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DEPARTMENT OF GENERAL AND OPERATIVE SURGERY

LYMPH NODES IN MAXILLOFACIAL SURGERY – IN NORM AND MOST COMMON DISEASES

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1. INTRODUCTION

The lymphatic system is undoubtedly the most important part of the defense mechanisms of primates, including humans. It is composed of lymphatic vessels, lymph nodes and other organs and plays a major role in the implementation of life-sustaining functions such as maintaining immune balance, draining interstitial fluid, lipid transport and building the immunological response to numerous pathological agents. From an anatomical and clinical point of view, the lymph nodes of the head and neck represent a special group of lymphatic structures that participate in a large number of processes at the local and systemic levels. They reflect the state of local tissues and organs and often serve as early indicators of a large number of serious diseases of systemic origin. This determines their extremely important importance in clinical practice and in maxillofacial surgery as a part of it, in which timely and adequate recognition and interpretation of lymphadenopathy is of key importance for the prognosis and treatment of the disease.

In medical practice, diseases of the lymph nodes of the head and neck range from benign and self-limiting conditions such as reactive lymphadenitis to life-threatening infectious diseases, autoimmune conditions, malignant neoplasias and metastatic involvement from other malignant processes. The correct diagnosis and adequate management of lymph node diseases requires the clinician to have both extensive clinical experience and in-depth knowledge of anatomy, pathophysiology and the necessary therapeutic approaches. The lymph nodes in this relatively small but extremely complex anatomical region are constantly exposed to many and different etiological factors, causing both frequent acute upper respiratory tract infections and rare systemic diseases and metastases, more often from primary tumors in the head and neck region and less often from other, more distant parts of the body.

The presence of enlarged and/or painful lymph nodes in the head and neck in patients is one of the most common reasons for consulting a specialist in maxillofacial surgery. Despite the availability of a large number of high-tech imaging, microbiological, laboratory and pathological methods of diagnosis, in a significant percentage of cases, establishing a definitive diagnosis requires the implementation of some invasive procedures such as fine-needle aspiration biopsy (FNAB) for cytological examination, partial (incisional biopsy) or complete (excisional biopsy) removal of a lymph node for histological examination. The correct choice of indications and methodology for surgical treatment and the assessment of the need for additional conservative therapy (symptomatic, antibacterial) are the basis for proper treatment and a good outcome of the disease and contribute to the favorable prognosis of the patient.

Nowadays, there is an increasing interest in modern medical literature in studying the local manifestations of systemic diseases and the role of the lymph nodes themselves as indicators and participants in these generalized processes and diseases. A special place is occupied by the study and analysis of antibiotic resistance in infectious diseases of the lymph nodes. The World Health Organization (WHO) and numerous national and global health institutions warn about the dangers associated with increased antibiotic resistance, which is mostly a result of the excessive and often irrational use of antibacterial agents. This is especially true for the treatment of acute and aggravated cervical lymphadenitis, where empirical antibiotic therapy is often applied before the results of the prepared microbiological examination, which takes several days, are obtained.

There is still a lack of comprehensive scientific studies that simultaneously examine the clinical profile of patients with lymph node diseases in the maxillofacial region and perform a statistical analysis of the associated demographic and therapeutic characteristics, which is the main objective of the present study. It is a retrospective review of all patients with lymphadenopathy of the head and neck who passed through the Clinic of Maxillofacial Surgery of the University Hospital "St. Marina" EAD - Varna for the period from January 1, 2015 to December 31, 2024. The

collected data cover a total of 563 patients with lymphatic pathology out of a total of 8325 hospitalized, which constitutes approximately 6.76% of all cases during the observation period.

Patients were divided into nine main diagnostic groups according to the established nosological units: actinomycosis, sarcoidosis, tuberculosis, felonitis, metastatic involvement of the lymph nodes ("meta colli"), lymphoproliferative diseases (including Hodgkin and non-Hodgkin lymphoma), chronic reactive lymphadenitis, abscesses and phlegmons originating from lymph nodes, and acute lymphadenitis (mainly cervical). These groups include both infectious and neoplastic, inflammatory and systemic diseases. An analysis of the distribution of diseases by gender, age, type of treatment (surgical or conservative) and the presence of antibiotic resistance in infectious forms was performed. Special attention was paid to the comparative analysis by age groups – under and over 18 years of age, which allows to deduce specific trends and differences between the pediatric and adult population.

In addition to the demographic age and gender distribution, the dissertation also includes a statistical analysis of therapeutic approaches using non-parametric methods, such as the Mann–Whitney U test and two-sided Fisher's Exact Test. In this way, the presence of statistically significant differences between the studied groups of patients treated surgically and conservatively is investigated, and a relationship is sought between the selected therapeutic approach and the demographic characteristics of the patients. The data from this analysis have not only scientific, but also practical value, as they can help form future algorithms for behavior in patients with lymphadenopathy of the head and neck.

A particularly valuable aspect of the study is the assessment of antibiotic resistance in inflammatory diseases of the lymph nodes in the maxillofacial region. Based on the microbiological results and the antibiotics used to treat these diseases, the levels of resistance of the isolated microorganisms to the main types of antibacterial agents are analyzed. The results are compared by age and gender, which allows conclusions to be drawn regarding the risk groups and the effectiveness of the antibiotics administered to them, creating the opportunity to formulate recommendations for rational antibiotic therapy in patients with infectious lymphadenitis (mainly acute) in the maxillofacial region.

2. PURPOSE

The objectives of this dissertation are:

1. to perform a modern and detailed cytological, histological, anatomical-topographical and anatomical-oncological description of the regional lymph nodes in the head and neck region, with an emphasis on their importance in maxillofacial surgery;
2. to analyze the diseases of the lymph nodes in the maxillofacial region in patients hospitalized in the Clinic of Maxillofacial Surgery, with distribution by gender, age and clinical diagnosis;
3. to classify the diseases of the lymph nodes into main diagnostic groups and to study their frequency and characteristics in clinical practice;
4. to study the etiological bacterial spectrum in patients with abscesses and phlegmons originating from the lymph nodes of the head and neck;
5. to study antibiotic resistance in patients with infectious diseases of the lymph nodes, with analysis of the relationship between gender, age and type of isolated microorganism.

3. GOALS

To achieve the present goals, the following tasks were set:

1. to conduct a systematic review of the modern scientific literature concerning the cytological, histological and anatomical structure of the lymph nodes in the head and neck region;
2. to describe the topographic location of the lymph nodes in the head and neck region and to systematize their distribution by anatomical levels in view of their clinical significance;
3. to analyze the anatomical-oncological role of the lymph nodes as regional structures in malignant neoplasms in the maxillofacial region;
4. to create a retrospective database of patients with lymph node diseases who have passed through the Clinic of Maxillofacial Surgery for a 10-year period;
5. to perform a statistical analysis of the frequency of lymph node diseases in the maxillofacial region depending on the age, sex and clinical diagnosis of the patients;
6. to make a detailed clinical analysis of representative cases from each main diagnostic group;
7. to prepare a diagnostic classification of diseases of the lymph nodes in the maxillofacial region by etiology - nonspecific, specific, reactive and chronic lymphadenitis, lymphoproliferative and metastatic diseases;
8. to study the distribution of patients according to the formed diagnostic groups and their frequency;
9. to compare the clinical features of each group in terms of gender, age and localization of the involved lymph nodes;
10. to determine and analyze the microbiological spectrum in patients with purulent-inflammatory processes originating from the lymph nodes of the head and neck;
11. to identify the main bacterial causative agents of lymphogenic abscesses and phlegmons and to determine their frequency;
12. to process the results of the antibiograms of patients with infectious diseases of the lymph nodes included in the study and to assess the degree of antibiotic resistance to the main groups of antimicrobial agents;
13. to analyze the relationships between antibiotic resistance, gender, age of patients and the type of isolated microorganisms;
14. to offer substantiated recommendations for empirical selection of antimicrobial treatment for infectious diseases of the lymph nodes in the maxillofacial region.

4. MATERIALS

The present study represents a retrospective and descriptive analysis of clinical, microbiological, imaging and histological data from patients with head and neck lymph node diseases who were hospitalized in the Clinic of Maxillofacial Surgery at the University Multi-profile Hospital for Active Treatment “St. Marina” EAD – Varna for a ten-year period (from 01.01.2015 to 31.12.2024). It was approved by the Research Ethics Committee (REC) at the Medical University “Prof. Dr. Paraskev Stoyanov” – Varna in 2025. The total number of patients who passed through the clinic was 8325 – 4756 men and 3569 women, who were treated both surgically and conservatively (figures 1 and 2).

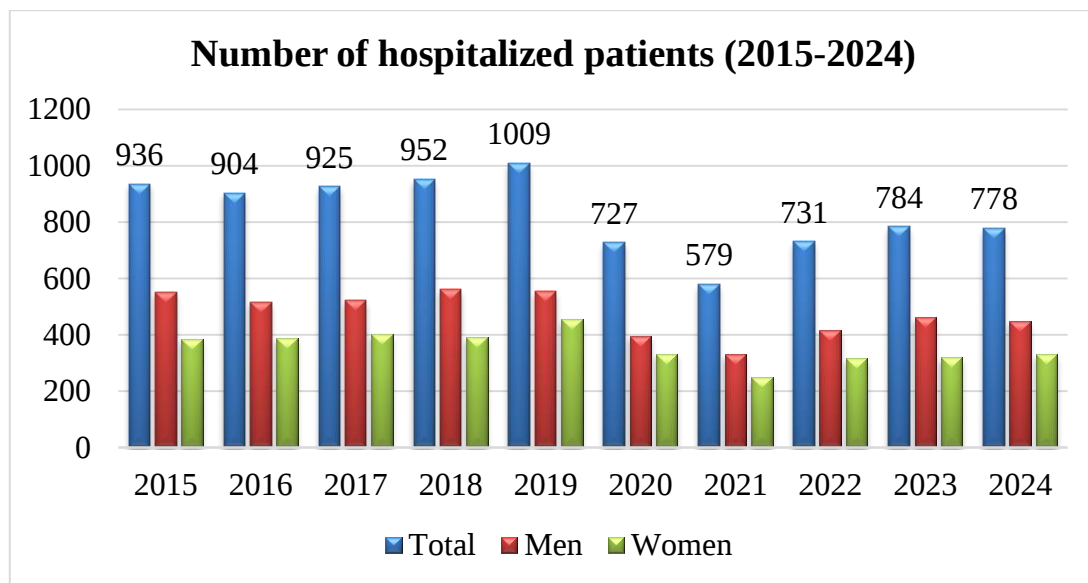


Figure 1. Distribution of patients hospitalized in the Clinic of Maxillofacial Surgery by year for the period from 2015 to 2024.

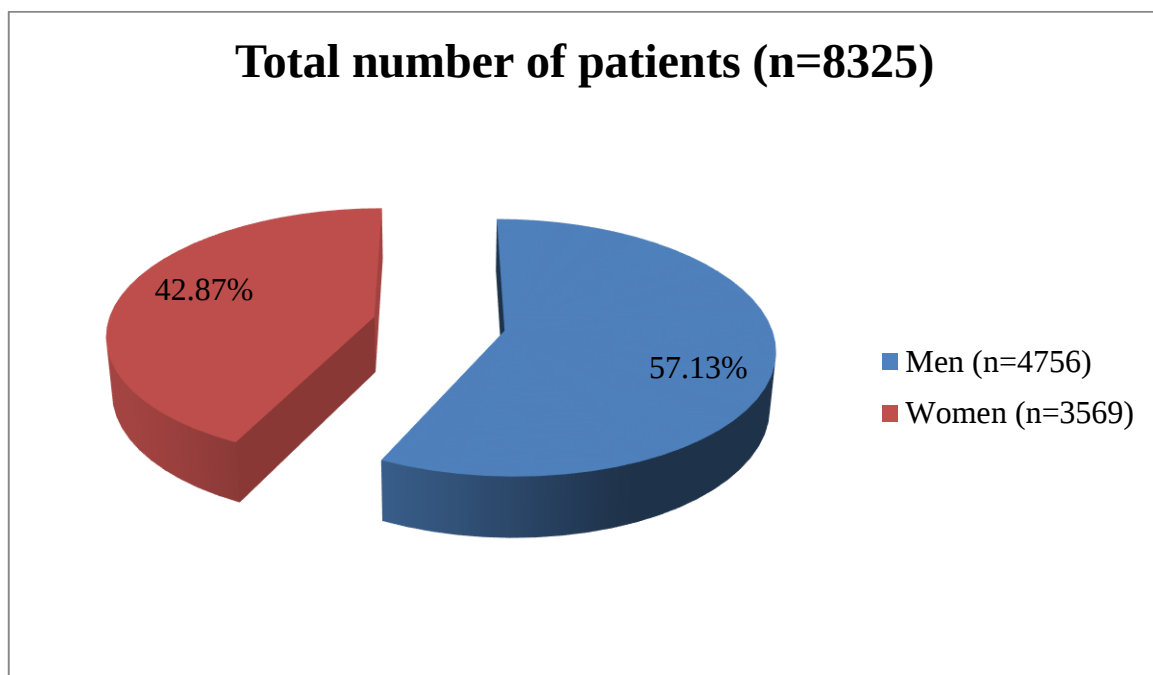


Figure 2. Gender distribution of patients hospitalized in the Clinic of Maxillofacial Surgery for the period from 01.01.2015 to 31.12.2024

The **inclusion criteria** for participation in this retrospective study were:

1. patients had to have been hospitalized in the Clinic of Maxillofacial Surgery at the University Hospital "St. Marina" EAD - Varna for the period from 01.01.2015 to 31.12.2024;
2. had proven disease of the lymph nodes of the head and neck;
3. had to have preserved medical documentation, allowing a comprehensive analysis of the processed data.

The study did not include patients (**exclusion criteria**) who:

1. had not been hospitalized in the Clinic of Maxillofacial Surgery at the University Hospital "St. Marina" EAD - Varna;
2. were hospitalized outside the period 01.01.2015 - 31.12.2024;
3. had no proven disease of the lymph nodes of the head and neck;
4. did not have fully preserved medical documentation, allowing subsequent data analysis.

Patients of both sexes were included in the present study, without age restrictions.

There were nine main groups of diseases to which all 563 hospitalized patients with diseases of the lymph nodes were assigned – actinomycosis, sarcoidosis, tuberculosis, felinosis, metastatic involvement of the lymph nodes, lymphoproliferative diseases (Hodgkin's and non-Hodgkin's lymphoma), chronic reactive lymphadenitis, abscessed lymph nodes and abscesses and phlegmons originating from them, and acute lymphadenitis. In the first eight diseases, the treatment of the patients was surgical, and in the group of patients with acute lymphadenitis of the head and neck, the therapy was entirely conservative (Figure 5).

Patients with lymph node diseases (n=563)

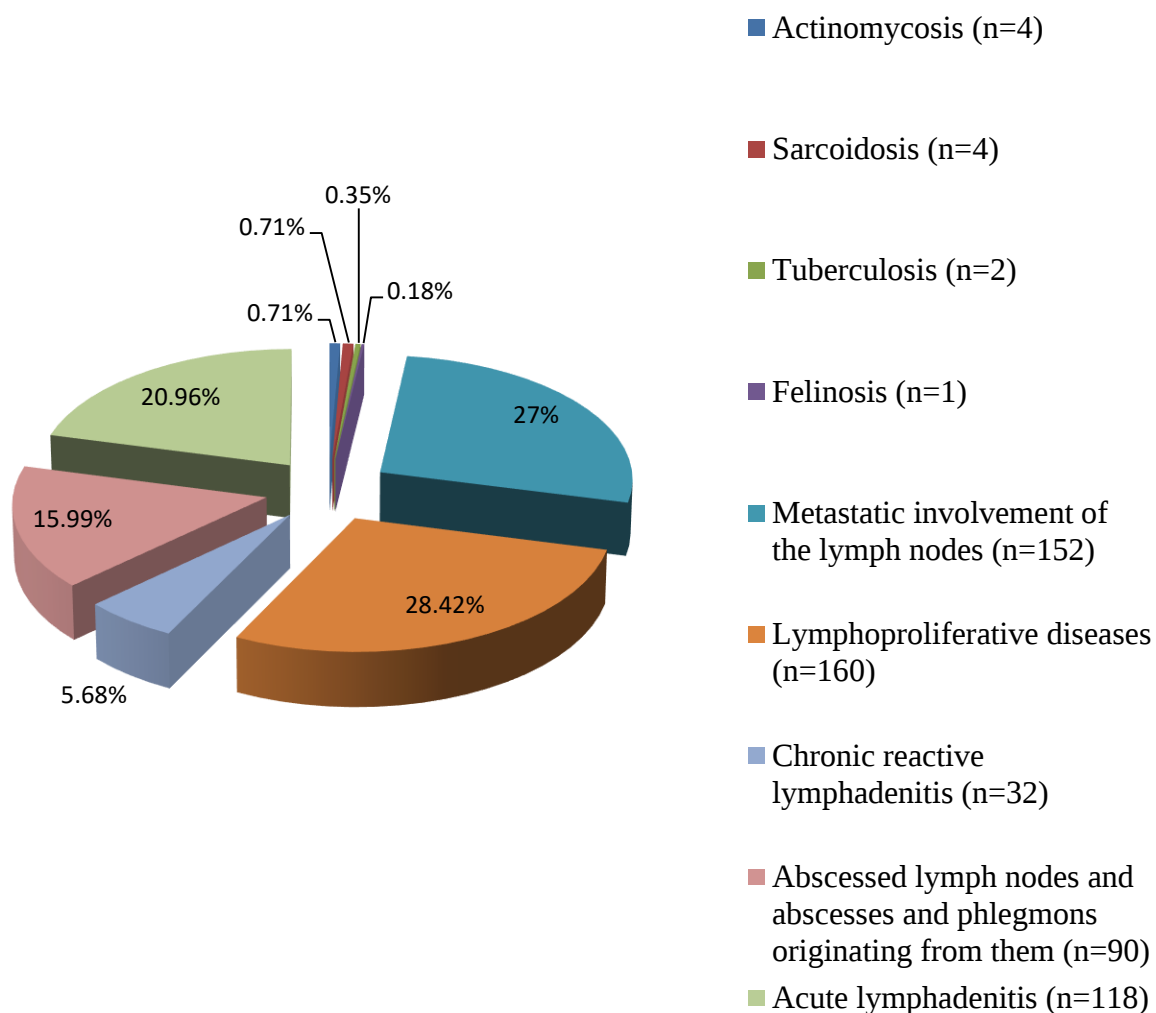


Figure 5. Distribution of the main nine disease groups in the studied patients with head and neck lymph node diseases

5. METHODS

The study was conducted using a complex, multidisciplinary approach, encompassing clinical, anatomical, histological, microbiological, imaging and statistical methods. The combination of retrospective analysis and comparative assessment allowed the collection and processing of reliable information on lymph node diseases in the head and neck region.

In all patients with head and neck lymph node diseases included in the study, the diagnosis was confirmed by conducting a histological pathoanatomical analysis, performed at the Clinic of General and Clinical Pathology at the University Hospital "St. Marina" EAD - Varna for patients with actinomycosis, sarcoidosis, tuberculosis, felinosis, metastatic involvement of the lymph nodes, lymphoproliferative diseases (Hodgkin's and non-Hodgkin's lymphoma) and chronic reactive lymphadenitis. In them, immediately after the excision of the specimen containing the pathological lymph nodes or part of them, it was stored in neutral formalin for no less than 24 hours and then the histological analysis itself was performed.

In patients with abscessed lymph nodes of the head and neck and abscesses and phlegmons arising from them, the diagnosis was confirmed in several successive stages - during the clinical examination, during which the presence of purulent infiltrate was established, during the imaging methods of examination (ultrasound, nuclear magnetic resonance or computed tomography with or without intravenous administration of contrast material) and during the surgical treatment in the volume of incision, lavage and drainage, during which a varying amount of pus was evacuated. In all of them, during the surgical treatment, material was taken for microbiological examination and preparation of an antibiogram for the isolated pathogens using a sterile cotton or gauze swab, which was sent directly or after storage in a transport medium to the Microbiology Laboratory at the University Hospital "St. Marina" EAD - Varna.

In patients with acute lymphadenitis of the head and neck, who were hospitalized and treated conservatively, the diagnosis was confirmed both during the clinical examination, during which the enlarged and painful lymph nodes of the head and/or neck were palpated, without palpatory data for collection and purulent discharge, and from the imaging studies performed.

The following different methods were used in the study of the studied patients: clinical method, anatomical-topographic method, histological method, microbiological method, epidemiological method and statistical evaluation of data and graphical presentation of results.

6. RESULTS AND DISCUSSION

6.1. Comparative demographic analysis of the studied patients and dynamics of cases during the years of observation

For the period from 2015 to 2024, a clear dynamics was established in the values of the average number of patients with diseases of the cervical and cephalic lymph nodes who were hospitalized and treated at the Clinic of Maxillofacial Surgery. The average annual values of their number varied in the interval from 3.00 ± 4.924 to 9.67 ± 8.718 . During the first four years (2015-2018), a relatively stable level was observed, with average values between 6.22 ± 7.362 and 7.22 ± 8.136 , which creates the impression of an initial phase of equilibrium in the number of studied patients. In 2019, however, a sharp jump to 9.67 ± 8.718 (Min=1; Max=22) was recorded, representing the highest average value for the period under review. The subsequent decline in 2020 and 2021 (respectively to 4.89 ± 6.489 and 3.00 ± 4.924) marked a distinct minimum, accompanied by lower maximum values (16 and 12), which indicates reduced variability and a more limited frequency of high observations. The reason for this is the global Covid-19 pandemic, during which, in addition to patients with this viral infection, mainly emergency and oncological patients were hospitalized.

In the next two years (2022-2023), a moderate increase in the average values is observed (5.44 ± 6.366 and 5.11 ± 6.585 , respectively), which indicates a partial recovery after the previous minimum caused by the Covid-19 pandemic. In 2024, a new peak of 8.00 ± 10.26 patients (Min=0; Max=27) is reported, which, however, is accompanied by the highest degree of interindividual dispersion for the entire period, suggesting significant heterogeneity in the data. It should be noted that the minimum value in most years is 0, which suggests the presence of individual cases without a registered event or zero results in the observation, due to patients with tuberculosis, felinosis, sarcoidosis and actinomycosis.

The trend analysis reveals a cyclical pattern of change, including a phase of growth until 2019, a decline until 2021 and a new rise after 2022. The linear regression analysis performed shows a weak negative trend ($\beta \approx -0.11$; $R^2 \approx 0.03$), which indicates the absence of a clear long-term trend. The prevailing fluctuations are more likely to reflect short-term, non-systemic fluctuations than a stable trend in the dynamics of the number of patients.

Table 2 shows the dynamics of cases over the years (2015-2024) and the average total number of patients with pathology of the cervical and cephalic lymph nodes, hospitalized and treated at the Clinic of Maxillofacial Surgery.

Table 2. Average number (Mean), standard deviation (SD), smallest number (Minimum) and largest number (Maximum) of patients with head and neck lymph node pathology who passed through the Clinic of Maxillofacial Surgery by year for the period from 2015 to 2024.

Total all patients (n=563)				
Year	Mean	SD	Minimum	Maximum
2015	6,44	6,207	0	15
2016	6,56	8,748	0	26
2017	6,22	7,362	0	21
2018	7,22	8,136	0	18
2019	9,67	8,718	1	22
2020	4,89	6,489	0	16
2021	3,00	4,924	0	12

2022	5,44	6,366	0	18
2023	5,11	6,585	0	16
2024	8,00	10,259	0	27

6.2. Comparative analysis of the studied patients with head and neck lymph node diseases in terms of their number

To better characterize the study population (n=563), a quantitative analysis of the number of hospitalized patients with various head and neck lymph node diseases was performed. The distribution by nosological unit is presented using basic descriptive statistics – mean (Mean), standard deviation (SD), and minimum (Min) and maximum (Max) limits – in order to outline both trends in the frequency of individual diagnoses and possible variations in their severity or prevalence within the study group. The descriptive statistics of the studied indicator for the various nosological units in the group of 563 patients with head and neck lymph node diseases show significant differences between the nine subgroups. The highest mean value is observed in patients with lymphoproliferative diseases (16,000±4,269; Min=12; Max=26), which suggests a relatively homogeneous, but shifted towards higher values, population. Similarly high values were reported in patients with cervical lymph node metastases (Meta colli) – 15,200±3,393 (Min=11; Max=22), as well as in patients with acute lymphadenitis 11,800±5,922 (Min=3; Max=21). Neck lymph node abscess showed a moderate mean value of 9,000±7,165 (Min=1; Max=27), but was characterized by the greatest dispersion, which suggests significant heterogeneity within this subgroup. Chronic reactive lymphadenitis is characterized by a lower mean value – 3.200±3.225 (Min=0; Max=8), and the lowest values are observed in rare nosologies such as actinomycosis, sarcoidosis, tuberculosis and felinosis, in which the mean value is below 0.500 with a weak variation (SD<0.700; Max≤2). In summary, the data show that the highest mean values of the studied indicator are observed in patients with lymphoproliferative diseases and Meta colli, while the lowest – in felinosis and tuberculosis, with significant variability being reported only in the abscess of the lymph nodes of the neck.

Table 7 shows the average total number of patients with pathology of the lymph nodes of the head and neck compared to the group of diseases hospitalized and treated at the Clinic of Maxillofacial Surgery during the studied period (2015-2024).

Table 7. Average number (Mean), standard deviation (SD), smallest number (Minimum) and largest number (Maximum) of patients who passed through the Clinic of Maxillofacial Surgery according to the group of diseases of the lymph nodes of the head and neck for the period from 2015 to 2024.

Total all patients (n=563)				
Disease	Mean	SD	Minimum	Maximum
Meta colli	15,200	3,393	11	22
Abscessus lymphonodi colli	9,000	7,165	1	27

Actinomycosis	0,400	0,699	0	2
Lymphoproliferative diseases	16,000	4,269	12	26
Acute lymphadenitis	11,800	5,922	3	21
Sarcoidosis	0,400	0,699	0	2
Tuberculosis	0,200	0,422	0	1
Felinosi	0,100	0,316	0	1
Chronic reactive lymphadenitis	3,200	3,225	0	8

6.3. Comparative analysis between the studied patients with surgical and conservative treatment

The results of the Mann-Whitney U test show that there is a statistically significant difference between the groups of patients treated conservatively and surgically, only in the total group of all 563 patients ($U=178.5$, $p=0.003$). This suggests that in general, patients undergoing surgical treatment have significantly higher values for the measured indicator compared to those treated conservatively ($M=55.60$ vs. $M=11.80$).

Table 12 compares the studied patients in whom surgical and conservative treatment was used.

Table 12. Average number of patients who passed through the Clinic of Maxillofacial Surgery by year for the period from 2015 to 2024.

Study Subgroup	Studied group	Average annual value (per number of patients)	SD	Mann-Whitney U	p-value
Total	Operative	55,60	7,24	178,5	<u>0,003</u>
	Conservative	11,80	5,92		
Men	Operative	24,60	4,61	157,5	<u>0,041</u>
	Conservative	4,50	2,61		
Women	Operative	3,79	2,63	125,0	0,098
	Conservative	5,40	3,17		
Boys under 18 years of age	Operative	2,25	1,18	37,0	0,418
	Conservative	1,83	1,17		
Girls under 18 years of age	Operative	1,73	1,49	31,0	0,858
	Conservative	1,33	0,52		

The current analysis examines the comparison between surgical and conservative treatment in hospitalized patients with head and neck lymph node diseases who passed through the Clinic of Maxillofacial Surgery for the period 2015-2024. The statistical data presented by the Mann-Whitney U test show the presence of a significant difference only in the combined group of all 563 patients, which points to a systematic difference between the treatment approaches.

The average value in patients undergoing surgical treatment is significantly higher ($M=55.60$; $SD=7.24$) than in those treated conservatively ($M=11.80$; $SD=5.92$), with the p-value being 0.003 ($U=178.5$). This is a strong indicator that in the general patient population, the surgical approach was necessary in more complex planned and emergency cases requiring surgical intervention. The data in Table 12 and the subsequent graphical visualizations (Figures 6 to 10) confirm this pattern and outline a persistent difference in therapeutic strategies.

Examining the structure of the diseases that led to the choice of therapeutic approach, we can identify several leading clinical scenarios. In surgically treated patients, purulent lymphadenitis and abscesses and phlegmons caused by them are most often encountered, requiring immediate surgical intervention to evacuate the formed pus. On the other hand, conservative treatment prevails in reactive lymphadenopathy, viral infections and early stages of specific granulomatous diseases. These differences in the clinical picture also determine the discrepancies in the mean values between the two groups.

6.4. Comparative analysis between the studied patients with lymphoproliferative diseases in the maxillofacial region

During the ten-year study period (2015-2024), incisional and excisional biopsies of cervical lymph nodes were performed for diagnostic purposes in 160 patients with lymphoproliferative diseases – 97 men, 56 women and 7 boys under the age of 18 (Table 13). No lymphoproliferative disease was detected in female patients under the age of 18.

Table 13. Tabular presentation of patients with lymphoproliferative diseases by number, gender and age group for the period 2015-2024.

Year	Men (n=97)	Women (n=56)	Boys (n=7)
2015	11	4	0
2016	16	8	2
2017	6	4	3
2018	14	3	1
2019	12	6	1
2020	8	8	0
2021	7	5	0
2022	8	4	0

2023	9	7	0
2024	6	7	0

A comparative analysis of the total number of hospitalized patients with lymphoproliferative diseases who underwent excisional biopsy of cervical lymph nodes for diagnostic purposes (n=160) was performed over the ten-year study period. Depending on the type of lymphoproliferative disease identified, patients were divided into two large groups – Hodgkin's lymphoma and non-Hodgkin's lymphoma. The average annual number of hospitalized patients in whom incisional and excisional biopsies showed that the lymphoproliferative process was Hodgkin's lymphoma was 6.3 with a standard deviation of 3.26, while for non-Hodgkin's lymphoma a higher average annual value was reported – 9.7 with a standard deviation of 8.05. The non-parametric Mann Whitney U Test ($U=9$; $p=0.901$) did not reveal a statistically significant difference between the two groups ($p>0.05$), suggesting that the observed differences may be due to random variation. The wider dispersion of values in non-Hodgkin lymphoma may be due to the greater heterogeneity of the disease and the variety of clinical subtypes. This suggests that the observed superiority in mean values in non-Hodgkin lymphoma is not sufficiently pronounced to be considered statistically significant. The larger standard deviation in non-Hodgkin lymphoma may be the result of fluctuations in the frequency of hospitalizations over the years or the larger number of cases.

Lymphoproliferative diseases involving the cervical lymph nodes represent an important part of the diagnostic spectrum in maxillofacial surgery. They include malignant conditions such as Hodgkin lymphoma and various types of non-Hodgkin lymphomas, which have their own epidemiological, clinical and histopathological features. Diagnostic confirmation often requires the performance of incisional or excisional biopsy, which also explains the high frequency of these interventions in specialized surgical clinics and departments focused on maxillofacial surgery.

The present analysis includes data on 160 patients who passed through the Clinic of Maxillofacial Surgery at the University Hospital "St. Marina" EAD - Varna in the period 2015-2024, in whom incisional or excisional biopsy of cervical lymph nodes was performed for diagnostic purposes. Patients were divided by gender and age into three main subgroups – men, women and children (boys under 18 years of age). Female patients under 18 years of age were not hospitalized and operated on. The main goal is to perform a comparative statistical analysis between cases of Hodgkin's and non-Hodgkin's lymphoma, followed over time and by groups, in order to identify possible patterns, trends and significant differences.

A general analysis of the studied population (2015-2024) revealed that within the ten-year observation period, 160 patients with lymphoproliferative diseases were diagnosed, which corresponds to an average of 16 cases per year. Of these, 97 (60.6%) were men, 56 (35.0%) were women, and 7 (4.4%) were boys under 18 years of age. Interestingly, no cases of lymphoproliferative diseases were recorded in girls under 18 years of age, which is consistent with other studies in which the incidence of childhood lymphomas shows a male predominance.

When distributed by lymphoma type, Hodgkin lymphoma is diagnosed with a mean frequency of 6.3 cases per year ($SD=3.26$), while non-Hodgkin lymphoma occurs with a significantly higher mean frequency – 9.7 cases per year ($SD=8.05$). Despite this difference, the

nonparametric Mann-Whitney U test ($U=9$; $p=0.901$) did not report a statistically significant difference between the two groups, suggesting that the observed variations are likely the result of random fluctuations or other unaccounted factors.

The higher standard deviation in non-Hodgkin lymphomas suggests greater heterogeneity, which is well known in the literature – this group includes over 60 different histological subtypes with variable aggressiveness, biological behavior and clinical presentation. This diversity can also lead to an uneven distribution of cases over time, as observed in the present study.

Comparative analysis in men shows that they represent the largest group in the sample ($n=97$) and allows for relatively reliable statistical analysis. For the period 2015-2024, the average annual number of men diagnosed with Hodgkin lymphoma is 3.5 ($SD=1.43$), while for non-Hodgkin lymphoma this value is 6.2 ($SD=1.31$). The difference is almost twofold, which can be interpreted as a clinically relevant trend, although the statistical test ($U=243$; $p=0.544$) does not show significance. It is important to emphasize that the values in men demonstrate relative stability over the years, with a lower standard deviation and limited fluctuations, which suggests a constant diagnostic activity and good targeting of these diseases. This conclusion is also supported by other epidemiological studies, which show that non-Hodgkin lymphomas have a higher incidence in men, especially in the older age groups. A comparative analysis in women shows that they constitute the second largest subgroup ($n=56$), with a mean annual incidence of Hodgkin lymphoma of 2.2 cases ($SD=1.40$) and of non-Hodgkin lymphoma – 3.4 cases ($SD=1.17$). Although the difference is smaller compared to that in men, it reflects a similar proportion in which non-Hodgkin forms are dominant. The results of the Mann-Whitney U test ($U=75.5$; $p=0.241$) did not show a statistically significant difference, which also confirms that the possible variations cannot be interpreted as systematic or justified by significant biological factors within this sample. Of interest is the fact that in women the standard deviation is lower, which may indicate a more even distribution of cases, but also a lower total number, limiting the sensitivity of the analysis. The comparative analysis in boys under 18 years of age shows that the group of patients under 18 years of age includes only 7 boys, which greatly limits the statistical power of the analysis. However, the data show that the average value of diagnosed cases of Hodgkin lymphoma is 0.6 cases per year ($SD=0.557$), while for non-Hodgkin lymphoma a value of 0.1 was reported (SD is not applicable due to low variability). The Mann-Whitney U test ($U=1.00$; $p=0.683$) did not report a statistically significant difference between the two forms of lymphoma in this group. The small sample size, the lack of female patients in the pediatric group, and the single reported cases of non-Hodgkin lymphoma limit the possibility of valid generalizations. However, the trend for a higher incidence of Hodgkin lymphoma in boys is consistent with other pediatric oncology reports.

6.5. Etiological spectrum of acute purulent inflammation of the lymph nodes in the maxillofacial region

All patients with abscessed lymph nodes ($n=90$; 100%) who passed through the Clinic of Maxillofacial Surgery for the period 2015-2024, underwent surgical treatment in the volume of incision, lavage and drainage, during which the available pus or purulent contents were evacuated from the inflamed lymph nodes of the head and neck and the adjacent soft tissue spaces, when they were involved in the inflammatory process. In all of them, using a sterile gauze or cotton swab, material was taken and sent for microbiological analysis and preparation of an antibiogram. In 22.22% ($n=20$) no microorganisms were isolated, i.e. the cultures remained sterile. The most likely reasons for this are taking a secretion for examination containing only pus, in which

microorganisms are absent, improper storage of the sample until it is submitted to the microbiology laboratory or improper transportation of the same (Figure 11).

In 16.67% (n=15) representatives of the resident polymicrobial (containing more than one bacterial species) microflora were isolated (Figure 11).

In 2.22% (n=2) of the patients (an 80-year-old man and a 37-year-old woman) the available isolates were from yeast fungi of the *Candida albicans* species (Figure 11).

In the remaining 58.89% (n=53), pathogens from single microbial species were isolated – *Staphylococcus aureus* (n=26; 28.89%), CoNS (coagulase-negative staphylococci) (n=18; 20%), intestinal bacteria (n=6; 6.67%) and *Streptococcus viridans* (n=3; 3.33%) (Figure 11).

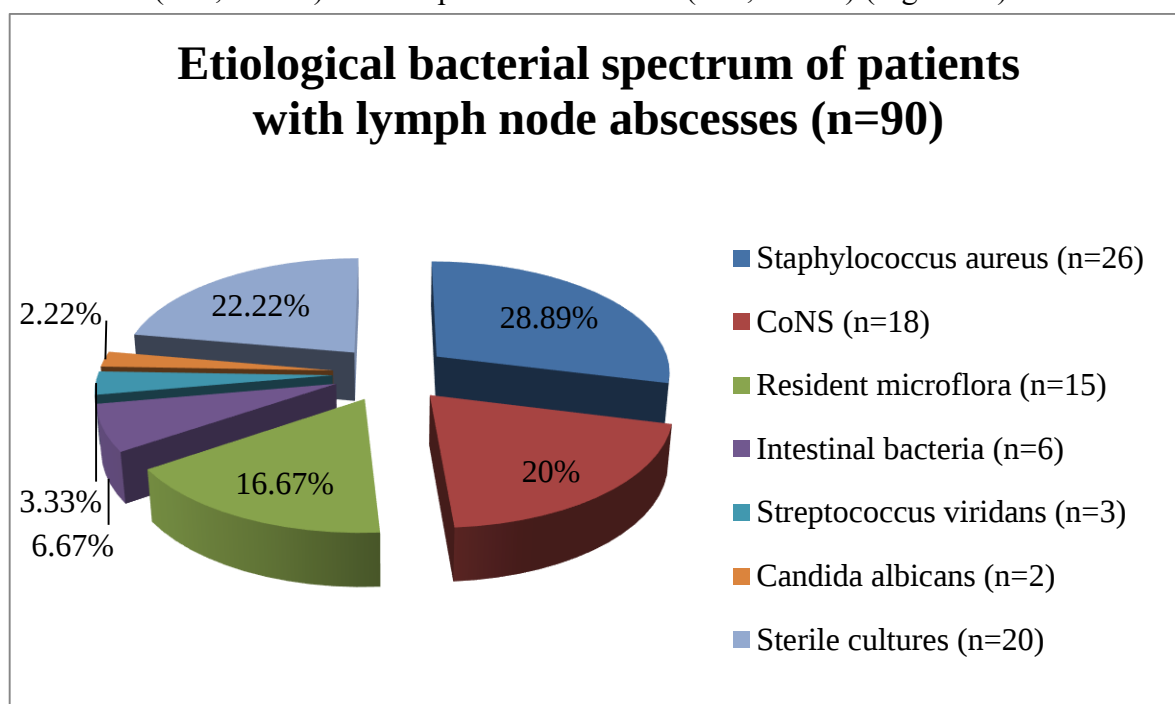


Figure 11. Etiological bacterial spectrum of patients with abscessed lymph nodes of the head and neck

6.6. Antibiotic resistance in acute suppurative inflammation of the lymph nodes in the maxillofacial region

Acute suppurative inflammations of the lymph nodes in the maxillofacial region are common clinical conditions that require timely diagnosis and adequate treatment. These inflammations are most often the result of bacterial infections, which lead to the formation of abscesses and phlegmons. The treatment of these infections often involves a combined approach with surgical intervention and antibiotic therapy. However, the increasing antibiotic resistance poses a serious challenge to clinicians and limits the effectiveness of standard antimicrobial agents.

6.6.1. Gender comparison in antibiotic resistance between study groups with different microbiological isolates

Antibiotic resistance is one of the most serious challenges facing modern medicine. It is a huge growing global problem with particular importance in hospital and surgical practice. In maxillofacial surgery, where acute purulent inflammations of the lymph nodes and deep cervical spaces are often encountered, inadequate choice of antibiotic therapy can lead to serious complications - sepsis, mediastinitis, necrotizing fasciitis and a number of others. Despite the

continuous development of new antimicrobial agents, bacterial pathogens continue to develop resistance mechanisms that significantly limit the effectiveness of treatment, especially in acute and complicated inflammatory processes in the head and neck area. The urgent need for an individualized therapeutic strategy based on local susceptibility data is crucial in the context of increasing resistance.

Effective empirical therapy requires up-to-date data on the local microbiological landscape and its susceptibility to antimicrobial agents. However, it is increasingly being reported that statistically and clinically significant differences in antibiotic susceptibility profiles may exist between the sexes. At the same time, gender differences in the clinical presentation, course and response to treatment of infectious diseases are still poorly understood, especially in the context of antibiotic resistance. Some studies suggest that women have different metabolism, immune response and hormonal status, which may affect the effectiveness of antibiotic treatment. Gender as a biological and social factor can influence antibiotic choice, pharmacokinetics and the likelihood of developing resistance. The reasons for these differences are complex and include biological factors (hormonal influence on the immune response, differences in drug metabolism), socio-behavioral factors (frequency and pattern of antibiotic use in the general population), as well as epidemiological characteristics of the predominant strains in different gender groups.

The aim of the present study is to perform a gender comparison of the frequency and nature of antibiotic resistance in patients with acute purulent-inflammatory diseases of lymph nodes in the maxillofacial region, by performing a detailed analysis of the isolated microorganisms and their sensitivity to various antibiotics.

Table 18 presents in tabular form the result of the intersex statistical analysis of the sensitivity of intestinal bacteria and staphylococci to piperacillin.

Table 18. Results of the statistical analysis for comparing the sensitivity between the two sexes to piperacillin

Piperacillin (n=26)					
Gender	Bacteria type	Susceptible (S)	Resistant (R)	Total number	Significance level (Fisher Exact, 2-sided)
Men	Intestinal bacteria	4 (100,0%)	0 (0,0%)	4	<u>0,021</u>
	Staphylococci	2 (22,2%)	7 (77,8%)	9	
	Total number	6 (46,2%)	7 (53,8%)	13	
Women	Intestinal bacteria	1 (100,0%)	0 (0,0%)	1	0,154
	Staphylococci	1 (8,3%)	11 (91,7%)	12	
	Total number	2 (15,4%)	11 (84,6%)	13	
Total	Intestinal	5 (100,0%)	0 (0,0%)	5	<u>0,001</u>

	bacteria				
	Staphylococci	3 (14,3%)	18 (85,7%)	21	
	Total number	8 (30,8%)	18 (69,2%)	26	

A total of 26 patients were tested for sensitivity/resistance to the antibiotic piperacillin to the isolated microorganisms – 5 with intestinal bacteria and 21 with staphylococci, of which 13 were men and 13 were from women.

Four cultures of intestinal bacteria were isolated from men and all of them (100%, n=4) were sensitive to piperacillin. Nine patients with staphylococci were also tested in the male population, of which 22.2% (n=2) were sensitive to the antibiotic and 77.8% (n=7) were resistant. For the entire male population (n=13), 46.2% (n=6) were sensitive and 53.8% (n=7) were resistant. The differences were statistically significant ($p=0.021$, two-sided Fisher Exact Test).

In women, intestinal bacteria were found in one case and it was sensitive (100%, n=1) to the antibiotic, and staphylococci were isolated in 12 of the patients. Only one of them, i.e. 8.3%, was sensitive to the antibiotic, 11 (91.7%) were resistant. In total for women, it can be said that in two of 13 cases (15.4%) sensitivity was established and in the remaining 11 cases (84.6%) – resistance to piperacillin, and this difference has no statistical significance, because $p=0.154$ (Fisher Exact Test, two-sided). In total for both sexes, all cases with intestinal bacteria (100%, n=5) were sensitive to the antibiotic, while in the representatives with staphylococci only 14.3% (n=3) were sensitive and 85.7% (n=18) were resistant. In general, in both sexes and for both types of isolates tested, sensitivity was established in eight of all 26 cases, i.e. in 30.8% and resistance in 18 cases i.e. in 69.2% and the difference is statistically significant ($p=0.001$, two-sided Fisher Exact Test).

Among aminoglycosides, amikacin shows stable activity against gram-negative bacteria and moderate activity against staphylococci. In enterobacteria, both sexes have 100% sensitivity. In staphylococci, men have twice as high sensitivity (50% vs. 25% in women). $p=0.061$ does not reach statistical significance, but the difference is clinically significant. Gentamicin retains high efficacy in both sexes (>85%), but women have slightly lower values (78.3% vs. 96%). This may be due to more frequent previous exposure in women or differences in pharmacokinetics.

Among the beta-lactam antibiotics penicillins (ampicillin, oxacillin and piperacillin), ampicillin has very high resistance in both sexes (>88%), without significant differences, oxacillin, however, shows a clear gender difference - in women, resistance is more than twice as high (52.2% vs. 9.5%) and piperacillin also stands out with a significant difference - $p=0.001$, with 91.7% resistance in women with staphylococcal purulent infections of the cervical lymph nodes. In combination penicillins (amoxicillin/clavulanic acid, piperacillin/tazobactam), amoxicillin/clavulanic acid has a sensitivity of 94.7% in men versus 52.9% in women. Piperacillin/tazobactam is 100% effective in men, but only 25% in women with staphylococcal isolates. This suggests a different approach to empirical therapy in women.

Looking at the cephalosporins cefazolin, cefepime, ceftriaxone, and cefuroxime axetil, they show higher resistance in women. The most drastic is for ceftazidime – 100% resistance in women versus lower values in men ($p=0.001$).

Among carbapenems, imipenem and meropenem retain high efficacy in both sexes, with minimal differences. This makes them valuable “back-up” antibiotics in severe infections, but their use must be strictly controlled to prevent the development of resistance.

The macrolides clarithromycin and erythromycin showed some of the largest gender differences. For clarithromycin, men had 75% susceptibility versus 18.2% for women, and for erythromycin, 85% versus 50%. This likely reflects higher prior use of macrolides by women in the general population.

Among lincosamides, clindamycin showed moderate gender differences, with women again having higher resistance.

Among fluoroquinolones, ciprofloxacin showed 91.7% susceptibility in men versus 52.4% in women—a clinically significant finding, although not statistically significant.

Among staphylococci, women consistently demonstrated higher resistance to a broad spectrum of antibiotics, including macrolides, penicillins, and some cephalosporins. Among enterobacteria, gender differences were minimal, with susceptibility being high for most agents. This suggests that biological and social factors have a stronger influence on gram-positive pathogens.

Hormonal differences can influence the immune response and the microbiome, and thus the selection of resistant strains. Social factors, such as the frequency of prescribing certain antibiotics, may also play a role. For example, macrolides are often prescribed to women with respiratory infections, which increases the likelihood of developing resistance. As a summary of the studied susceptibility and its comparison in both sexes, it can be said that a statistically significant gender dependence was found for piperacillin - the proportion of susceptible isolates was more than three times higher in men (6 of 13 isolates; 46.2%) compared to women (2 of 13 isolates; 15.4%). The two-sided Fisher’s Exact Test confirms the significance of this difference ($p=0.021$).

6.6.2. Age-related comparison of antibiotic resistance between study groups with different microbiological isolates

Antibiotic resistance is a global health problem that directly impacts the treatment of infectious diseases, including those in the head and neck area. The increasing resistance of bacteria limits therapeutic options and increases the risk of complications. Inflammatory processes affecting the cervical lymph nodes are often secondary to a primary infectious focus in the maxillofacial area, and their treatment requires precise selection of antibacterial therapy.

Age is a factor that can influence both the frequency of bacterial isolates and their antibiotic susceptibility. The pediatric population often demonstrates different patterns of bacterial resistance compared to adults, due to peculiarities in the immune system, previous exposure to antibiotics, frequency of hospitalizations and a different spectrum of etiological agents. In turn, in elderly patients, the cumulative effect of repeated antibiotic therapy and contact with different health care facilities can lead to a wider spread of multiresistant strains.

The present analysis is based on a systematic statistical review of susceptibility and resistance to a wide range of antibiotics, with patients categorized into two age groups – under 18 years and over 18 years. Two main types of isolates are considered – enteric bacteria and staphylococci, because statistically significant differences between the two analyzed groups were not found for the

remaining pathogens. The study evaluates the extent of antibiotic resistance, the statistical significance of the differences and the clinical consequences of the observed trends.

The analysis shows that aminoglycosides retain high activity against enteric bacteria, with 100% sensitivity in most cases regardless of age. However, the effectiveness is lower for staphylococci, especially for amikacin, where high levels of resistance are observed in the pediatric group. Gentamicin demonstrates relatively good activity against both types of bacteria and in both age groups, with minor differences.

Beta-lactam antibiotics (amoxicillin/clavulanic acid, ampicillin, cefazolin, cefepime, cefoperazone, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, cefuroxime axetil, cephalothin, oxacillin, penicillin, piperacillin) demonstrate highly heterogeneous results. Ampicillin and penicillin are practically ineffective, with extremely high levels of resistance in both age groups. Newer-generation cephalosporins (cefepime, cefotaxime and ceftriaxone) retain high efficacy, especially against enteric bacteria. Piperacillin shows a clear dependence on the type of bacteria - complete efficacy against enteric bacteria and almost complete ineffectiveness against staphylococci. Oxacillin is moderately effective against staphylococci, but without any difference between ages.

Macrolide resistance was moderate to high in staphylococci, with no significant differences between age groups. Clarithromycin and erythromycin showed similar resistance profiles, suggesting a likely cross-resistance mechanism.

The lincosamide representative clindamycin retained high efficacy against staphylococci, with over 79% susceptibility in both age groups. The lack of significant differences suggests that age is not a factor in its activity.

Fluoroquinolones (ciprofloxacin, levofloxacin and moxifloxacin) demonstrated excellent efficacy against enteric bacteria and more moderate against staphylococci. Levofloxacin and moxifloxacin showed 100% efficacy, while ciprofloxacin showed a decrease in susceptibility in adult staphylococcal isolates.

Among carbapenems (imipenem, meropenem), both antibiotics retained excellent efficacy against enteric bacteria. A statistically significant difference was reported for imipenem, with higher efficacy against enteric bacteria compared to staphylococci. Meropenem showed complete efficacy against both types of bacteria.

The oxazolidinone linezolid has demonstrated complete efficacy against staphylococci in all age groups, positioning it as a key agent in severe resistant infections.

Analysis of antibiotic resistance in patients with inflammatory diseases of the lymph nodes in the head and neck region showed that the age of the patients is not an independent predictor of the presence or absence of antibiotic sensitivity. In the majority of the antibiotics studied, no statistically significant differences were found between the two main age groups – under 18 years and over 18 years. Differences in sensitivity are determined primarily by the type of isolated microorganism (intestinal bacteria or staphylococci), and not by the age of the patient.

Intestinal bacteria demonstrated universally high sensitivity to the majority of the applied antibiotics and antibiotic combinations (amikacin, cefazolin, cefepime, cefoperazone, cefotaxime, ceftazidime, ceftriaxone, cefuroxime axetil, ciprofloxacin, gentamicin, levofloxacin, meropenem, imipenem, piperacillin, piperacillin/tazobactam, teicoplanin, tetracycline, tigecycline, tobramycin, trimethoprim-sulfamethoxazole and vancomycin, doxycycline) and high resistance to ampicillin. In none of the age subgroups was clinically significant resistance detected. This confirms the effectiveness of these antibacterial drugs in acute inflammation of the lymph nodes of the head and neck, regardless of age.

Staphylococci were 100% susceptible to levofloxacin, linezolid, meropenem, moxifloxacin, rifampin, teicoplanin, tigecycline, trimethoprim-sulfamethoxazole, vancomycin, doxycycline, mupirocin, fusidic acid and cefuroxime.

Staphylococci showed significantly higher levels of resistance to all antibiotics compared with intestinal isolates, but these data were not statistically significant ($p > 0.05$).

Statistically significant differences between age groups were found for a limited number of antibiotics. Ceftazidime showed a clear resistance in staphylococci, especially in the adult group ($p = 0.024$) and in the combined adult and pediatric sample ($p = 0.001$). Similarly, for the antibiotic imipenem, a statistically significant relationship between isolate type and susceptibility was reported ($p = 0.049$), with a trend towards higher susceptibility in enteric bacteria compared to staphylococci, but age did not have a significant effect on its own. Piperacillin also demonstrated statistically significant differences ($p = 0.009$ for children, $p = 0.011$ for adults and $p = 0.000$ for the entire sample), reflecting complete susceptibility in enteric isolates and high resistance in streptococcal strains.

For other antibiotics, including amoxicillin/clavulanic acid, ceftriaxone, cefepime, cefuroxime axetil, ciprofloxacin and others, differences in sensitivity were found between intestinal bacteria and staphylococci, but without reaching statistical significance between age groups ($p > 0.05$). In conclusion, the data from the present study indicate that the age factor does not play a significant role in determining the antibiotic sensitivity of the isolated microorganisms. The type of pathogenic agent remains the main factor determining the choice of antibiotic therapy. This emphasizes the need for an individualized approach to antimicrobial treatment, based on microbiological results, and not only on clinical characteristics such as age. Intestinal bacteria in general remain highly sensitive to a wide range of drugs, while staphylococci often exhibit partial or high resistance and require more precise selection of treatment.

7. CONCLUSIONS

1. The number of hospitalized patients with head and neck lymph node diseases varies cyclically between 2015 and 2024 – with an increase until 2019, a decline during the Covid-19 pandemic (2020-2021), and a recovery thereafter.
2. There is no long-term and clearly defined trend in the number of hospitalized patients with head and neck lymph node diseases, but rather short-term fluctuations reflecting external factors (such as the Covid-19 pandemic) and individual variability.
3. Hospitalized patients with head and neck lymph node diseases treated surgically are almost four times more than those treated conservatively.
4. The most common head and neck lymph node diseases among the entire studied population of hospitalized patients are oncological, and the rarest are leishmaniasis and tuberculosis.
5. In hospitalized men with cervical lymph node diseases, malignant diseases – lymphomas and metastases – dominate, and in hospitalized women – lymphoproliferative and acute nonspecific lymphadenitis.
6. In hospitalized men, there are higher average values, but fewer different diseases of the lymph nodes of the head and neck, while women show a greater variety of diagnoses, but with a more even distribution between them.
7. Isolated Gram-positive microorganisms in hospitalized patients with acute lymphadenitis of the head and neck and with abscesses and phlegmons arising from them are over ten times more than Gram-negative ones.
8. Age alone is not a significant predictor of antibiotic resistance in most cases of acute purulent inflammation of the lymph nodes of the head and neck in hospitalized patients. The differences in sensitivity are mainly due to the type of isolated microorganism, and not to the age of the patients.
9. In even small representative samples (nine cases for levofloxacin and seven for meropenem), all isolates studied in purulent lymphadenitis of the head and neck showed 100% sensitivity to levofloxacin and meropenem - antibiotics with universal sensitivity.
10. Intestinal bacteria isolated in acute purulent infections of the lymph nodes of the head and neck in hospitalized patients remain highly sensitive to a wide range of antibiotics, while in patients with isolated staphylococci, the latter often exhibit partial or high resistance and require a more precise choice of therapy.
11. There is no antibiotic to which both staphylococci and intestinal bacteria are absolutely resistant.
12. A statistically significant gender dependence was found for piperacillin - the proportion of sensitive isolates is more than three times higher in men than in women with acute purulent lymphadenitis.
13. Males with acute purulent lymphadenitis have higher sensitivity to most antibiotics, while females show higher levels of resistance.

8. CONTRIBUTIONS

1. A complete cytological, histological and anatomical-topographic analysis of the regional lymph nodes in the head and neck region was performed, with an emphasis on their importance in maxillofacial surgery.
2. A detailed analysis of the age and gender demographic distribution of patients with lymph node diseases in the maxillofacial region was performed.
3. For the first time in Bulgaria, a large and detailed comparison between surgical and conservative treatment in patients with lymphadenopathy in the maxillofacial region was made, which reflects the significant predominance of surgical interventions.
4. The etiological bacterial spectrum of acute purulent lymphadenitis of the head and neck and the abscesses and phlegmons arising from them was described.
5. An assessment of the antibiotic resistance of the isolated strains in purulent lymphadenitis of the head and neck was made, which allows for a more precise choice of antibiotic treatment.
6. Recommendations for clinical practice in the treatment of patients with metastatic involvement of the lymph nodes in the neck have been developed.
7. High antibiotic sensitivity of intestinal bacteria and contrasting partial to high resistance of staphylococci to a number of antibacterial agents in purulent infections of the lymph nodes in the maxillofacial region have been proven, which may assist in the selection of their empirical antibacterial treatment.
8. Gender-specific antibiotic sensitivity has been proven in acute purulent lymphadenitis of the head and neck, against which the antibiotic piperacillin is three times more effective in men than in women.
9. Recommendations for optimizing antibiotic therapy in acute purulent lymphadenitis in the maxillofacial region have been formulated, based on established patterns in sex-specific resistance - men have higher sensitivity to most antibiotics, while women require more precise selection.