THE IMPACT OF DRUGS ON THE JAWS

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The contemporary epidemiological landscape of oral and maxillofacial surgery is characterized by a rapid escalation in the incidence of toxic jaw osteonecrosis, predominantly driven by the chronic abuse of illicitly manufactured synthetic psychostimulants. This aggressive pathology is accompanied by profound impairments in regional blood circulation, critical alterations in bone mineral composition, and severe secondary immunodeficiency, which collectively undermine the efficacy of conventional surgical modalities. Developing and implementing comprehensive, pathogenetically grounded methods of rehabilitation for this group of patients represents a crucial challenge in modern regenerative medicine.

The aim of the study – *to evaluate the clinical and epidemiological features, investigate alterations in bone mineral composition using energy-dispersive X-ray spectroscopy (EDS), and assess the clinical efficacy of a newly developed multimodal treatment protocol for substance-induced toxic jaw osteonecrosis in the Republic of Moldova.*

Material and Methods. *Written informed consent was obtained from all patients for participation and data processing in strict accordance with the Declaration of Helsinki. A retrospective analysis of 203 medical records of patients treated at the Department of Oral and Maxillofacial Surgery of the IMSP IMU between 2005 and 2024 was performed. Inclusion criteria: age ≥18 years; confirmed clinical and radiological diagnosis of jaw osteonecrosis; documented history of chronic Perventin or α-PVP abuse; availability of comprehensive archival records (CT, orthopantomograms, laboratory profiles). Exclusion criteria: osteonecrosis of non-narcotic etiology (MRONJ induced by bisphosphonates or anti-angiogenic therapies in non-addicted individuals); a history of radiation therapy to the head and neck region; decompensated systemic comorbidities; incomplete medical records. A comprehensive set of research methods was employed: clinical and anamnestic analysis (evaluation of medical histories, gender, age, and social parameters), laboratory serological screening (HIV and Hepatitis C testing), microbiological methods (pathogen isolation via wound cultures and antimicrobial susceptibility evaluation using the disk-diffusion method), radiological imaging (cone-beam computed tomography and orthopantomography to evaluate bone destruction limits), and physicochemical microanalysis of the bone tissue via scanning electron microscopy (SEM) and energy-dispersive X-ray spectroscopy (EDS) on an INCA system. Statistical processing of the data was carried out using SPSS Statistics and Statistica software. Pearson's chi-squared test ($\chi 2$) and Fisher's exact test were used to compare categorical variables, while Student's t-test and the Mann-Whitney U-test were utilized for continuous variables. The threshold for statistical significance was set at $p < 0.05$.*

Results. *It was established that in 2005, the clinical field was heavily dominated by traditional pathologies, where odontogenic (47.2%) and post-traumatic (41.5%) mandibular osteomyelitis prevailed, while the share of toxic forms was negligible (<3%). However, a dramatic surge in incidence was observed by 2013, with a peak referral rate of 15.30%. A gradual decline in hospitalizations after 2017 (dropping to 3% by 2024) is directly associated with the emergence of the highly aggressive narcotic α-PVP, which induces rapid, irreversible destructive changes in vital organs, tragically causing premature mortality before advanced jaw complications can fully manifest. The primary etiological factor among the 203 patients was Perventin abuse (78.3%), followed by α-PVP (15.8%), non-narcotic medication-related bisphosphonate osteonecrosis (3.9%), and post-radiation osteoradionecrosis (2.0%). Combined bimaxillary lesions simultaneously affecting both jaws constituted the largest share (41.9%), while isolated maxillary and mandibular necrosis accounted for 32.0% and 26.1%, respectively. Serological screening revealed a high rate of blood-borne co-infections: Hepatitis C in 81.3% and HIV in 15.8% of patients. EDS microanalysis of the bone matrix in Perventin abusers demonstrated a critical accumulation of phosphorus (weight percentage of 6.42%-12.63% vs. 0.35%-0.81% in controls) and calcium (10.64%-19.12% vs. 0.32%-1.27% in controls), confirming pathogenic toxic complex retention. Staphylococcus epidermidis was the predominant isolated pathogen, showing the highest susceptibility to gentamicin and ofloxacin. The application of the developed multimodal protocol (radical necrectomy, periosteal stem cell implantation, and early removable prosthodontic functional loading)*

Keywords: *toxic osteomyelitis of the jaws, osteonecrosis, Perventin, α-PVP, energy-dispersive X-ray spectroscopy, stem cells, regenerative medicine, prosthodontic rehabilitation.*

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achieved complete resolution of extensive maxillary defects within 2 to 3 years, strictly contingent upon substance cessation. In the group under study, the complete clinical recovery rate reached 24.1%, and mortality dropped significantly to 6.4%, whereas no cases of complete recovery were noted in the conventional treatment group, and mortality reached 19.4% (p<0.001).

Conclusions. *It has been proven that the widespread abuse of clandestinely synthesized psychostimulants (Perventin and α-PVP) has fundamentally altered the structure of maxillofacial bone pathologies in the Republic of Moldova, with toxic osteonecrosis accounting for 1.6% of all hospitalized patients treated at the specialized department during 2005-2024. Using EDS elemental microanalysis, the underlying pathogenic mechanism of necrosis was verified, manifesting as a critical, osteotoxic intraosseous accumulation of exogenous phosphorus (6.42%-12.63%) and calcium (10.64%-19.12%) within the bone matrix. The implementation of staged surgical management combined with periosteal cell therapy and early prosthetic functional stimulation significantly accelerates bone regeneration within a tight 2-to-3-year window and dramatically reduces patient mortality from 19.4% to 6.4% (p < 0.001).*

ВПЛИВ НАРКОТИЧНИХ РЕЧОВИН НА ЩЕЛЕПИ

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Key words: *токсичний остеомієліт щелеп, остеонекроз, Первентин, α-PVP, енергодисперсійна рентгенівська спектроскопія, стовбурові клітини, регенеративна медицина, ортопедична реабілітація.*

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Сучасний епідеміологічний ландшафт щелепно-лицевої хірургії характеризується стрімким зростанням частоти випадків токсичного остеонекрозу щелеп, зумовленого хронічним зловживанням нелегальними синтетичними психостимуляторами. Ця агресивна патолологія супроводжується глибокими порушеннями регіонарного кровообігу, мінерального складу кісткової тканини та вторинним імунодефіцитом, що зумовлює низьку ефективність традиційних хірургічних підходів. Розробка та впровадження комплексних, патогенетично обґрунтованих методів реабілітації таких пацієнтів є критично важливою проблемою сучасної регенеративної медицини.

Мета роботи – *вивчити клініко-епідеміологічні особливості, зміни мінерального складу кісткової тканини за даними енергодисперсійної рентгенівської спектроскопії (EDS) та оцінити ефективність розробленого мультимодального методу лікування пацієнтів із токсичним остеонекрозом щелеп на тлі наркотичної залежності в Республіці Молдова.*

Матеріал і методи. *Усі пацієнти підписали інформовану згоду на участь у дослідженні та обробку персональних даних відповідно до Гельсінської декларації. Проведено ретроспективний аналіз 203 медичних карток пацієнтів, які перебували на лікуванні у відділенні щелепно-лицевої хірургії IMSP IMU у 2005-2024 рр. Критерії включення у дослідження: вік ≥18 років; підтверджений клініко-рентгенологічний діагноз остеонекрозу щелеп; задокументований анамнез хронічного вживання «Первентину» або α-PVP; наявність повних архівних даних (КТ, ОПТГ, лабораторні профілі). Критерії виключення: остеонекрози ненаркотичної етіології (MRONJ, викликані бісфосфонатами або антиангіогенними препаратами у хворих без наркотичної залежності); променева терапія голови та шиї в анамнезі; декомпенсована системна патологія; неповні медичні карти.*

У роботі використано комплекс методів: клініко-анамнестичний (збір медичної історії, оцінка гендерно-вікових та соціальних характеристик), лабораторний серологічний (скринінг на ВІЛ та гепатит С), мікробіологічний (ідентифікація патогенів методом посіву вогнища ураження та оцінка антибіотикочутливості за допомогою диско-дифузійного методу), рентгенологічний (конусно-променева комп'ютерна томографія та ортопантомографія для оцінки поширеності деструкції), а також фізико-хімічний мікроаналіз ураженої кістки методом скануючої електронної мікроскопії (SEM) та енергодисперсійної рентгенівської спектроскопії (EDS) на системі INCA. Статистичне опрацювання результатів здійснювали за допомогою пакета програм SPSS Statistics та Statistica. Для порівняння якісних показників використовували критерій хі-квадрат (χ2) Пірсона, Fisher's exact test, а для кількісних – t-критерій Стьюдента та U-критерій Манна-Уітні. Рівень статистичної значущості було прийнято за p < 0.05.

Результати. *Встановлено, що у 2005 році в структурі остеомієлітів переважали*

одонтогенний (47.2%) та посттравматичний (41.5%) остеомієліти нижньої щелепи, тоді як частка токсичних форм становила <3%. Проте до 2013 року зафіксовано стрімке зростання захворюваності з піком звернень на рівні 15.30%. Певний спад частоти госпіталізацій після 2017 року (до 3% у 2024 р.) пов'язаний із появою на ринку агресивного наркотику α-PVP, що викликає швидкі незворотні ураження життєво важливих органів і високу летальність пацієнтів до моменту розвитку розлогих некрозів. Основним етіологічним фактором некрозу у 203 пацієнтів став «Первентин» (78.3%), рідше – α -PVP (15.8%), бісфосфонати у хворих без наркоманії (3.9%) та променева терапія (2%). За анатомічною локалізацією домінували поєднані ураження обох щелеп (41.9%), ізольований некроз верхньої щелепи становив 32.0%, нижньої – 26.1%. Серологічно виявлено високу частоту супутніх інфекцій: гепатит С – у 81.3% пацієнтів, ВІЛ – у 15.8%. За даними EDS-аналізу кісткової тканини, у пацієнтів після вживання «Первентину» зафіксовано критичне накопичення фосфору (масова частка 6.42%-12.63% проти 0.35%-0.81% у контролі) та кальцію (10.64%-19.12% проти 0.32%-1.27% у контролі), що свідчить про затримку токсичних комплексів. Основним патогеном у вогнищі був Staphylococcus epidermidis, найбільш чутливий до гентаміцину та офлоксацину. Застосування розробленого мультимодального підходу (некректомія, періастальна імплантація стовбурових клітин, рання ортопедична реабілітація знімними протезами) дозволило досягти повного закриття кісткових дефектів верхньої щелепи за 2-3 роки (за умови відмови від наркотиків). У групі комплексного лікування рівень повного одужання (практично здорові) становив 24.1%, а летальність знизилася до 6.4%, тоді як у контрольній групі (традиційне лікування) одужання не зафіксовано, а летальність досягла 19.4% (p < 0.001).

Висновки. *Доведено, що поширення кустарних психостимуляторів («Первентину» та α-PVP) змінило структуру патології щелепно-лицевої ділянки в Республіці Молдова, вивівши токсичний остеонекроз на рівень 1.6% від усіх госпіталізованих хворих за 2005-2024 рр. Методом EDS-рентгеноспектрального мікроаналізу підтверджено патогенетичний механізм некрозу, який полягає в критичному остеотоксичному накопиченні екзогенного фосфору (6.42%-12.63%) та кальцію (10.64%-19.12%) у матриксі кістки. Впровадження етапного хірургічного лікування у поєднанні з періастальною клітинною терапією та раннім протезуванням (ортопедичним навантаженням на окістя) достовірно прискорює регенерацію кістки за 2-3 роки та знижує летальність пацієнтів з 19.4% до 6.4% (p < 0.001).*

Introduction

According to a study conducted among the 15-24 age group, 0.1% of respondents reported having used heroin. The drugs listed in the tables and lists of narcotic and psychotropic substances and controlled precursors in the Republic of Moldova include heroin, opium (raw opium), Cocaine, LSD, LSD stamps, dried poppy straw, green poppy straw, poppy extract, hemp plants, Perventin and substances clandestinely synthesized based on preparations from the amphetamine series and α-PVP (α-pyrrolidinovalerophenone) [1-4].

It is important to implement programs for children's personal development in schools, which guide them toward a healthy lifestyle in areas such as physical and emotional health, healthy eating, and combating harmful habits (drugs, alcohol, smoking, and various other influences). These programs include content units such as "Say NO to drugs and other dangerous substances," the dangers of drug use, high-risk situations, recruitment of users, the impact of drug use on physical, mental, and emotional health during adolescence, drug addiction, prevention of drug use, and social consequences. In primary and general secondary schools, parent associations play an important role in raising public awareness about drug use prevention activities, along with alcohol and tobacco use, both in organizing thematic meetings with parents and in activities with students [1, 5-7].

Over the past 20 years, there has been an increase in cases of toxic osteomyelitis of the jaws in the Republic of Moldova, which occurs as a result of drug use. The urgency of this issue lies in identifying the causes of this condition, developing diagnostic methods, and, most importantly, establishing effective treatment methods. Recently, due to increase in the number of synthetic drug users in the Republic of Moldova, there has been a rise in atypical osteomyelitis of the facial skeleton. This disease entity has been defined as "toxic osteomyelitis." Drug addiction is a social problem of recent years that has taken on pandemic proportions. Recently, there have been reports in the Republic of Moldova of a trend toward the spread in various regions of the drug "Perventin," which is clandestinely synthesized from compounds in the amphetamine series and α-PVP (α-pyrrolidinovalerophenone) [8,9].

Toxic osteomyelitis (necrosis) of the jaw, sometimes called osteonecrosis, is a form of odontogenic osteomyelitis that occurs predominantly following tooth extraction, characterized by the absence of clear boundaries and a lack of tendency toward long-term healing [10-17]. It occurs in the context of the use of drugs with high phosphorus and ephedrine content, bisphosphonate therapy, and radiation therapy. In the Oral and Maxillofacial (OMF) Surgery Department of the IMSP IMU, patients with maxillary necrosis were treated; this condition is clinically distinct from other types of

osteomyelitis (odontogenic or post-traumatic).

The aim of the study – to evaluate the clinical and epidemiological features, investigate alterations in bone mineral composition using energy-dispersive X-ray spectroscopy (EDS), and assess the clinical efficacy of a newly developed multimodal treatment protocol for substance-induced toxic jaw osteonecrosis in the Republic of Moldova.

Material and Methods

Study Design and Patient Population. To conduct this descriptive, observational, and retrospective study, we reviewed the contemporary medical literature, relevant scientific articles, and clinical and laboratory patient data. The primary data were obtained from the archives of the Institute of Emergency Medicine (IMSP IMU, Chisinau, Republic of Moldova) for the period from 2005 to 2024, specifically focusing on the records from the Department of Oral and Maxillofacial Surgery.

The population under study comprised patients diagnosed with drug-induced jaw necrosis. The medical histories revealed a characteristic epidemiological pattern within the region: drug abuse (initially involving substances such as heroin and cocaine) frequently begins during adolescence or young adulthood. Due to subsequent financial constraints, addicted users commonly switch to cheaper, illicitly synthesized synthetic narcotics. In the Republic of Moldova, the most prevalent of these substances is Perventin, which is clandestinely manufactured from amphetamine-series precursors and α-PVP α -pyrrolidinovalerophenone). The chronic use of these synthetic stimulants acts as a primary etiological factor for severe post-extraction and spontaneous maxillofacial complications, including progressive bone necrosis of the maxilla and mandible, perimaxillary soft tissue infections, chronic sinusitis, lymphadenitis of the maxillofacial region, and life-threatening systemic conditions such as meningitis, mediastinitis, cavernous sinus thrombosis, and septicemia.

Laboratory and Imaging Examinations. All patients included in the study underwent a comprehensive laboratory and instrumental evaluation to assess their systemic status, bone tissue characteristics, and the severity of complications.

The laboratory protocol included: hematological and Urinalysis Profiles: general blood analysis (complete blood count) and general urine analysis. Biochemical Profile: comprehensive biochemical blood analysis. Coagulation Assays: evaluation of coagulogram indices, including prothrombin index, fibrinogen content, activated partial thromboplastin time (APTT), thrombin time, and the ethanol gelation test. Microbiological Analysis: culturing of wound/exudate samples (exudate seeding) followed by the assessment of microbial sensitivity to antibacterial agents (antibiogram). Serological Screening: determination of blood group and Rh-factor, alongside screening for viral and infectious markers, specifically anti-HBV (Hepatitis B), anti-HCV (Hepatitis C), and HIV/AIDS antigens. Bone Tissue Analysis: radiospectral analysis of the affected jaw bone tissue using radiographic spectroscopy to evaluate structural and mineral changes.

The neuroradiological and dental imaging baseline was established through the detailed review and analysis of a total of 256 orthopantomograms (OPTGs) and 160 computed tomography (CT) scans.

Inclusion Criteria: age ≥ 18 years at the time of hospitalization (or documented adolescent age if minors are analyzed separately). Diagnosis of jaw necrosis (maxillary and/or mandibular bone necrosis) confirmed clinically and radiologically. Documented anamnesis of chronic use of synthetic narcotics, specifically Perventin, amphetamine-series compounds, or α-PVP (α-pyrrolidinovalerophenone). Complete archival medical records from the IMSP IMU (2005-2024), including comprehensive data from the Department of Oral and Maxillofacial Surgery. Availability of baseline imaging data, including orthopantomograms (OPTG) and/or computed tomography (CT) scans. Availability of standard laboratory profiles (complete blood count, biochemical profile, and coagulogram).

Exclusion Criteria: jaw necrosis of non-narcotic etiology, including classic medication-related osteonecrosis of the jaw (MRONJ) induced by bisphosphonates or anti-angiogenic drugs. History of radiation therapy to the head and neck region (radiation-induced osteoradionecrosis). Idiopathic, purely bacterial (non-drug-induced) chronic osteomyelitis of the jaws. Severe, decompensated systemic comorbidities (e.g., end-stage renal failure, uncompensated diabetes mellitus) that independently cause bone tissue degradation, unrelated to substance abuse. Incomplete or severely fragmented medical records (e.g., missing critical laboratory data, lack of imaging scans, or untraceable treatment outcomes).

Statistical Analysis. The obtained quantitative and qualitative data were processed using variational statistics in accordance with standard biological and medical research methods. Statistical correlations between qualitative parameters were evaluated using contingency tables.

The hypothesis of independence between rows and columns was tested using the chi-squared ($\chi 2$) criterion. The information content for each component of the $\chi 2$ vector was further assessed by calculating the Fisher statistical criterion. Continuous variables and intergroup differences were analyzed using the Fisher-Student (F and t) criteria. Statistical significance was defined at $p < 0.05$.

Written informed consent was obtained from all patients for participation and data processing in strict accordance with the Declaration of Helsinki.

Results and discussion

According to the obtained data, the systemic effects of the investigated illicit drugs on the human body include profound inhibition of tissue metabolism, suppression of vascular endothelial growth, tissue sclerosis, disruption of regional blood circulation, alterations in hemostasis, and the rapid development of secondary immunodeficiency. The significantly increased incidence of osteomyelitis in the jaws compared to other skeletal bones is explained by the higher likelihood of odontogenic infection during tooth extraction, frequent mechanical microtrauma, and the constant presence of pathological biofilm on the oral mucosa and within periodontal pockets. The radiological hallmark of this specific pathology is its continuous, aggressive spread, characterized by the absence of classic

sequestrum formation or clear margins over a long period of time, alongside the progressive involvement of adjacent teeth and surrounding anatomical structures in the destructive process.

Osteonecrosis of the jaw is a severe condition that occurs predominantly in patients history-positive for the chronic use of "Perventin" – a synthetic drug clandestinely manufactured from amphetamine derivatives and α-PVP (α-pyrrolidinovalerophenone) – as well as in patients receiving long-term bisphosphonate therapy [18-20].

A retrospective analysis of the medical records from the IMSP IMU archives for the years 2005–2024 allowed for the identification of specific epidemiological and clinical data within the Department of Oral and Maxillofacial Surgery. The frequency and chronological distribution of jaw necrosis cases recorded during this 19-year period are presented in Figure 1.

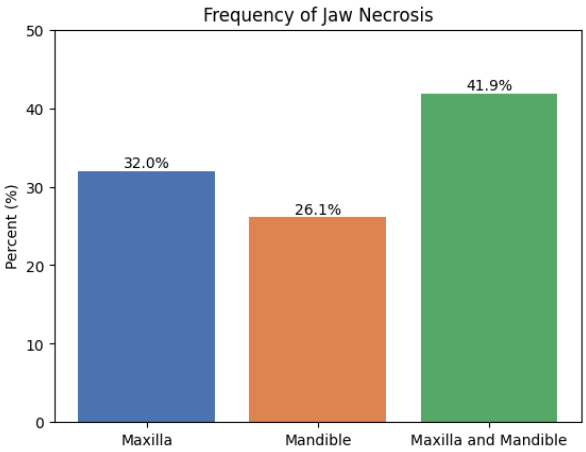

Fig 1. The frequency of jaw necrosis

As demonstrated in Figure 1, the anatomical localization of drug-induced toxic osteomyelitis among the studied cohort reveals a high prevalence of extensive bone destruction. Combined lesions simultaneously affecting both the maxilla and the mandible constitute the largest proportion of cases, accounting for 41.9%. Isolated necrosis of the maxilla is observed in 32.0% of patients, while isolated mandibular involvement is the least frequent, noted in 26.1% of cases. This high rate of combined bimaxillary necrosis (41.9%) underscores the aggressive, generalized nature of synthetic drug-induced osteonecrosis, which significantly complicates subsequent surgical debridement and patient rehabilitation.

According to the statistical data, out of 203 patients studied, the maxilla was affected in 32%, the mandible in 26.1% and both the maxilla and mandible in 41.9%.

Figure 2 illustrates the dynamic changes in the structured distribution of various osteomyelitis etiologies between 2005 and 2013. In 2005, the clinical landscape was heavily dominated by traditional pathologies, where odontogenic osteomyelitis of the mandible (OOMd) accounted for 47.2% and post-traumatic mandibular osteomyelitis (OPMd) stood at 41.5%, whereas toxic variants (OTMd and OTMx) represented a negligible combined share of less than 3%. However, the chronological analysis over the subsequent years reveals a dramatic epidemiological shift characterized by a progressive expansion of toxic osteomyelitis cases. By 2013, the proportions of drug-induced toxic osteomyelitis of the mandible and maxilla expanded significantly, substantially displacing the shares of conventional odontogenic and post-traumatic infections. This striking trend directly reflects the escalating impact of synthetic drug abuse on the changing structure of maxillofacial bone pathologies within the region.

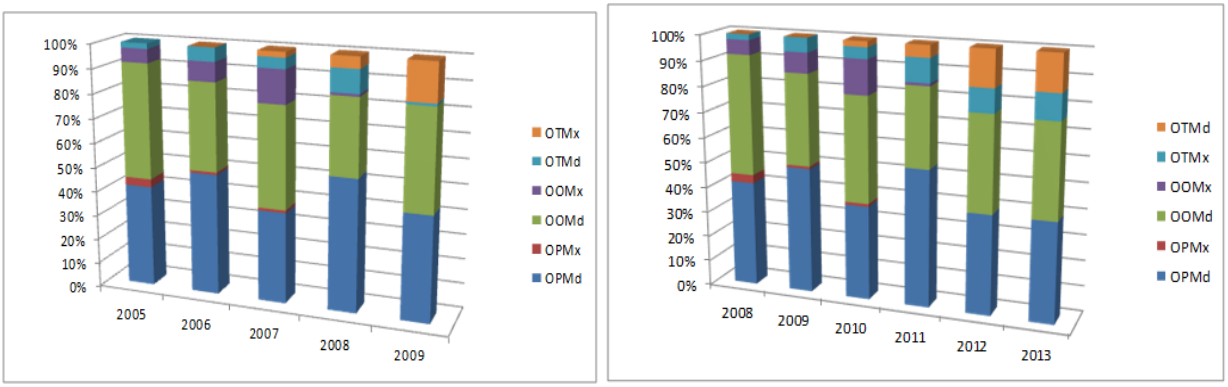

Fig. 2. Frequency of osteomyelitis-related necrosis from 2005 to 2013

Figure 3 illustrates the long-term dynamics of patient referrals for jaw osteomyelitis between 2006 and 2024. Starting from 2006, the proportion of patients presenting with maxillary necrosis began to rise progressively, reaching its absolute peak in 2013 at 15.30%. Following another substantial spike in 2016 (14.30%), the number of cases began to drop sharply, declining to 5.40% by 2018, and eventually falling to a minimum of 3.00% by 2024. Clinical and epidemiological analysis suggests that this downward trend after 2017 is directly associated with the emergence of α-PVP (α-pyrrolidinovalerophenone) on the illicit drug market in the Republic of Moldova. This

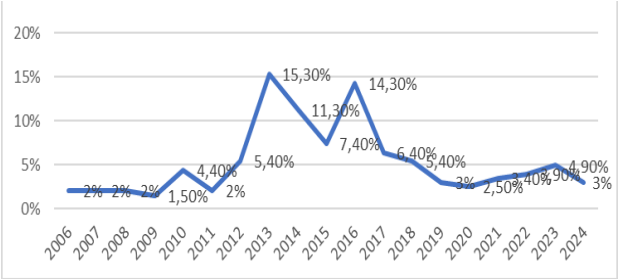

Fig. 3. Dynamics of patients referrals with jaw osteomyelitis between 2006 and 2024

significantly more aggressive synthetic narcotic substance induces not only severe maxillofacial osteonecrosis but also triggers rapid, irreversible destructive changes in vital organs, tragically reducing overall patient survival rates before advanced jaw complications can fully manifest.

Figure 4 presents the distribution of maxillary osteomyelitis cases based on their primary etiology from 2006 to 2024. A detailed medical history of the 203 evaluated patients revealed that illicit substance abuse was the overwhelming cause of jaw necrosis, with Perventin identified in 159 cases (78.3%) and α-PVP confirmed in

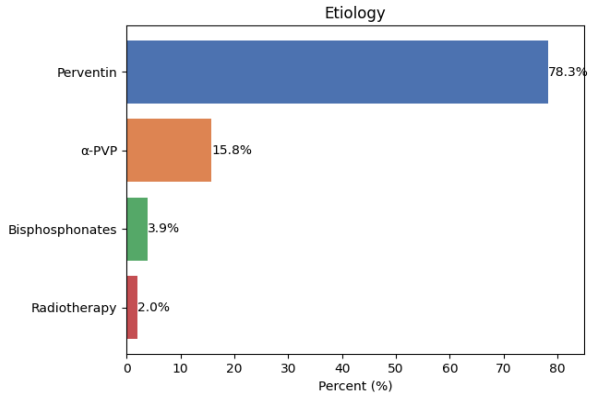

Fig. 4. Frequency of maxillary osteomyelitis by etiology for the years 2006–2024, based on patient visits to the IMSP IMU in Chișinău

32 patients (15.8%). In contrast, non-narcotic factors represented a minor fraction of the cohort, where medication-related osteonecrosis induced by bisphosphonates was detected in 8 patients (3.9%), and radiation therapy was the primary cause in 4 patients (2.0%) ($p < 0.05$). This pronounced etiological disproportion clearly demonstrates that illicit synthetic psychostimulants, particularly clandestine amphetamine derivatives, constitute the dominant driving factor behind the surge of maxillofacial necrosis in the region. Furthermore, while the overall study confirms that the absolute peak of toxic osteomyelitis admissions occurred between 2011 and 2013, the high cumulative share of Perventin (78.3%) highlights its long-term, devastating role as a primary chemical osteotoxic agent within the analyzed population.

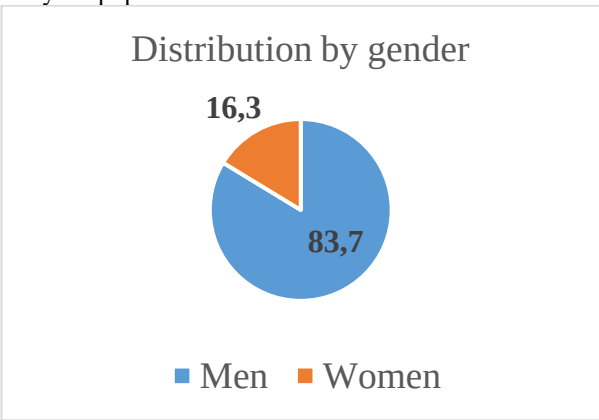

Fig. 5. Demographic profile of the analyzed cohort based on gender distribution.

After evaluating the general data of the 203 patients diagnosed with toxic osteomyelitis of the maxilla and other facial bones, it was found that men constituted the overwhelming majority, comprising 170 individuals (83.7%), whereas women accounted for only 33 cases (16.3%). Within the control group, there were 55 men (88.7%) and 7 women (11.3%), while the study group consisted of 115 men (81.6%) and 26 women (18.4%). This stark gender imbalance may be attributed to distinct socio-psychological and behavioral triggers associated with substance abuse pathways. A detailed collection of medical histories revealed that male patients frequently initiated Perventin use as a functional stimulant to maintain alertness during occupational night shifts or as a maladaptive response to socio-economic stressors such as unemployment. Conversely, female patients more commonly reported initiating narcotic consumption due to interpersonal dynamics, often at the insistence of an intimate partner, highlighting the necessity for gender-specific approaches in both prevention and psychosocial rehabilitation.

Furthermore, the serological screening of the study group revealed a critically high prevalence of blood-borne co-infections, which severely compromised the patients' systemic immune response. It should be noted that 15.8% of the evaluated patients were history-positive for HIV/AIDS, and an overwhelming 81.3% tested positive for Hepatitis C (anti-HCV antigens). This alarming rate of viral co-morbidities directly correlates with the parenteral route of illicit drug administration and fully explains the rapid progression of aggressive bone tissue necrosis and perimaxillary phlegmons under conditions of profound, drug-induced secondary immunodeficiency.

Figure 6 displays the scanning electron microscopy (SEM) imaging and energy-dispersive X-ray spectroscopy (EDS) microanalysis of the affected maxillary bone tissue. The EDS elemental analysis showed that in healthy bone control sections, the weight percentage (wt%) of phosphorus (P) ranged from 0.35% to 0.81%, while calcium (Ca) ranged from 0.32% to 1.27%. Conversely, in patients with a history of chronic Perventin abuse, a critical alteration in bone mineral composition was observed: the weight percentage of phosphorus in the maxillary bones was heavily elevated, ranging from 6.42% to 12.63%, and calcium values surged to between 10.64% and 19.12%. Based on these microanalytical data, it can be hypothesized that the exogenous intake of red phosphorus during clandestine Perventin synthesis disrupts normal bone remodeling, leading to the intraosseous accumulation of hyper-concentrated, poorly soluble calcium-phosphate complexes. This pathogenic retention prevents the physiological clearance and elimination of toxic chemical by-products from the bone matrix, triggering local microvascular thrombosis, severe osteotoxicity, and subsequent extensive necrosis of the jawbone tissue.

The treatment of drug-induced toxic osteonecrosis of the jaws remains one of the most challenging dilemmas in maxillofacial surgery due to the compromised regenerative capacity of the bone matrix and severe secondary immunodeficiency characteristic of these patients. Traditional surgical approaches, such as conservative sequestration or isolated radical resections without immediate reconstruction, often result in persistent, non-healing bone defects, chronic oronasal communications, and catastrophic functional loss, which is consistent with

the findings reported by Bun et al. [21] and Ispiryan [15]. In such non-interventional or sub-optimally treated cohorts, spontaneous bone regeneration is virtually non-existent, and defects can remain unchanged or progressively expand over 10 to 15 years.

In contrast, our multimodal protocol –combining radical necrectomy, periosteal stem cell implantation, and early functional prosthetic rehabilitation –demonstrated a profound acceleration of the osteogenic process. While Sergent et al. [22] and Adamska et al. [23] emphasize that complete cessation of the toxic agent is the absolute primary prerequisite for any stabilization of jaw necrosis, our long-term 20-year data prove that substance cessation alone is insufficient for rapid anatomical restoration. The introduction of cellular therapy into the periosteal niche dramatically counteracts the local osteotoxicity induced by clandestine Perventin by providing a viable pool of osteoprogenitor cells.

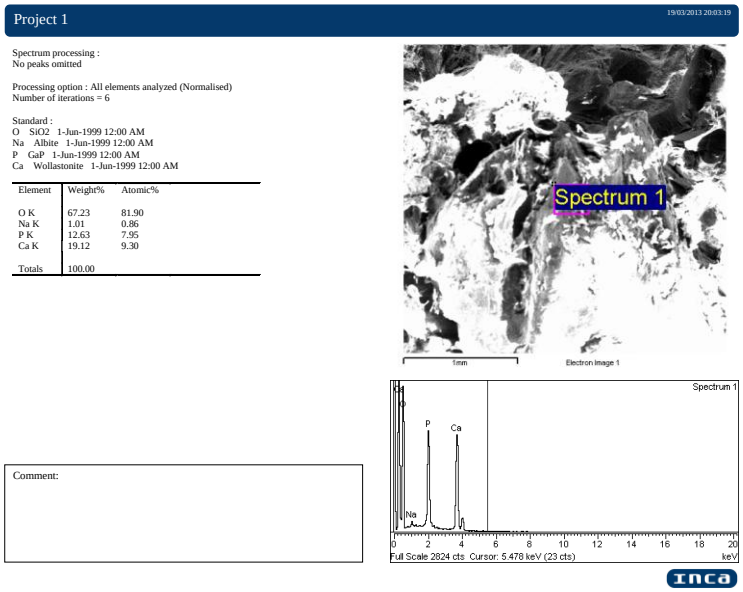

Fig. 6. Radiospectral analysis of maxillary bone tissue using radiographic spectroscopy

Furthermore, the innovative use of early removable prosthodontic appliances in our study introduced a crucial biomechanical factor. According to Wolff's Law of bone transformation, mechanical strain is a primary driver of architectural remodeling. The controlled functional loading and intermittent pressure exerted by the removable prosthesis directly onto the vascularized periosteum stimulated localized microcirculation and up-regulated signaling pathways responsible for accelerated bone matrix deposition. This synergistic effect explains why substantial reduction or complete closure of extensive maxillary defects was achieved within a tight 2-to-3-year post-operative window in our study group, whereas Cossa et al. [24] noted that conventional prosthetic management without cellular pre-treatment frequently causes further mucosal breakdown and secondary pressure necrosis. Thus, the integration of regenerative medicine with functional biomechanical stimulation establishes a highly effective therapeutic standard for this difficult patient population.

Conclusions

1. A retrospective review of archival statistical records from the Department of Oral and Maxillofacial Surgery at the IMSP IMU spanning 2005 to 2024 revealed that patients presented not only with classic odontogenic and post-traumatic forms of osteomyelitis but also with an atypical, aggressive avascular form of osteonecrosis not previously documented in traditional clinical practice. Detailed anamnesis established that the overwhelming majority of these patients with extensive jaw necrosis shared a common history of abusing the illicit, clandestinely synthesized synthetic stimulant "Perventin" (containing red phosphorus, iodine, and amphetamine derivatives) or α-PVP, whereas non-narcotic etiologies, such as bisphosphonate therapy or radiation-induced osteoradionecrosis, were identified only in a minor fraction of cases.

2. Comprehensive epidemiological data confirmed that jaw necrosis in 78.3% of the evaluated cohort in the Republic of Moldova developed as a direct consequence of abusing "Perventin," owing to its low cost and ease of clandestine manufacturing. A comparative analysis with specialized scientific literature from other regions where substance-associated jaw necrosis is prevalent indicates that our findings strongly align with epidemiological and clinical patterns reported in extensive studies from Ukraine.

3. Within the studied population of the Republic of Moldova, patients hospitalized with drug-induced toxic osteomyelitis accounted for 1.6% of the total number of individuals treated in the Oral and Maxillofacial Surgery Department for all maxillofacial pathologies during the 2005–2024 period. Among the 203 analyzed cases, the definitive etiological distribution of jaw necrosis was established as follows: Perventin abuse in 78.3% of cases, α-PVP consumption in 15.8%, bisphosphonate administration in 3.9%, and post-radiation osteoradionecrosis in 2.0% ($p < 0.05$).

3. Energy-dispersive X-ray spectroscopy (EDS) microanalysis of the maxillary bone architecture showed that in healthy bone controls, the weight percentage (wt%) of phosphorus ranged from 0.35% to 0.81%, and calcium from 0.32% to 1.27%. Conversely, in Perventin abusers,

the intraosseous weight percentage of phosphorus was critically elevated to a range of 6.42%-12.63%, and calcium values escalated to 10.64%-19.12%. These microanalytical data substantiate the hypothesis that exogenous phosphorus and systemic calcium bind into hyper-concentrated, poorly soluble toxic complexes that permanently deposit within the bone matrix, preventing physiological clearance and inducing catastrophic bone tissue ischemia and necrosis.

4. Microbiological screening and antibiogram analysis from 2005 to 2024 indicated that *Staphylococcus epidermidis* was the most frequently isolated pathogen in the etiology of secondary infection in toxic osteomyelitis, predominantly manifesting in patients with severely compromised systemic resistance. Experimental in vitro evaluation of antimicrobial efficacy demonstrated that gentamicin and ofloxacin possessed the highest therapeutic potency against the isolated bacterial strains in this specific pathology.

5. The long-term 19-year follow-up of 203 patients yielded highly significant differences in overall treatment and survival outcomes between the two managed groups ($p < 0.001$). In Control Group I (conventional therapy), clinical improvement was achieved in 80.6% of cases, none achieved complete practical health, and the mortality rate reached 19.4%; in Study Group II (multimodal protocol), 69.5% showed improvement, 24.1% achieved complete clinical recovery (practical health), and the mortality rate was significantly reduced to 6.4%. These data conclusively prove that an active, staged surgical strategy (radical necrectomy combined with reconstructive intervention) and early functional loading ensure substantially faster recovery and rehabilitation compared to conservative approaches. Given the young demographic profile of substance-induced osteonecrosis, an intensive educational and preventive campaign targeting adolescents aged 12 to 18 must be urgently integrated into school programs.

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All authors have read and approved the final version of the submitted manuscript.

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