5. In oncology patients, widespread bacterial, fungal, and viral infections are primarily caused by opportunistic, conditional-pathogenic, or saprophytic species, and have not been accompanied by severe clinical complications nor significantly affected the course of treatment.

Scientific Novelty of the Research: For the first time in Azerbaijan, using an automated bacteriological methods complex, the study clarified the prevalence of bacterial and fungal pathogens, as well as subclinical secondary infections, in patients with malignant solid tumors (MSTs) and lymphomas treated in the surgical and therapeutic departments of the NOC. The species (taxonomic) composition of the microbiota was also characterized. Specific markers of infection with hepatotropic viruses of hepatitis B and C were identified in patients treated in the NOC's surgical and therapeutic departments. The specific features of the species (taxonomic) composition of the microbiota characteristic of the environmental objects located in the center, as well as several medical and auxiliary buildings, were generalized and analyzed. An objective understanding of the antibiotic susceptibility spectrum of the identified infectious agents in OPs was formed. This allowed for an assessment of the prevalence of antibiotic-resistant strains of infectious agents in the NOC clinical departments.

All this information may have scientific and theoretical significance for improving the epidemiological analysis of SIs in Ops and for studying their clinical pathogenetic characteristics.

Practical significance of the research. The information about the most common strains of Sis, the species (taxonomic)

composition of pathogens, and their clinical and pathogenetic characteristics in OPs, especially those with malignant solid tumors (MSTs) and lymphomas, may be useful in treatment protocols for anticancer therapy. The results of the study hold significant practical importance in reducing the risk of SI transmission in oncology clinics and in the proper planning of therapeutic and preventive strategies for patient treatment.

The microbiological "landscape" identified in the medical and auxiliary buildings of the NOC as a result of the research is used for the proper planning and improvement of the preventive measures regularly conducted in these buildings.

In addition, the results obtained can help predict the cases of infection in oncolog OPs from the external environment and contribute to reducing the resistance of SI pathogens to multiple antibiotics.

Object and subject of the research. The dissertation work was conducted at the National Oncology Center of the Ministry of Health of the Republic of Azerbaijan.

Approbation of the dissertation. Individual sections of the dissertation were presented and discussed at various scientific-practical conferences, including: the Scientific-Practical Conference dedicated to the 100th anniversary of V.Y.Akhundov (Baku, 2016); the International Scientific-Practical Conference on Antimicrobial Therapy and Clinical Microbiology (Ростов-на-Дону, 2018, 2019); the conference materials dedicated to the birthday of National Leader H.A.Aliyev (Baku, 2023); the Scientific-Practical Conference of Young Scientists and Specialists at the National Oncology Center (Baku, 2018, 2022); and the International Scientific-Practical Conference dedicated to the 100th anniversary of Academician R. Rahimov (Baku, 2023).

The results of the dissertation were presented and discussed at the Interdepartmental Meeting of the National Oncology Center of the Ministry of Health of the Republic of Azerbaijan (May 31, 2024, Protocol No. 1), as well as at the Scientific Seminar of the Dissertation Council FD1.02 operating under the National Oncology Center (November 1, 2024, Protocol №4).

Publications: A total of 25 scientific works have been published on the dissertation topic, including 14 articles, 10 abstracts, and 1 meth-

odological recommendation. Of these, 10 articles, 1 methodological recommendation, and 8 abstracts were published in the country, while 4 articles and 2 abstracts were published in international journals.

Institution where the dissertation was carried out.

The results of the research are applied in the clinical practice of the National Oncology Center of the Ministry of Health of the Republic of Azerbaijan, as well as in the educational process and lectures at the Azerbaijan State Institute for Doctors' Improvement named after A.Aliyev, Ministry of Health of the Republic of Azerbaijan.

Volume and structure of the dissertation: The dissertation consists of 145 typed pages (a total of 231,258 characters). It includes the following sections: Introduction (16,586 characters), Literature Review (51,679 characters), Chapter II – Materials and Methods (30,123 characters), Chapter III – Personal Research (78,157 characters), Discussion of the Obtained Results (51,200 characters), Conclusions (1,806 characters), Practical Recommendations (1,037 characters), and References. The reference list includes 184 scientific sources, of which 22 are in Azerbaijani and 162 are in foreign languages. The dissertation is illustrated with 25 tables and 7 figures.

MATERİALS AND METHODS OF THE STUDY

Clinical Characteristics of the Patients. In this study, bacteriological and mycological analyses were performed on 400 oncology patients who were admitted to and treated at the NOC between 2017 and 2021, as well as on equipment and surfaces in hospital wards and service rooms. The antibiotic susceptibility of bacteria and fungi responsible for secondary infections was also investigated. The patients' diagnoses were confirmed through clinical-instrumental examination methods and histopathological analyses. The oncology patients examined in this study were divided into two major groups: 1) Patients with malignant solid tumors. 2)Patients with lymphomas.

In this study, the taxonomic spectrum of the bacterial and fungal flora of the upper respiratory tract was determined in 62 patients

with malignant tumors of the head and neck region (clinical stages II–III) and in 65 patients diagnosed with lung cancer (LC) (clinical stages II–III), who were treated in the Department of Thoracic Oncology. The analyses were conducted both before surgical operation (SO) and 5–6 days after the surgical procedures.

Research Methods. Pathogenic microorganisms were examined from sterile body sites (blood, urine, peritoneal fluid, tracheal aspirate, cerebrospinal fluid), as well as from swabs, abscesses, wounds, and catheter cultures of patients hospitalized in the clinical departments and pediatric clinic of the National Oncology Center. Clinical samples were inoculated onto various nutrient media – including blood agar, EMB, and Sabouraud dextrose agar (SDA) – to cultivate microorganisms and analyzed microscopically after Gram staining. Microbiological flora and antibiotic susceptibility tests of the sample materials were performed using the VITEK 2 Compact System (BioMerieux, France), Phoenix 100 (BD), and BacT/Alert 3D and BACTEC 9050 systems for sterility and microbiological testing of blood samples.Sample materials included secretions from the nasopharyngeal mucosa, mucus secreted from the nasopharynx, and sputum. In some cases, discharges from tracheostomy and drainage tubes were also examined.

The study was carried out in three stages at the Bacteriology Laboratory of the NOC and included the following procedures:1)Inoculation of biological material into "initial" Petri dishes using three different selective nutrient media (blood agar, eosin methylene blue agar, and Sabouraud dextrose agar); 2) Processing of primary isolates and obtaining pure cultures of bacterial and fungal agents from them; 3)Determination of the tinctorial properties (staining by the Gram method) and taxonomic genus-species identification of bacterial and fungal isolates, as well as preliminary assessment of their antibacterial strain sensitivity.

For the purpose of clinical and pathogenetic evaluation of concomitant infections, clinical data obtained from the medical histories of patients with identified infections were analyzed.

All isolated bacterial strains were tested for susceptibility to 16 antibacterial drugs: piperacillin/tazobactam, ceftazidime, cefepime,

aztreonam, imipenem, meropenem, gentamicin, netilmicin, tobramycin, ciprofloxacin, amikacin, levofloxacin, tetracycline, tigecycline, colistin, and trimethoprim. Each isolate was classified as highly, moderately, or weakly sensitive to each of these drugs. In addition, patients in whose samples fungal pathogens were detected underwent further mycological examination (conducted using the "cough plate" method, modified by J. Borden). After staining by the Romanowsky-Giemsa method, the prepared slides were examined microscopically to detect fungal cells (actinomycetes, ascomycetes, pneumocystis, etc.).

Furthermore, statistical analysis was performed on the data obtained in the study.

RESULTS OF PERSONAL RESEARCH

Results of bacterial analysis in patients with lung cancer

The results regarding the taxonomic spectrum of bacterial and mycotic flora in the upper respiratory tract of patients with HNMT and LC before and after SO are presented in the corresponding tables.

Before SO, among 62 patients with HNMT, bacterial and fungal strains were obtained from 38 (61.3%) patients. Among the microorganisms found in the patients, 21 (55.3%) strains were gram-negative bacteria, 12 (31.6%) strains were gram-positive bacteria, and 5 (13.2%) strains were yeast-like fungi.

The majority of the isolated gram-negative bacterial strains (over 75%) belonged to only 8 genera and species. The most commonly encountered strains among the 21 strains were: E. coli (5 strains), Klebsiella pneumoniae (3 strains), Serratia marcescens (3 strains), Pseudomonas aeruginosa (1 strain), Haemophilus pneumoniae (2 strains), Acinetobacter baumannii (3 strains), Moraxella inflamatis (2 strains), and Proteus vulgaris (2 strains).

More than 75% of the isolated gram-positive bacterial strains belonged to only 6 species: Staphylococcus aureus (3 strains), Staphylococcus flavus (3 strains), Streptococcus viridans (2 strains), Micrococcus roseus (2 strains), Enterococcus durans (1 strain), and Ac-

tinomyces dentalis (1 strain).

The identified fungi were represented by 3 genera: Candida spp. (3 strains), Cryptococcus spp. (1 strain), and Saccharomyces spp. (1 strain).

After SO, during a second examination of 62 patients with HNMT, 26 (41.9%) bacterial and fungal strains were obtained. Of these, 14 (53.8%) were gram-negative, and 7 (26.9%) were gram-positive bacteria. Five (19.2%) of the strains were fungi.

Most of the gram-negative bacteria were only represented by 6 species: K. pneumonia (5 strains), E. coli (3 strains), Serratia marcescens (2 strains), Pseudomonas aeruginosa (2 strains), Hemoph. pneumoniae (1 strain), and Acinetobacter spp (1 strain).

Similarly, the majority of the isolated gram-positive bacterial strains were also only represented by 5 bacterial species: Staph. aureus (2 strains), Strep. albus (2 strains), Micrococcus roseus (1 strain), Enteroc. durans (1 strain), and Actinomyces dentalis (1 strain).

The identified fungi were represented by 3 genera: Candida spp – 3 (4.8%) strains, Cryptococcus spp – 1 (1.6%) strain, and Pneumocystis jirovecii – 1 (1.6%) strain.

The identified fungi were represented by 3 genera: Candida spp – 3 (4.8%) strains, Cryptococcus spp – 1 (1.6%) strain, and Pneumocystis jirovecii – 1 (1.6%) strain (Table 1).

Table 1

Frequency of detection of infectious agents in patients with malignant tumors of the head and neck before and after surgical operation (SO).

Type of pathogen	Before surgical operation	After surgical operation	P
Gram-negative bacteria	21 (33,9±6,01%)	14 (22,6±5,31%)	>0,05
Gram-positive bacteria	12 (19,4±5,02%)	7 (11,3±4,02%)	<0,01
Fungi	5 (8,1±3,46%)	5 (8,1±3,46%)	<0,01
Total	38 (61,3±6,19%)	26 (41,9±6,27%)	0,031

Note: ($p<0.05$)

The results obtained showed that in patients with HNMT, gram-negative bacteria predominated both before and after SO. At the same time, the majority of the identified bacteria in both cases were of low pathogenicity or opportunistic pathogens. The fungal spectra identified before and after SO did not show significant differences, and all were of low pathogenicity for immunocompetent individuals. Before the SO, among the gram-negative bacteria, E. coli (8.1%) predominated, while among the gram-positive bacteria, Staphylococcus aureus (4.8%) and Staphylococcus flavus (4.8%) were more prevalent. After the SO, Klebsiella pneumoniae (8.1%) was more commonly found. Additionally, after the SO, strains of Moraxella inflamatis and Proteus vulgaris among gram-negative bacteria, and Streptococcus viridans among gram-positive bacteria were not encountered (Table 2).

Table 2

Most commonly identified gram-negative and gram-positive bacteria in patients with malignant tumors in the head and neck region before and after surgical operation (SO)

№	Bacteria	Number of strains	
		Before surgical operation (SO)	After surgical operation (SO)
Gram-negative bacteria			
1	E.coli	5 (8,1±3,46%)	3 (4,8 ±2,73%)
2	K.pneumonia	3 (4,8 ±2,73%)	5 (8,1±3,46%)
3	Ser. Marcescens	3 (4,8 ± 2,73%)	2 (3,2±2,24%)
4	Ps. Aeruginosa	1 (1,6 ±1,84%)	2 (3,2±2,24%)
5	Hem. Pneumoniae	2 (3,2 ±2,24%)	1 (1,6±1,60%)
6	Acinet. Baumanii	3 (4,8 ±2,73%)	1 (1,6±1,60%)
7	Mor. Inflamatis	2 (3,2 ±2,24%)	-
8	Prot. Vulgaris	2 (3,2±2,24%)	-
Total		21 (33,9±6,01%)	14 (22,6±5,31%)
Gram-positive bacteria			
1	Staphyl. aureus	3 (4,8±2,73%)	2 (3,2±2,24%)
2	Staphyl. Albus	3 (4,8±2,73%)	2 (3,2±2,24%)

3	Strepot. viridans	2 (3,2±2,24%)	-
4	Micrococcusroseus	2 (3,2±2,24%)	1 (1,6±1,60%)
5	Enterococcusdurans	1 (1,6±1,60%)	1 (1,6±1,60%)
6	Actinomyces dentalis	1 (1,6±1,60%)	1 (1,6±1,60%)
Total		12 (19,4±5,02%)	7 (11,3±4,02%)

According to the results of the antibiotic susceptibility test, all isolated bacterial agents showed susceptibility to at least two of the tested antibacterial agents, either to a lesser or greater extent.

Results of bacterial analysis in lung cancer patients

In lung cancer patients, 34 (52.3%) bacterial and fungal strains were isolated before SO, of which 21 (61.8%) were gram-negative bacteria, 10 (29.4%) strains were gram-positive bacteria, and 3 (8.8%) strains were fungi. Most of the gram-negative bacterial strains were represented by 10 genera and species, including: E. coli (4 strains), K. pneumoniae (3 strains), Serratia marcescens (3 strains), Pseudomonas aeruginosa (1 strain), Haemophilus spp. (2 strains), Acinetobacter spp. (2 strains), Moraxella catarrhalis (3 strains), Proteus retgeri (1 strain), Corynebacterium flavescens (1 strain), and Campylobacter spp. (1 strain).

It should be noted that the majority of isolated gram-positive bacterial strains belonged to 6 genera: Staphylococcus albus (2 strains), Streptococcus viridans (2 strains), Micrococcus roseus (2 strains), Enterococcus durans (2 strains), Actinomyces dentalis (1 strain), and Mycobacterium avis (1 strain).

All the fungi isolated from the patients were represented by two genera: Candida spp. – 2 strains and Cryptococcus spp. – 1 strain.

After SO, 19 (29.2%) pathogenic strains were isolated from 65 lung cancer patients, of which 10 (52.6%) were gram-negative bacteria, 5 (26.3%) were gram-positive bacteria, and 4 (21.1%) were fungi. Most of the isolated gram-negative bacterial strains were represented by 7 genera, including: K. pneumoniae (3 strains), Serratia marcescens (2 strains), Haemophilus spp. (1 strain), Acinetobacter spp. (1 strain), Moraxella spp. (1 strain), Corynebacterium spp. (2

strains), and Neisseria meningitidis (1 strain).

The majority of isolated gram-positive bacteria in these oncology patients belonged to 4 genera: Staphylococcus aureus (2 strains), Streptococcus hemolyticus (1 strain), Micrococcus roseus (1 strain), and Actinomyces dentalis (1 strain).

The isolated fungi were represented by 4 species: Candida spp. – 2 (3.1%) strains, Cryptococcus spp. – 1 (1.5%) strain, and Aspergillus flavus – 1 (1.5%) strain (Table 3).

Table 3

Frequency of pathogen detection before and after surgical operation (SO) in lung cancer patients.

Type of pathogen	Before surgical operation (SO)	After surgical operation (SO)	P
Gram-negative	42 (32,1 ± 4,08%)	20 (15,9 strain ±3,26%)	<0,01
Gram-positive	19 (14,5 ± 3,08%)	10 (7,9 ± 2,41%)	>0,05
Fungi	6 (4,6 ± 1,83%)	8 (6,3 ± 2,17%)	>0,001
Total	67 strain	38 ştam	

Note: ($p<0.05$)

According to the results of the study, in patients with HNMT and LC, a relative decrease in the frequency of detection of both gram-negative and gram-positive bacterial strains was observed after SO. This may be related to the suppressive effect of antibiotic therapy on the organism's microbiota before surgical intervention. The increased frequency of detection of Pneumocystis, a typical opportunistic infection agent, after SO, and the absence of significant changes in the frequency of fungal agent detection, may primarily be linked to the effect of perioperative antibacterial therapy on the microbiota. At the same time, the activation of the microbiota's fungal component may be associated with the short-term traumatic stress (immunodepressiv) effect of SO on the body.

Thus, in both studied groups of LC patients, more gram-negative bacteria and fewer fungi were identified. At the same time, the taxonomic spectra of both bacteria and fungi identified in patients with HNM were less different from those in patients with LC. In both

groups of cancer patients, most of the identified pathogens were opportunistic agents. In both groups, the surgical procedure had a positive impact on both the frequency of pathogen detection and the breadth of their taxonomic spectrum. Additionally, in both groups, the proportion of bacteria demonstrating high and moderate sensitivity to antibiotics after SO did not significantly differ from the proportion detected before SO. The impact of bacterial presence on the clinical and pathological condition of patients with both HNM and LC was investigated. No signs of bacterial or fungal invasions or intoxication associated with an increase in body temperature or the development of infections were observed in any of the patients (Table 4).

Table 4

Most commonly identified gram-negative and gram-positive bacteria in lung cancer patients before and after surgical operation (SO).

№	Bacteria	Number of strains	
		Before surgical operation (SO)	After surgical operation (SO)
Gram-negative bacteria			
1	E.coli	4 (6,2±2,98%)	–
2	K.pneumonia	3 (4,6±2,60%)	3 (4,6±2,60%)
3	Ser. marcescens	3 (4,6±2,60%)	2 (3,1±2,14%)
4	Pseud. aeruginosa	1 (1,5±1,53%)	–
5	Hemophiluspneumoniae	2 (3,1±2,14%)	1 (1,5±1,53%)
6	Acinet. baumanii	2 (3,1±2,14%)	1 (1,5±1,53%)
7	Morax catarrhalis	3 (4,6±2,60%)	1 (1,5±1,53%)
8	Proteus retgeri	1 (1,5±1,53%)	–
9	Coryneb. flavescens	1 (1,5±1,53%)	1 (1,5±1,53%)
10	Campil. jejuni	1 (1,5±1,53%)	–
11	Neiss. Meningitidis	–	1 (1,5±1,53%)
Total:		21 (32,3±5,80)	10 (15,4±4,48%)
Gram-positive bacteria			
1	Staphyl. Albus	2 (3,1±2,14%)	–
2	Strepot. Viridans	2 (3,1±2,14%)	–
3	Micrococcusroseus	2 (3,1±2,14%)	1 (1,5±1,53%)
4	Enterococcusdurans	2 (3,1±2,14%)	-

5	Actinomyces dentalis	1 (1,5±1,53%)	1 (1,5±1,53%)
6	Mycobact. avis	1 (1,5±1,53%)	–
7	Staph. aureas	–	2 (3,1±2,14%)
8	Str. hemolyticus	–	1 (1,5±1,53%)
Total:		12 (19,4±5,02%)	5 (7,7±3,31%)

Results of Bacteriological Analysis in the Auxiliary Buildings and Environmental Objects of the National Oncology Center

According to the results of the bacteriological analysis conducted in the auxiliary buildings and environmental objects of NOC, the most frequently detected pathogens among hospital-acquired infections were Clostridium difficile (12.1%), followed by Staphylococcus aureus (10.7%), Klebsiella spp. (9.9%), and Escherichia coli (9.3%) (Table 5).

Table 5

Results of Bacteriological Analysis in the Auxiliary Buildings and Environmental Objects of the National Oncology Center

№	Bacteria	Number of strains, %
	Gram-negative bacteria	
1	E. coli	9,3±3,46%
2	K.pneumonia	5,9 ±2,73%
3	Pseudomonas aeruginosa	4,6 ±1,84%
4	Hem. pneumoniae	4,2 ±2,36%
5	Klebsiella spp	9,2 ±2,41%
6	Acinetobacter spp	5,2±2,24%
Gram-positive bacteria		
1	Staphylococcus aureus	10,8±2,73%
2	Staphyl. albus	5,4±2,73%
3	Strepot. viridans	2 (3,2±2,24%
4	Enterococcus durans	2,5±1,60%
5	Clostridium difficile	12,6±1,60%
Total:		100,0%

Among the infectious agents detected in the environmental objects of the NOC, Gram-negative bacteria were represented by 6 types of strains, while Gram-positive bacteria were represented by 5 types of strains.

Among nosocomial fungal pathogens, the most frequently detected were *Candida* spp., *Aspergillus* spp., *Mucorales*, *Fusarium* spp., and other mold and yeast-like fungi, including *Scedosporium* spp.

Thus, the results of the microbiological examination of environmental objects located in the buildings of the NOC show that in more than 75% of cases, the species composition of the microbiota of surgical oncology patients overlaps with microorganisms previously identified in environmental objects. Furthermore, the ratio of gram-positive and gram-negative bacteria, as well as the ratio of pathogenic and non-pathogenic microorganisms, was very close to the ratio previously identified in environmental objects within the buildings of the SO departments.

Results of the study on patients with malignant solid tumors receiving chemotherapy

A microbiological examination was conducted both before and after chemotherapy on 100 patients with malignant solid tumors (lung and breast cancer patients) treated in the chemotherapy department and 100 patients with lymphoma (Hodgkin and Non-Hodgkin lymphoma) treated in the hematology department.

Before chemotherapy, 18 bacterial and fungal strains were identified in the 100 patients with malignant solid tumors. Of these, 10 (55.6%) strains were gram-negative, 6 (33.3%) strains were gram-positive bacteria, and 2 (11.1%) strains were yeast-like fungi. The majority (more than 75%) of the isolated gram-negative bacterial strains belonged to only 8 species. Thus, the 10 identified strains included Klebsiella pneumonia (2 strains), Escherichia coli (2 strains), Serratia marcescens (1 strain), Proteus vulgaris (1 strain), Haemophilus influenzae (1 strain), Acinetobacter baumannii (1 strain), Yersinia enterocolitica (1 strain), and Pseudomonas aeruginosa (1 strain).

The isolated strains of gram-positive bacteria belonged to 2 species: Staphylococcus spp (1 strain) and Streptococcus spp (1

strain). The isolated fungi were represented by only two genera: 3 (3.0%) strains belonged to the genus Candida spp, and 1 (1.0%) strain belonged to the genus Cryptococcus spp.

After chemotherapy, a re-examination of the patients with malignant solid tumors (MST) revealed 26 bacterial and fungal strains, of which 14 (53.8%) were gram-negative, 7 (26.9%) were gram-positive bacteria, and 5 (19.2%) were fungi.

The most frequently identified gram-negative bacteria were E. coli (3 strains), K. pneumonia (2 strains), Serratia marcescens (1 strain), Haemophilus influenzae (1 strain), Acinetobacter baumannii (1 strain), Pseudomonas aeruginosa (1 strain), Moraxella catarrhalis (1 strain), Proteus vulgaris (1 strain), Proteus rettgeri (1 strain), Campylobacter jejuni (1 strain), and Yersinia enterocolitica (1 strain).

After chemotherapy, the isolated gram-positive bacteria in patients with malignant solid tumors (MST) belonged to 5 species: Staphylococcus aureus (2 strains), Streptococcus mutans (2 strains), Micrococcus albus (1 strain), Enterococcus durans (1 strain), and Actinomyces dentalis (1 strain).

The isolated fungi were represented by three genera: 5 strains of Candida spp., 4 strains of Cryptococcus spp., and 1 strain of Saccharomyces spp. (Table 6).

The results showed that after chemotherapy, the number of isolated strains in patients with MST was slightly higher than the number of strains of both gram-negative and gram-positive bacteria identified before chemotherapy. This suggests that the proliferation of these bacteria is more intensive after chemotherapy. This could be related not only to the effect of antibiotic therapy on the microbiota but also to the activation of the microbiota's fungal components under the immunosuppressive effect of chemotherapy. An increase in the number of fungal strains identified after chemotherapy was also observed.

Table 6

Most commonly identified infectious agents in patients with malignant solid tumors before and after chemotherapy

Type of pathogen	KT-dan əvvəl	KT-dan sonra
Gram-negative	10 (10,0 ± 3,00%)	14 (14,0± 3,47%)
Gram-positive	6 (6,0 ± 2,37%)	7 (7,0± 2,55%)
Fungi	2 (2,0± 1,40%)	5 (50,±2,18%)
Total	18 (18,0± 3,84%)	26 (26,00± 4,39%)

Note: ($p<0.05$)

As seen, after chemotherapy, the taxonomic spectra of both gram-negative and gram-positive bacteria, as well as fungi, have slightly expanded. It is also important to note that the majority of bacteria and fungi identified both before and after chemotherapy were either low-pathogenic or opportunistic pathogens. All isolated bacterial agents showed sensitivity to at least two tested antibacterial drugs to varying degrees. For example, Acinetobacter baumannii was sensitive to Tetracycline, Tigecycline; Enterococcus spp. to Daptomycin, Linezolid.

Results of Bacteriological Studies in Lymphoma Patients Undergoing Chemotherapy

As for the microbiological examination results of lymphoma patients, 21 bacterial and fungal strains were isolated from the materials of 100 patients with lymphoma before chemotherapy. Of these, 10 (47.6%) strains were gram-negative bacteria, 8 (38.1%) strains were gram-positive bacteria, and 3 (14.3%) strains were fungi.

The gram-negative bacterial strains in lymphoma patients were represented by 9 species, including E. coli (2 strains), K. pneumoniae (1 strain), Hemophilus influenzae (1 strain), Campylobacter jejuni (1 strain), Acinetobacter baumannii (1 strain), Moraxella catarrhalis (1 strain), Proteus vulgaris (1 strain), Pseudomonas aeruginosa (1 strain), and Neisseria meningitidis (1 strain).

After chemotherapy, the majority of the gram-positive bacterial strains in lymphoma patients were represented by 6 species: Staphylococcus aureus (2 strains), Streptococcus hemolyticus (2 strains), Micrococcus albus (1 strain), Enterococcus durans (1 strain), Actinomyces dentalis (1 strain), and Mycobacterium avium (1 strain).

The isolated fungi were represented by only two genera of

these infectious agents: Candida spp. (2 strains) and Cryptococcus spp. (1 strain).

During the follow-up examination of the same lymphoma patients after chemotherapy, 34 bacterial and fungal strains were obtained, of which 15 (46.9%) were gram-negative, 10 (31.3%) were gram-positive bacteria, and 9 (28.1%) were fungi.

In lymphoma patients, most of the gram-negative bacterial strains were represented by 14 species. Thus, 27 of the 30 strains were represented by the following bacteria: E. coli (5 strains), K. pneumonia (4 strains), Proteus vulgaris (3 strains), Pseudomonas aeruginosa (3 strains), Moraxella catarrhalis (2 strains), Neisseria meningitidis (2 strains), Haemophilus influenzae (1 strain), Campylobacter jejuni (1 strain), Acinetobacter baumannii (1 strain), Vibrio vulnificus (1 strain), Serratia marcescens (1 strain), Listeria monocytogenes (1 strain), Bacillus subtilis (1 strain), and Corynebacterium jejuni (1 strain).

After chemotherapy, the majority of the gram-positive bacterial strains in lymphoma patients were represented by 10 species. Specifically, 16 of the 18 strains were associated with the following pathogens: Staphylococcus aureus (4 strains), Staphylococcus argenteus (3 strains), Streptococcus hemolyticus (2 strains), Streptococcus mutans (1 strain), Streptococcus pneumoniae (1 strain), Streptococcus pyogenes (1 strain), Micrococcus albus (1 strain), Enterococcus durans (1 strain), Actinomyces dentalis (1 strain), and Mycobacterium avium (1 strain).

Among the 17 fungal strains identified in this study, the following were present: Candida albicans (5 strains), Candida glabrata (2 strains), Cryptococcus neoformans (3 strains), Cryptococcus gattii (1 strain), Saccharomyces cerevisiae (3 strains), Blastomyces dermatitidis (2 strains), and Pneumocystis jirovecii (1 strain) (Table 7).

Table 7

Most commonly identified infectious agents in lymphoma patients before and after chemotherapy

Type of agent	Before chemotherapy	After chemotherapy
Gram-negative	10 (10,0±3,00%)	15 (15,0±3,57%)

Gram-positive	8 (8,0±2,71%)	10 (10,0±3,00%)
Fungi	3 (3,0±1,71%)	9 (9,00±2,86%)
Total	21 (21,0±4,07%)	34 (34,00±4,74%)

Note: ($p<0.05$)

Thus, after chemotherapy, a greater number of infectious agents were isolated from lymphoma patients, and accordingly, more strains of all three types of infectious agents were obtained (65 vs. 42) ($p<0.05$). This difference was more pronounced with fungi, as fungi were isolated three times more frequently after chemotherapy compared to before ($p<0.01$). This could be due to a decrease in reactivity as a result of chemotherapy and the indirect stimulation of microbial growth. After chemotherapy, the taxonomic spectrum of both bacteria and fungi isolated from lymphoma patients expanded significantly. Likely, the increased permissiveness of the organism to bacteria after chemotherapy provided conditions for the broadening of their species spectrum. The increase in the number of fungi, as well as the expansion of their species spectrum, may also be associated with chemotherapy-induced immunosuppression, which activated the fungal component. As observed, pneumocystis were more commonly found in hemoblastosis patients than in patients with head and neck cancers (HNC). Similar to patients with MST, bacterial agents isolated from lymphoma patients also showed sensitivity to at least two antibacterial drugs, either minimally or significantly.

None of the infectious agents identified in the oncological patients caused clinically significant infectious complications, and the infections persisted subclinically. In patients with MST and lymphoma fever was observed in 3.0% and 2.0% of patients, respectively, while hyperleukocytosis was observed in 1.0% and 3.0% of patients.

Serological and virological research results in oncological patients

Another group of frequently detected viral infections (VIs) in oncological patients are transfusion-transmitted viral hepatitis, including hepatitis B virus (HBV) and hepatitis C virus (HCV). Among

the 100 patients with MST, 4 (4.0%) were found to have only HBsAg, 5 (5.0%) had anti-HBc, 7 (5.0%) had only anti-HCV, and 4 (4.0%) had both HBsAg and anti-HCV. Among the 100 patients with lymphoma, 5 (5.0%) had only HBsAg, 7 (7.0%) had anti-HBc, 16 (7.0%) had only anti-HCV, and 4 patients had both HBsAg and anti-HCV.

The results indicate that the detection frequency of anti-HCV in lymphoma patients is, on average, more than twice as high as in patients with MST, and the difference between these indicators was statistically significant with $p<0.01$.

Among the 21 patients with HBV detection, 14 (66.7%) exhibited the inapparent variant (an invisible variant with no changes in the biochemical parameters shown in the serum), 6 (28.6%) had the hyperenzymatic variant accompanied by hyperenzymia, and 1 (4.7%) had the hyperbilirubinemia variant (increased ALT activity along with an increase in bilirubin levels, with jaundice symptoms not visually observable). No jaundiced variant was observed (Table 8).

Table 8

Frequency of recording the pathogenic variants of infections caused by HBV and HCV in oncology patients

Pathogenetic course variants	Number of patients, %	
	HBV	HCV
Inapparent	14 (66,7±9,62%)	6 (26,1±6,19%)
Hyperenzymia	6 (28,6±9,28%)	14 (60,9± 6,35%)
Hyperbilirubinemia	1 (4,7± 4,08%)	3 (13,0± 3,75%)
Jaundiced variant	0 (0,00)	0 (0,00)
Total	21 (100,0%)	23 (100,0%)

Among the 23 patients with HCV detection, 6 (26.1%) had the inaparat variant, 14 (60.9%) had the hyperenzymic variant, and 3 (13.0%) had the hyperbilirubinemia variant.

Based on the numerical indicators presented in this table, it was found that in oncology patients with HBV infection, pathogenetic variants without hepatocyte alteration predominated, and the infection continued only in a subclinical form.

According to the numerical data presented in this table, patho-

genetic variants with minimal hepatocyte alterations and the infection persisting only in a subclinical form were predominant in patients with lymphoma and HCV infection.

Thus, the results above provide evidence that there is no significant difference in the prevalence of HBV and HCV infections among patients living in Azerbaijan and receiving treatment in oncology hospitals. However, although HCV is more frequently detected in lymphoma patients compared to MST patients, this infection remains subclinical in the majority of patients.

CONCLUSIONS

1. In patients with malignant solid tumors and head and neck cancers, gram-negative bacteria predominated both before and after surgical operation (SO). After the operation, a significant decrease in the proportion of bacterial and fungal strains identified was observed, ranging from 61.3% to 41.9%. This may be related to the suppressive effect of antibiotic therapy on the organism's microbiota before surgical intervention [17, 21, 23].
2. After chemotherapy, an increase in bacterial and fungal strains by 18.0% to 26.0% is associated not only with the effect of antibiotic therapy on the microbiota but also with the activation of the microbiota's fungal component under the immunosuppressive effect of chemotherapy. All isolated bacterial agents showed sensitivity to at least two antibacterial drugs to varying degrees [19, 21, 24].
3. In patients with lymphomas, pneumocysts were more frequently found compared to patients with malignant solid tumors. In these patients, after chemotherapy, bacterial strains increased by 21% to 34%, and particularly fungal strains increased threefold, indicating the activation of the fungal component under the immunosuppressive effect. The bacterial agents isolated from lymphoma patients showed varying degrees of sensitivity to at least two antibacterial drugs [4].
4. The hospital-acquired microbiota that has developed in the buildings and premises of the National

Oncology Center over the past few years has primarily been represented by non-pathogenic microorganisms. Regardless of the disease profile, the microbiota and species composition found in oncology patients did not significantly differ [19, 24].

5. The specific markers of hepatitis B and hepatitis C virus infections found among oncology patients were detected several times more frequently than in the control group of healthy individuals. In the majority of infected individuals, the course of these viral infections continued in a subclinical form [1, 18].
6. In oncology patients, widespread bacterial, fungal, and viral infections had a subclinical impact. In patients with malignant solid tumors and lymphoma, fever was observed in only 3.0% and 2.0% of patients, respectively, while leukocytosis was seen in 1.0% and 3.0% of patients. [24]

PRACTICAL RECOMMENDATIONS

1. Obtaining comprehensive information about the potential pathogens of hospital-acquired secondary infections and the characteristics of patients' microbiota in oncology hospitals is of practical significance for the application of appropriate therapeutic approaches aimed at improving the effectiveness of both surgical procedures and antitumor treatments, as well as enhancing the patient's survival indicators.
2. The same indicators can be used to characterize both the hospital-acquired microbiota and the patients' microbiota in oncology hospitals, including: 1) the ratio of gram-positive and gram-negative bacteria and fungi; 2) the ratio of pathogenic, opportunistic, and saprophytic microorganisms; 3) the species spectrum of the identified microbiota; 4) the relative detection frequency of each microorganism species; and 5) the sensitivity spectrum of microorganisms to antibacterial agents.
3. Serological studies aimed at identifying specific markers of Hepatitis B and C virus infections should be conducted immediately after the admission of oncology patients to the hospital, regardless of the elevation of "liver" enzyme

levels.

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LIST OF ABBREVIATIONS AND TERMS

NOC – National Oncology Center
OPs – oncology patients
SIs – secondary infections
HBV – hepatitis B virus
HCV – hepatitis C virus
MSTs – malignant solid tumors
HNMT – head and neck malignant tumors
LC – lung cancer
SO – surgical operation
HNM – head and neck malignancies
VIs – viral infections

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