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GENERAL SURGERY

3 (10) | 2024

ЗАГАЛЬНА ХІРУРГІЯ

Experience in treating patients with autoimmune pancreatitis

Bifocal endometriomas involving a Pfannenstiel incision

Difficult choledocholithiasis

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BIOGRAPHIES

БІОГРАФІЇ

ORIGINAL RESEARCH

ОРИГІНАЛЬНІ ДОСЛІДЖЕННЯ

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The golden era of Kyiv surgery

The article discusses the academic and university surgery in Kyiv during the 1920s. It is based on data obtained from extensive archival research and available bibliographic sources, and it highlights a specific period of the work of the Faculty Surgical Clinic of Kyiv St. Volodymyr University, which is now known as Bogomolets National Medical University. The article presents information about the lives and professional journeys of the heads and staff of the surgical clinic, including Yevhen Cherniakhivskyi, Yurii Voronyi, Vira Hedroyts, Mykola Volkovych, and Oleksii Lazurenko.

Kyiv St. Volodymyr University

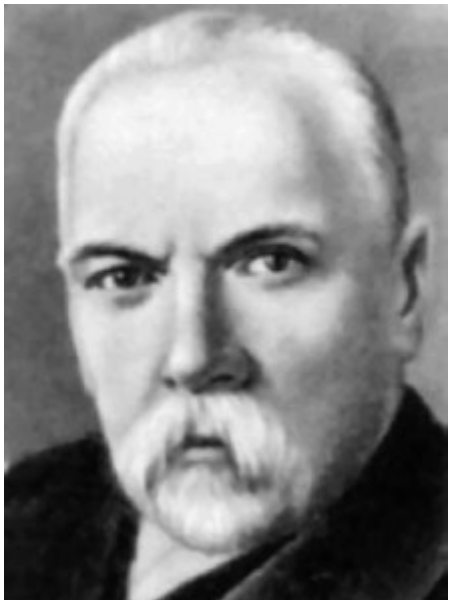
Kyiv St. Volodymyr University was established in 1833, with the medical faculty commencing surgical procedures in 1841. As per its charter, the faculty initially had two surgical departments: 1) operative surgery with topographic anatomy, desmurgy, and surgical clinic; 2) theoretical surgery with ophthalmology. In 1847, a hospital surgical clinic with 64 beds was inaugurated at the Kyiv Military Hospital, which eventually became the relevant base for the department. In 1885, the discipline of operative surgery with topographic anatomy was granted a separate department, and in 1899, the Department of Surgical Pathology was formed. By the end of the 19th century, the medical faculty had four surgical departments. These departments were based at the Oleksandrivska Hospital , the Kyiv Military Hospital, and the Faculty Surgical Clinic. The clinic operated eight months a year, had 20 beds, and was situated in the university's central (red) building. Oleksandr Karavayev had run the clinic since its establishment. In 1885, the clinic was relocated to a new building at 17 Shevchenko Boulevard, which now houses Kyiv Municipal Clinical Hospital No 18.

The University Faculty Clinic

The idea of creating a full-fledged university clinic in Kyiv had been around for almost 190 years. A crucial step in that direction was the opening of university faculty clinics in 1885—1888: surgical, therapeutic, ophthalmic, and obstetrics and gynecology. The clinics were situated in the main building of St. Volodymyr University, a location that was unsuitable for patient treatment and caused inconvenience for students from other university faculties. In addition to faculty clinics, the medical faculty also included hospital clinics (departments) located in other Kyiv hospitals. Thus, faculty clinics served as educational and treatment centres for only a few clinical departments. There was a project to create a separate university clinic for hospital departments. In 1913, its construction began on Batieva Gora (a historical district in Kyiv). During the First World War (1915), 90% of the completed buildings housed military infirmaries. In 1925, the KGB took over these buildings from the medical institute to establish a «police academy», which now houses the F. G. Yanovsky National Institute of Phthisiology and Pulmonology [2].

The Faculty Surgical Clinic on Shevchenko Boulevard (formerly Bibikovsky Boulevard until 1919) originally had two floors, with two more built in the 1960s. Professors Oleksandr Rinek and Lev Malinovsky headed it at the end of the 19th century. The clinic had 30 beds for outpatient and inpatient care (with separate areas for men and women). The clinic personnel included the director (head of the department), full-time and part-time residents, docents and private docents, and trainees (up to 10 people in total). The data provided show that the faculty surgical clinic performed worse than surgical care institutions in Kyiv.

Mykola Volkovich became the dean of the Department of Faculty Surgery (and clinic) in 1911.



Mykola Volkovich

Prior to this period, he served as the head of the surgical department of the Oleksandriv Hospital., and from 1908, he led the Kyiv Society of Surgeons, which he founded.

In 1922, Professor Yevhen Chernyakhivskyi directed the clinic. During that period, the clinic was under the jurisdiction of the Kyiv Medical Institute. It was founded in 1920 by combining the medical faculties of St. Volodymyr University and the Ukrainian National University, the Women's Medical Institute, and the Odontological Institute. The institute introduced the position of «director of faculty clinics» in the late 1920s, which involved financial management responsibilities. The head of the department was considered the head of the clinic and was responsible for medical issues [4].

The «Report of Departments and Clinics of the Institute for 1922—1923» describes the state of the department as follows: «At the Faculty Surgical Clinic, there is a laboratory and a museum, but due to unfavorable material conditions (lack of fuel, lack of reagents, and accessories), the laboratory and museum do not work. The supply of various medical assets is severely limited. The medical equipment is in such a state that it requires significant repair and renewal. The clinic's premises, particularly the operating room, are in dire need of major repairs. Last winter, the clinic did not function due to a lack of fuel (the average temperature in the operating room and dressing rooms was 2 degrees). (...) the department hosts scientific meetings where clinic employees discuss all interesting and difficult cases. The meetings are held every week.» During that period, the clinic had 35 beds.

In 1928—1929 Professor Vera Gedroits ran the clinic.

The «Report of Departments and Clinics of the Institute for 1935» describes the state of the department as follows: «The Faculty Surgical Clinic is located in building No. 17 on Shevchenko Boulevard, occupying 1,123 square meters. The clinic occupies the building that dates back to 1880. It is a 2-story brick building with an iron roof. The clinic occupies the lower floor. The house has central heating, exhaust ventilation, electric lighting, water supply, and sewage. The premises need major renovation. The clinic has 65 beds. The clinic features an auditorium, but it lacks an outpatient clinic. The department lacks adequate equipment. It has a lot of old property, partially damaged surgical instruments, and a poorly equipped laboratory. The clinic has a library consisting of a large number of both Russian and foreign magazines of the pre-revolutionary period."

During the Nazi occupation of Kyiv (1941—1943), the corresponding department of the city hospital, later the German military hospital, functioned in the building of the Faculty Surgical Clinic.

After the Second World War, the buildings of the faculty clinics were gradually transferred from the institute to the municipal property; the departments continue to function in them (today, the Department of Surgery No. 1 of Bogomolets National Medical University is located here).

In the historical context, the Faculty Surgical Clinic is defined mostly by the prominent people who worked in it. The period of the 1920s and 30s of the last century, when the Faculty's Surgical Clinic experienced the heyday of its scientific potential, appears to be particularly vivid. However, important social processes occurred within the hospital's walls over those years. These processes hold a special significance in today's world.

Yevhen Chernyakhivskyi

Early Soviet authorities announced a policy of Ukrainianization, which directly affected the Kyiv Medical Institute, at the beginning of its approval process. It provided for conducting the scientific and medical process in the Ukrainian language. In 1922, the faculty surgical clinic and the corresponding department were headed by Professor Yevhen Chernyakhivskyi. He graduated from Kyiv University and had two brothers, Oleksandr and Mykhailo, who were doctors.

Mykhailo Chernyakhivskyi, also a surgeon, was one of the co-founders of the student scientific society at the medical faculty of St. Volodymyr University. He worked in a military hospital in Kyiv. After defending his thesis, he received the title of professor.

Yevhen Chernyakhivskyi

In 1900, he headed the Department of Surgery at Warsaw University. During the First World War, this university was evacuated to Rostov-on-Don, where he continued to lead and was the initiator of the construction of a surgical clinic.

Oleksandr Chernyakhivskyi is a histologist, head of the histology department at the Kyiv Medical Institute in the 1920s and at the beginning of the 1930s at the Donetsk Medical Institute. Professor Chernyakhivskyi is the author of the first Ukrainian-language textbook on histology and the Ukrainian-Latin dictionary of medical terminology. Oleksandr Chernyakhivskyi and his wife, Lyudmila Chernyakhivska-Starytska, are bright representatives of the Ukrainian intelligentsia who suffered Stalinist repressions. In 1930, they were arrested on a fabricated case of the SVU (Union for the Liberation of Ukraine).

Yevhen Chernyakhivskyi, after graduating from the medical faculty, worked as a surgeon at the Oleksandrivska Hospital. He authored the first report in a scientific journal in the Russian Empire, detailing the successful suturing of a heart wound from a stab wound. In the Oleksandrivska hospital, he worked under Professor Mykola Volkovich's leadership, who in 1908 founded the Kyiv Society of Surgeons. Yevhen Chernyakhivskyi became the first secretary of the society. In addition to medical work, he conducted scientific research on transplantation issues. He authored reports and publications on experimental vascular surgery. During the revolutionary events of 1917—1921, Professor Chernyakhivskyi took an active pro-Ukrainian political position. With his brother Oleksandr, he participated in creating the medical faculty of the Ukrainian National University, the first higher education institution with the Ukrainian language of instruction. In 1918, he held the post of chief physician of the Oleksandriv Hospital. In 1920, he became the first rector of the newly established Institute of Health Care (later the Kyiv Medical Institute). In 1922, he headed the faculty surgical clinic. Yevhen Chernyakhivskyi actively introduced vascular surgery into practice and continued to deal with issues of experimental transplantation. In 1928, he was arrested on a fabricated case and dismissed from the medical institute without the right to practice medicine and teach. While leading the clinic, the professor invited graduate student Yury Voronyi, professor Mykola Volkovych, professor Vira Gedroyts, and professor (and future academician) Oleksiy Krymov to work at the department [1].

Yurii Voronyi

Yuriy Voronyi, the son of the world-famous Ukrainian mathematician Georgy Voronyi, entered the medical faculty of Kyiv University in 1913. In 1918, as part of a student unit, he participated in the battle near Kruty with Bolshevik troops. In 1921, he graduated from the Kyiv Medical Institute and entered postgraduate studies under the supervision of Professor Yevhen Chernyakhivskyi. Yuriy Voronyi admired his manager's ideas about transplantation. In 1926, he moved to Kharkiv. In 1933, Yuriy Voronyi was the first in the world to transplant an entire human organ, namely, a cadaveric kidney [3].

Yurii Voronyi

Vira Gedroits

Vira Gedroits graduated from the medical faculty of the University of Lausanne, Switzerland, in 1898. She worked at the university under the leadership of the world's leading surgeon, Caesar Roux. She successfully defended her thesis twice, in 1903 and 1912, earning the title of «Doctor of Medicine." She worked as a military surgeon during the Russo-Japanese and First World Wars. She worked as one of the doctors of the imperial family. Vira Gedroits, in addition to medical practice, was the author of numerous poems and prose works. In 1918, while working at the front, she was wounded and evacuated to Kyiv. Since 1919, Vira Gedroits had been working as a surgeon in the polyclinic. In 1920, she took part in the head and neck surgery clinic's organisation and began working at the Kyiv Medical Institute. In 1921, at the invitation of Professor Yevhen Chernyakhivskyi, he began working in the faculty surgical clinic. In 1923, she became the first female surgeon in the world to receive the title of «professor». In 1928, she headed the Department of Faculty Surgery of the Kyiv Medical Institute and became the world's first woman head of the Department of Surgery. In 1930, for political reasons, Vira Gedroits was dismissed from the medical institute without the right to teach and practice medicine.

Thus, outstanding professionals, including the founder of the Kyiv Society of Surgeons and the

Vira Gedroits

author of the classic approach to the appendix vermiformis, the world's first female professor of surgery, and the surgeon who performed organ transplantation for the first time in world history, all worked together in the Faculty Surgical Clinic of the Kyiv Medical Institute, under the leadership of the first rector, Yevhen Chernyakhivskyi.

In the same period, associate professor Oleksiy Lazurenko worked at the department. In 1941, he became the rector of the Kyiv Medical Institute (since 1942, the Polymedical Institute), which functioned from 1941 to 1943 in Nazi-occupied Kyiv. Oleksiy Lazurenko petitioned the German command to open a higher medical educational institution in Kyiv. About 1,000 students studied there during its existence, and 41 departments operated. In 1942, he was arrested by the Gestapo and shot in Babiy Yar. References to Oleksiy Lazurenko and the existence of a medical institute in Kyiv during the Nazi occupation were strictly prohibited by the Soviet authorities, and archival documents were kept under the label «secret» until recently.

In the 1930s, Stalin's terror reached its maximum scale. For the Ukrainians, it began at the end of the 1920s, and among the employees of the faculty surgical clinic, only Professor Krymov managed to avoid persecution. Others became victims of the merciless and senseless Soviet repressive machine. Most of the names of these people were unjustly erased from history. Thus, in the «Report of Departments and Clinics of the Institute from 1935, it is noted that Professor Krymov had been in charge of the department since 1913 (although he headed the department only in 1930), and the names of Professors Volkovych, Chernyakhivskyi, and Gedroits, who managed the clinic in the period between 1913 and 1930 years, are absent. There is no mention of these professors in the book dedicated to the 100th anniversary of the Kyiv Medical Institute (published in 1947). Instead, the chapter on the history of Kyiv surgery is summarised as follows: «The Great October Socialist Revolution finally freed Soviet surgery from foreign dependence and opened wide prospects for its independent development».

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D. Dubenko

Kyiv Municipal Clinical Hospital No 18

Золоті часи київської хірургії

Д. Дубенко

Київська міська клінічна лікарня № 18

У статті описані аспекти функціонування академічної та університетської хірургії в Києві у 1920-х. На основі даних, отриманих після широкого архівного пошуку та аналізу наявних бібліографічних джерел, проілюстровано один із періодів роботи факультетської хірургічної клініки Київського університету святого Володимира (нині — Національний медичний університет імені О.О. Богомольця). Наведено факти про життєвий і професійний шлях керівників та працівників хірургічної клініки, зокрема, Євгена Черняхівського, Юрія Вороного, Віри Гедройц, Миколи Волковича, Олексія Лазуренка.

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Experience in treating patients with autoimmune pancreatitis

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Objective — to establish the main diagnostic signs of autoimmune pancreatitis and aspects of patient treatment.

Materials and methods. The study analyzed the results of examination and treatment of 17 patients with autoimmune pancreatitis (AIP) from 2010 to 2022. Among the total number of patients with AIP, there were 11 men (65 %) and 6 women (35 %). The average age of the patients was 52.4 years. Among all patients with AIP, focal involvement of the pancreas was found in 3 (18 %) patients, with a predominant involvement of the head of the pancreas. Segmental form of AIP was diagnosed in 6 (35 %) patients, while diffuse form was found in 8 (47 %) patients. Type 1 AIP was identified in 13 (76 %) patients, and type 2 AIP in 4 (24 %) patients. For all patients suspected of AIP, the HISORt criteria were assessed: instrumental visualization, serological and histological verification, determination of the volume of pancreatic involvement, and response to steroid therapy.

Results. Recurrence of AIP was observed in 8 (47.0 %) patients with type 1 AIP and 1 (5.8 %) patient with type 2 AIP. AIP recurred in patients with proximal bile duct involvement, diffuse pancreatic involvement, persistently elevated IgG4 levels after steroid induction, delayed radiological remission, and damage to more than two organs. Increased serum levels of IgG, IgG4, apnd eosinophilia indicated a recurrence of IgG4-RD. A repeat induction of steroids was performed in patients with recurrent AIP, which proved to be very effective, resulting in high remission rates, specifically in 7 (70 %) patients with type 1 AIP and in 1 (100 %) patient with type 2 AIP. Among all AIP patients that were operated on, 3 (40 %) underwent Roux-en-Y hepaticojejunostomies, 1 (20 %) pancreaticoduodenectomy, and 1 (20 %) a Frey procedure.

Conclusions. The low incidence of AIP necessitates the use of a clear diagnostic algorithm, and the peculiarities of the disease's course require compliance with all the principles of conservative treatment and surgical interventions in case of surgical complications.

Keywords
autoimmune pancreatitis; type 1 AIP, type 2 AIP, IgG4-related pancreatitis.

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The chronic form of pancreatitis, known at present as autoimmune pancreatitis (AIP), was first described by Sarles H. et al. in 1961 as primary inflammatory sclerosis of the pancreas [21]. In subsequent scientific works, AIP has been referred to as lymphoplasmacytic sclerosing pancreatitis, non-alcoholic duct-destructive pancreatitis, inflammatory pseudotumor of the pancreas, and others [6].

The overall prevalence and incidence of AIP remain almost unknown. According to data from Japan, the prevalence is 4.6 per 100,000, and the incidence is 1.4 per 100,000 people [5]. According зto data from various global authors, the incidence of autoimmune pancreatitis ranges from 4.8 % to 11 % [3, 8, 25]. The average age of patients is around 55 years (30—70), with a male-to-female ratio of 1.7 : 1 to 2 : 1 [17]. In the structure of chronic pancreatitis of all etiologies, AIP type 1 is observed in up to 1—2 % [2]. Approximately 5 % of patients suspected of pancreatic cancer are diagnosed with AIP as a result [17].

The predominant etiological factor in the development of autoimmune pancreatitis remains the theory of lymphocyte activation by IgG4, which is normally one of the least abundant immunoglobulins of class G, exhibiting both pro-inflammatory and anti-inflammatory activity. Typically, the

disease is diagnosed upon the detection of IgG4 immunoglobulins and the absence of other signs of pancreatic damage. Experts in the field of clinical gastroenterology suggest a leading role of hereditary predisposition; during medical-genetic studies, an association of the autoimmune process with HLA serotypes $DR\beta_1$ — 0405, $DQ\beta_1$ — 0401, and $DQ\beta_1$ — 57 was established [2].

A key link in the pathogenesis of autoimmune pancreatitis is considered to be the accumulation in the connective tissue of persistent activated T- and B-lymphocytes, neutrophils, and eosinophils, which provoke fibrotic-sclerotic processes. The triggering mechanism for changes in the pancreas and other organs is the binding of serum IgG4 to autoantigens of acinar cells, normal pancreatic epithelial cells, bile, salivary ducts, and others. Antigenic damage is accompanied by the disruption of apoptosis in immune system cellular elements. It is believed that eosinophils play an important pathogenetic role in AIP because patients with AIP exhibit peripheral eosinophilia and the formation of eosinophilic infiltrates. Peripheral eosinophilia in AIP is observed in 28 % of patients, while allergic disorders are present in 15 % of patients. Interestingly, the Th2 immune response, which is enhanced in AIP, includes the induction of IL-4, IL-5, and IL-13, leading to the expression of eotaxin-3, a chemoattractant cytokine for eosinophils that directs them to sites of inflammation via the STAT6 pathway. The expression of eotaxin-3 induced by Th2 cytokines plays a certain role in the pathophysiology of AIP and eosinophilic pancreatitis [13]. The serum level of IgG4 is elevated in patients with AIP, and IgG4 antibodies are characteristically deposited in affected organs, leading to fibrosis and obliterative phlebitis [13]. The production of IgG4 is promoted by Th2 cells that produce IL-10 and IL-13, as well as regulatory T cells (Tregs) that produce IL-10 [11, 28]. Various additional cell types, including T follicular helper cells, $CD4^+$ cytotoxic T cells, plasmacytoid dendritic cells, basophils, and monocytes, enhance the secretion of IgG4 and contribute to the pathogenetic mechanisms of AIP and IgG4-RD [13]. Recently, interferon-I (IFN-I) has been linked to the immunopathogenesis of autoimmune pancreatitis (AIP), which is produced by plasmacytoid dendritic cells. IFN-I is responsible for the increase of IL-33, which is involved in the induction of fibrotic processes in the pancreatic duct cells [1]. IFN-I also stimulates plasma cells to produce IgG4 [16]. Dysregulation of the IFN-I system is also implicated in several autoimmune rheumatic diseases, such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, and inflammatory myositis.

Activated IgG4-positive leukocytes induce a diffuse or localized process, which is characterized by a pronounced infiltration of lymphocytes and plasma cells, followed by their activation into fibroblasts and the formation of focal fibrosis. Histological examination reveals signs of fibrosis and sclerosis in the pancreatic stroma in the absence of pseudocysts and stones. Due to lymphoplasmacytic, neutrophilic, and eosinophilic infiltration, the walls of the ducts are thickened, narrowed, and fragmented in the prolonged course of the autoimmune process. The spread of inflammatory infiltration to the lobules of the pancreas leads to the loss of the lobular structure of the organ. Autoimmune pancreatitis is also associated with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) gene, a negative regulator of T-cell response. Single nucleotide polymorphisms (SNPs) involving the CTLA-4 gene are implicated in several autoimmune diseases, such as type 1 diabetes, autoimmune thyroid disease, autoimmune hepatitis, and primary biliary cirrhosis [27]. Umemura et al. concluded that autoimmune pancreatitis is associated with the CTLA-4 polymorphism and positively correlates with sCTLA-4 levels [24].

Objective — to establish the main diagnostic signs of autoimmune pancreatitis and aspects of patient treatment.

Materials and methods

The study analyzed the results of examination and treatment of 17 patients with autoimmune pancreatitis from 2010 to 2022. Among the total number of patients with AIP, there were 11 men (65 %) and 6 women (35 %). The average age of the patients was 52.4 years. All patients underwent CT scan, and magnetic resonance cholangiopancreatography (MRCP) to determine the prevalence of the fibrotic-sclerotic process of the pancreas, to detect autoimmune involvement of other organs, and to assess the condition of the ductal system.

Among all patients with AIP, focal involvement of the pancreas was found in 3 (18 %) patients, with a predominant involvement of the head of the pancreas. Segmental form of AIP was diagnosed in 6 (35 %) patients, while diffuse form was found in 8 (47 %) patients. Type 1 AIP was identified in 13 (76 %) patients, and type 2 AIP in 4 (24 %) patients. Isolated autoimmune pancreatitis was observed in 13 (76 %) patients, while syndromic autoimmune inflammation IgG4-RD was noted in 4 (24 %) patients, characterized by elevated levels of IgG4 in serum, presence of autoantibodies (autoAB), and involvement of other organs. There were 2 (50 %) cases exhibiting sclerosing cholangitis, while in 1 (25 %) case

there was intra-abdominal lymph node involvement and 1 (25 %) case of Riedel's thyroiditis.

All patients diagnosed with AIP were treated with prednisone 40 mg/day for 4 weeks, followed by a gradual reduction to 5 mg/week. The response to treatment was assessed clinically and objectively by measuring IgG4 levels in serum, as well as through repeated imaging control during and after the 4-week treatment course. After the induction of steroid therapy, the decision to start maintenance therapy was made individually, taking into account the response to therapy and the presence of side effects. Maintenance therapy included the administration of low doses of steroids (5 mg), which were discontinued after 12 months.

For cases resistant to steroids, immunomodulators (azathioprine) or rituximab were used. Immunomodulators are ineffective in monotherapy regimens, so they were prescribed with steroid intake. Rituximab was used for both induction and maintenance therapy. Induction included a 4-week therapy with a dose of 375 mg/m^2 of body surface area at intervals of every 2 weeks.

In cases of ineffective conservative treatment and the development of surgical complications, patients with AIP underwent various surgical interventions. Among all 17 patients with AIP, 5 (29.4 %) underwent surgery.

3 (60 %) patients with AIP who developed tubular stenosis of the common bile duct underwent the majority of Roux-en-Y hepaticojejunostomies.

Among all AIP patients who were operated on, 2 (40 %) had resectional surgical interventions, 1 (20 %) had a pancreaticoduodenectomy, and 1 (20 %) had a Frey procedure.

Results

For all patients suspected of AIP, the HISORt criteria were assessed: instrumental visualization, serological and histological verification, determination of the volume of pancreatic involvement, and response to steroid therapy. In 3 patients suspected of AIP, pancreatic cancer was verified after assessing the HISORt criteria, and treatment was modified. Recurrence of AIP was observed in 8 (47 %) patients with type 1 AIP and in 1 (5.8 %) patient with type 2 AIP. Signs of AIP recurrence included deviations in laboratory parameters and results from instrumental examination methods. Only in the presence of clinical symptoms (i.e., abdominal pain without signs of pancreatic inflammation) or isolated elevation of IgG4 levels in serum (without confirmatory radiological or biochemical results), which were observed regardless of AIP activity, did not indicate a recurrence of the disease. Recurrence of AIP was observed in patients with proximal bile duct involvement, diffuse pancreatic involvement, persistently elevated IgG4 levels after steroid induction, delayed radiological remission, and damage to more than two organs. Increased serum levels of IgG, IgG4, and eosinophilia indicated a recurrence of IgG4-RD. In patients with recurrent AIP, a repeat induction of steroids was performed, which proved to be very effective, achieving high remission rates, specifically in 7 (70 %) patients with type 1 AIP and in 1 (100 %) patient with type 2 AIP.

Discussion

There are two main forms of AIP that are defined by unique features:

Type 1 — lymphoplasmacytic sclerosing pancreatitis typically occurs in late adulthood with an average age of diagnosis of 50 years and older and affects males three times more commonly than females. Type 1 AIP may be a manifestation of the IgG4-RD spectrum, characterized by elevated serum IgG4 levels, the presence of autoantibodies, and widespread involvement of multiple organs: eyes (pseudolymphoma), bile ducts (sclerosing cholangitis), lymph nodes (mediastinal, intra-abdominal, and hilar adenopathy), salivary glands (sclerosing sialadenitis), thyroid gland (Riedel's thyroiditis), kidneys (interstitial nephritis), and lungs (fibrosis). In this form of AIP, there is a predominance of infiltration by immunoglobulin-producing cells, pronounced fibrosis of the pancreatic stroma, and obliterative phlebitis. There is a pattern of association between type 1 AIP and IgG4-associated pathology, along with frequent recurrent courses and progression of sclerotic changes.

Type 2 is idopathic duct-centric chronic pancreatitis. This form of AIP is dominated by neutrophie infitration with cellular clusters resembling microabscesses and less pronounced phlebitis and pancreatic fibrosis. Serum IgG4 levels typically remain normal, and in 30 % of cases, type 2 AIP is associated with ulcerative colitis, Evans syndrome, and Hashimoto's thyroiditis and is relapse-free. Type 2 AlP is 3.5—4 times less common than type 1 AIP [19, 10]. On the contrary, type 2 AIP does not manifest itself as a systemic disease but as a specific isolated disease of the pancreas [7]. When examining patients with type 2 AIP, normal IgG parameters are more often determined; IgG4 and autoAT are not detected.

Painless mechanical jaundice is the most common clinical symptom [20]. Jaundice in AIP is associated with biiary tract involvement, most commonly in

the extra-pancreatic region (66 % of patients with AIP) [15]. Other less common symptoms include mild abdominal or back pain, fatigue, and weight loss. Abdominal pain in type 1 AIP may be mild or absent. In patients with type 2 AIP, 68 % have a more severe pain syndrome [20]. In addition, AIP is associated with exocrine and endocrine pancreatic insufficiency in 80 % and 70 % of cases, respectively [23]. In a study conducted in China, mechanical jaundice was observed in 72 % and abdominal pain in 44 % of patients, while a multicenter study conducted in Spain showed that pain was observed in 65.4 % and jaundice in 52 % of patients [12]. In pancreatic cancer, jaundice progresses gradually and does not respond to conservative treatment, while in AIP, jaundice is characterized by spontaneous disappearance [5]. One study showed that 29.7 % of patients were misdiagnosed with pancreatic cancer, and these patients underwent surgery. Only 10 % of patients with pancreatic cancer have elevated IgG4 levels, but only 1 % of patients have IgG4 levels > 280 mg/dI [25].

Conclusions

The low incidence of AIP necessitates the use of a clear diagnostic algorithm, and the peculiarities of the disease's course require compliance with all the principles of conservative treatment and surgical interventions in case of surgical complications.

Declaration of interests

The authors declare no conflicts of interest.

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Authors contributions

Conception and design — O. I. Dronov, Y. P. Bakunets; data collection, critical revision of the article — Y. P. Bakunets; analysis and interpretation of data — Y. P. Bakunets, F. O. Prytkov; drafting the article — F. O. Prytkov.

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Досвід лікування пацієнтів з автоімунним панкреатитом

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Мета — визначити основні діагностичні ознаки автоімунного панкреатиту й аспекти лікування пацієнтів.

Матеріали та методи. Проаналізовано результати обстеження та лікування 17 пацієнтів з автоімунним панкреатитом (АІП) у період з 2010 до 2022 року. Чоловіків було 11 (65 %), жінок — 6 (35 %). Середній вік хворих становив 52,4 року. Вогнищеву форму ураження підшлункової залози із переважним ураженням головки виявлено в 3 (18 %) пацієнтів, сегментарну форму АІП — у 6 (35 %), дифузну форму — у 8 (47 %). АІП 1-го типу діагностовано в 13 (76 %) пацієнтів, АІП 2-го типу — у 4 (24 %). У всіх пацієнтів із підозрою на АІП проводили інструментальну візуалізацію, серологічну та гістологічну верифікацію, визначення об'єму ураження підшлункової залози та відповіді на стероїдну терапію.

Результати. Рецидив АІП зареєстрували в 8 (47 %) пацієнтів із АІП 1-го типу та в 1 (5,8 %) з АІП 2-го типу. Рецидив АІП спостерігали в пацієнтів з ураженням проксимальних жовчних проток, дифузним ураженням підшлункової залози, стійко підвищеним рівнем IgG4 після індукції стероїдами, відстроченою рентгенологічною ремісією та захворюванням двох органів або більше. Підвищені сироваткові рівні IgG, IgG4 та еозинофілія вказували на рецидив IgG4-RD. У пацієнтів із рецидивом АІП проводили повторну індукцію стероїдами, яка була дуже ефективною з досягненням високих показників ремісії — у 7 (70 %) пацієнтів з АІП 1-го типу та в 1 (100 %) пацієнта з АІП 2-го типу. Серед прооперованих хворих з АІП 3 (60 %) пацієнтам виконано гепатикоєюностомію на Ру-петлі, 1 (20 %) — панкреатодуоденальну резекцію, ще 1 (20 %) — операцію Фрея.

Висновки. Низька захворюваність на АІП потребує використання чіткого діагностичного алгоритму, а особливості перебігу цього захворювання — дотримання всіх принципів консервативного лікування та оперативних втручань при хірургічних ускладненнях.

Ключові слова: автоімунний панкреатит, АІП 1-го типу, АІП 2-го типу, IgG4-асоційований панкреатит.

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Peculiarities of the botulinum toxin type A injection technique and its effectiveness in the surgical treatment of large ventral hernias

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Ventral hernias (VH) continue to be one of the most common surgical pathologies in planned and emergency surgery. Surgical treatment of large VH (≥ 10 cm) requires the use of traumatic surgical techniques in order to align the edges of the hernia defect and restore the integrity of the anterior abdominal wall.

Objective — to assess the effectiveness of the botulinum toxin type A (BTA) injections and to study the peculiarities of their administration into the muscles of the anterior abdominal wall in patients with large VH in the preoperative period.

Materials and methods. A prospective cohort study included 66 patients with large VH, primary (PVH), and incisional (IH). From June 2017 to August 2024, all patients underwent treatment and received injections of 100 units of BTA into the anterior abdominal wall muscles in the preoperative period. The patients' average age was 58.98 ± 9.48. There were 23 men (34.8 %) and 43 women (65.2 %). Before BTA, the average width of the hernial defect in PVH patients was 12.29 ± 1.93 cm, whereas IH was 13.46 ± 2.06 cm. All patients underwent surgical intervention for their hernias 4—5 weeks after the injection of BTA.

Results. No complications were detected throughout the BTA administration or the 4—5 weeks of observation before the surgical hernia repair. After injection, the length of the anterior abdominal wall muscles increased by an average of 1.7 cm (min 0.1 cm, max 4.01 cm) on each side. Patients with PVH had an average hernial defect width reduction of 4.17 ± 0.68 cm, whereas those with IH had an average reduction of 5.14 ± 0.75 cm ($p < 0.001$). After BTA administration, the volume ratio of the hernia sac to the abdominal cavity decreased from 4.97 ± 3.55 % to 3.70 ± 2.77 % in patients with PVH ($p = 0.008$) and from 5.59 ± 3.71 % to 4.21 ± 2.88 % in patients with IH ($p = 0.008$).

Conclusions. The administration of 100 units of botulinum toxin type A in the preoperative period consistenly increases the length of the abdominal wall muscles, reduces the width of the hernial defect, and enhances the possibilities of further surgical treatment of large VH using laparoscopic technologies.

Keywords
incisional hernia, ventral hernia, hernioplasty, botulinum toxin.

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Hernias of the anterior abdominal wall are a common pathology. Every fifth adult develops a primary ventral hernia (PVH) [10]. The incidence of incisional hernias (IH) ranges from 10 to 31 % after «open» surgery [9, 13] and can reach 23 % after laparoscopic and laparoscopic-assisted operations [4]. IH recurrence is on average 18—21 % after 12 months of observation, although it can reach 37 % after 48 months [12]. The type and size of the ventral hernia (VH) impact the rate of recurrence, which can reach 40 % for patients who underwent mesh surgery and can increase progressively every year [1]. The European Hernia Society (EHS) classifies hernias with a defect width of ≥ 4 cm as «large» in PVH, but a hernia width of ≥ 10 cm is considered «large» in IH [15]. If there are no technical difficulties in comparing the

edges of the aponeurosis defect for a large PVH, suturing the hernia is more challenging as it becomes wider. When treating a large VH with a hernial defect width of more than 10 cm, laparoscopic technologies may present technical difficulties and limitations, necessitating the use of additional patient preparation measures in the preoperative period [2].

In 2009, T.R. Ibarra-Hurtado et al. first proposed using botulinum toxin type A (BTA) injections to relax and enhance the elasticity of anterior abdominal wall muscles in patients with VH [11]. A comprehensive review of 23 studies published in 2021 found that BTA injections were successful for lengthening the lateral abdominal wall muscles and improving suturing for an aponeurosis defect. At the same time, it was emphasized the need to standardize the approach to patients selection, the dosage, and technique for BTA injections in the treatment of large hernias [17]. BTA injections are administered in a variety of doses and methods, with the most common being 300 units of Botox (Allergan, USA) with ultrasound guidance [21]. Individual publications demonstrate the use of lower doses of BTA in the treatment of hernias and the closure of defects of the anterior abdominal wall. However, the effectiveness of using a total dose of BTA less than 200 units has controversial results [3, 14, 22].

Objective — to assess the effectiveness of the botulinum toxin type A (BTA) injections and to study the peculiarities of their administration into the muscles of the anterior abdominal wall in patients with large VH in the preoperative period.

Materials and methods

General characteristics of patients

A prospective cohort study included 66 patients with large VH. Considering that hernia defects less than 10 cm in width can be sutured without tension and using separation techniques, we did not include patients with PVH and widths ranging from 4 to 9 cm. All patients were treated between June 2017 and August 2024.

The average width of the hernial defect for PVH was 12.29 ± 1.93 cm (from 10 to 16 cm), whereas for IH, it was 13.46 ± 2.06 cm (from 10 to 16 cm). The patient characteristics are shown in Table 1.

In addition to an objective examination, all patients underwent an ultrasound examination of the anterior abdominal wall 4—5 weeks and one day before surgery. We also performed computed tomography (CT) with three-dimensional modelling of the abdominal cavity and anterior abdominal wall, and measured the volume of the hernia sac, the volume of the abdominal cavity, and the length and thickness of the abdominal wall muscles in comparable sections.

The BTA injection technique

All patients received BTA injections into the anterior abdominal wall muscles 4—5 weeks before surgery according to clinic's established approach. We developed a novel method of administering botulinum toxin type A and secured Ukrainian utility model patent No 142997 on 07/10/2020, titled «Method of treating large VH using botulinum toxin type A injection into the anterior abdominal wall muscles.» This method is based on the analysis of literary data as well as the clinical and anatomical characteristics associated with the development of large VH, including the location and size of the aponeurosis defect, deformation, thickness, signs of hyperplasia and/or sclerotic changes in the musculo-aponeurotic layer of the anterior abdominal wall. The technique involves the administration of BTA into the transverse, external, and internal oblique muscles of the abdominal wall, ensuring a double control over the drug's introduction into the specified muscle. We administered BTA at 6 sites, with 3 injection points on each side. The total volume of injected BTA was 100 units (Botox, Allergan, USA). We divided the dose into two equal portions and injected 50 units into the anterior abdominal wall muscles on the right and left sides. The technique enabled the customization of three predetermined entry points on each side of the abdominal wall, according to the specific location of the hernial defect. 15 units of BTA were injected into the external oblique muscle of the abdomen, 4 cm above the navel, along the line between the anterior axillary and mid-clavicular lines. Another 15 units of BTA were

Table 1. **Demographic and pre-operative data**

Characteristics	n = 66
Women	43 (65.2%)
Men	23 (34.8%)
Average age, years	58.98 ± 9.48
Body mass index, kg/m^2	31.69 ± 4.88
ASA score	
I	8 (12.1%)
II	55 (83.3%)
III	3 (4.6%)
IV	0
Obesity	32 (48.5%)
Type of hernia*	
Primary ventral hernia	27 (40.9%)
Incisional hernia	39 (59.1%)

* According to EHS (European Hernia Society) classification.

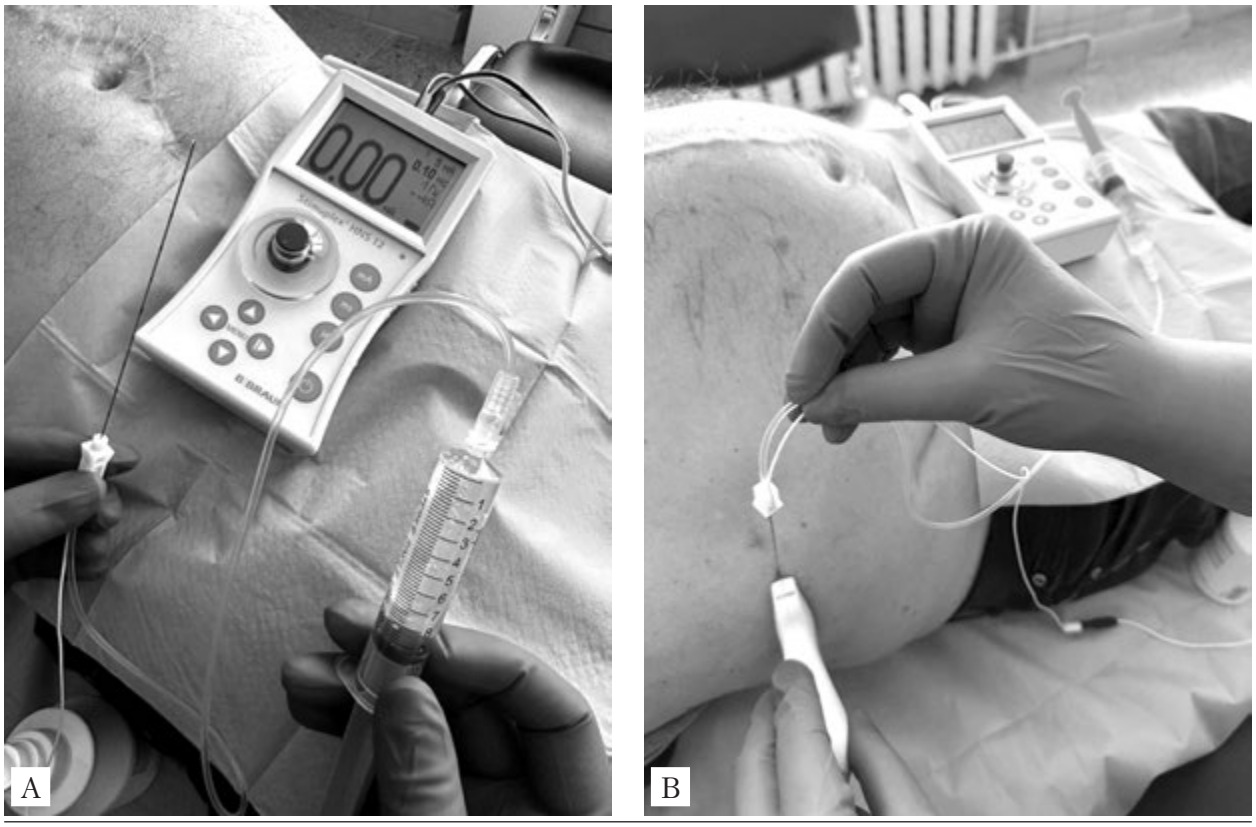

Figure 1. **Photo of BTA administration into the muscles of the anterior abdominal wall:**
A — equipment for BTA injections (needle, neurostimulator, and syringe with BTA);
B — view of the one-point BTA injection under the ultrasound control

injected into the transversus abdominis muscle at the level of the navel along the mid-clavicular line. 20 units were injected into the internal oblique muscle of the abdomen at a point 3 cm below the navel along the mid-clavicular line.

The introduction of BTA was carried out using a special stimulating puncture needle, Stimuplex A (BBRAUN, Germany), with an insulating coating of size 21G, with a diameter of 0.80 mm, a length of 100 mm. Stimuplex HNS-12 neurostimulator (BBRAUN, Germany) was connected to this needle through an electrode built into it, and BTA was injected through the built-in extension line-catheter (Fig. 1). The movement of the needle in the thickness of the anterior abdominal wall was monitored in real time on the monitor of the ultrasound machine using a linear ultrasonic sensor. A step-by-step puncture of the muscles of the anterior abdominal wall was performed on the right and left sides. At the same time, before the introduction of BTA, the accuracy of placing the tip of the needle in the thickness of the selected muscle was additionally monitored using a neurostimulator. With a short-term (3—5 s) supply of electric current with a strength of up to 5 mA and placement of the tip of the needle in the selected muscle, a visual contraction of this muscle was observed during the examination of the patient and on the monitor of the ultrasound machine. With the «incorrect» placement of the needle tip, in the thickness of the fascial sheath of the muscle, tendon, fatty tissue, the aforementioned muscle contractions were not observed.

Patients with giant hernias with a width of the hernia defect greater than 20 cm were not included in this study. The expected effect of the introduction of BTA was considered as lengthening of the lateral muscles of the anterior abdominal wall on the right and left sides. The total reduction in the width of the hernial defect was planned to 10 cm.

In this study, the authors adhered to the ethical principles of medical research involving human subjects, set forth in the Helsinki Declaration of the World Medical Association and current regulations of Ukraine. The research protocol was approved by the ethics committee of Bogomolets National Medical University. The research was carried out as part of the scientific work of the department «Improvement of diagnostic methods, surgical treatment of pathologies of abdominal organs, anterior abdominal wall, and metabolic syndrome» (No 0123U105130). Written informed consent was obtained from all patients.

Statistics analysis

Data were analysed with the statistical package IBM SPSS Statistics Base (version 22). All results were considered statistically significant at a value of $p < 0.05$. Quantitative data are presented as mean (M) ± standard deviation (SD), unless otherwise stated. The normality of the data distribution was checked using the Shapiro-Wilk test ($p > 0.05$).

Results and discussion

When administrating BTA injections, standard injection points were used in 47 (71.2 %) cases, as planned at the beginning of the study. In 19 (28.8 %) patients, asymmetric placement of the edges of the hernial defect in accordance with the midline was observed. At the same time, in the group of patients with PVH, lateral localisations of hernias were not observed, whereas in the group with IH, 8 (12.1 %) patients had L 1-L 4 type of hernia according to the EHS classification [15]. In all 19 cases with asymmetry of the edges of the hernial defect, an individual approach was used to choose the BTA injection point on the side where the scarred aponeurotic edge of the hernia deformed the anterior abdominal wall. The BTA injection point was chosen under ultrasound guidance according to the actual localisation of each of the three layers of muscles of the anterior abdominal wall.

Puncture of each of the three layers of the abdominal wall muscles (external, internal oblique, and transverse muscles) was performed under ultrasound control using a linear ultrasonic sensor with a frequency of 7—10 MHz depending on the thickness of the abdominal wall. Additionally, control of the location of the needle tip using a neurostimulator was used immediately before the introduction of BTA. Upon visual placement of the needle tip in the thickness of the muscle selected for puncture, 35 (53.0 %) patients had a need for repeated puncture and/or correction of needle placement in at least one of the six injection points, as no muscle contraction was observed during current stimulation. At the same time, in 15 (22.7 %) cases there was a need to correct the location of the needle in two points, in 5 (7.6 %) patients — in three or more points of injection. It is worth noting that cicatricial changes in the thickness of the muscles of the anterior abdominal wall in patients with IH can cause technical difficulties when introducing BTA only under ultrasound control, so we consider it necessary to supplement visualisation with additional control using a neurostimulator. According to P. H. Ferreira et al., ultrasound correlates well with electromyography for punctures of the internal oblique and transverse muscles, but not enough for the external oblique muscle of the abdomen [8]. CT navigation is also used as a separate method in addition to ultrasound in patients with obesity and a thickened anterior abdominal wall [5, 6]. In our study, there was no need for additional navigation with the help of CT; visualisation of the thickness of the anterior abdominal wall was sufficient for performing a puncture in all cases.

During the introduction of BTA and in the subsequent period of observation, we did not record any complications. The use of BTA as a method of preparation for surgical treatment of hernias belongs to the off — label category. However, researchers have thoroughly studied the potential uses and side effects of BTA in the treatment of various diseases. BTA has low antigenic activity and extremely rare cases of allergic reactions. There have been no reports of major side effects from using BTA before hernia repair. Less than 5 % of patients report minor side effects such as local pain at the injection site, cough, and superficial bruising, or none at all [5].

During the follow-up examination of patients 4—5 weeks after the introduction of BTA, changes in the size of the hernia and abdominal cavity, as well as the characteristics of the thickness and length of the muscles of the anterior abdominal wall, were observed in all cases, which is presented in Table 2.

The length of the abdominal wall was measured from the lateral margin of the quadratus lumborum muscle to the medial margin of the rectus muscle from the comparable axial CT image (section) and increased after BTA. The average increase in the length of the abdominal wall in patients with PVH was 1.71 ± 1.24 cm on the right and 1.77 ± 0.99 cm on the left side, whereas in patients with IH, it was 1.77 ± 1.22 cm and 1.78 ± 1.12 cm, respectively ($p < 0.001$). On average, the length of the anterior abdominal wall in patients with PVH increased by 6.6 % on the right and 8.2 % on the left side, whereas in patients with IH, it inceased by 6.7 % on the right and 7.8 % on the left.

Patients with PVH experienced an average significant decrease in the thickness of the anterior abdominal wall by 10.4 % on the right and 9.3 % on the left, while patients with IH experienced a decrease of 9.1 % and 6.7 %, respectively. In absolute numbers, the thickness of the anterior abdominal wall decreased minimally, and on average, its decrease did not exceed 2 mm, although it varied from 0.3 to 4.8 mm.

After the introduction of BTA, the size of the hernial defect also changed. The width of the aponeurosis defect was significantly reduced by an average of 34.9 % in patients with PVH and by 38.8 % in patients with IH. At the same time, the defect width, which was ≥ 10 cm in all patients before the introduction of BTA, decreased to less than 10 cm in 44 (66.7 %)

Table 2. **Characteristics of the hernia and abdominal wall muscles change after BTA (M ± SD)**

Indicator	Primary ventral hernia			Incisional hernia		
	Before BTA	After BTA	Δ	Before BTA	After BTA	Δ
Length of abdominal wall, cm						
Right side	25.14 ± 6.07	26.85 ± 6.80*	+1.71 ± 1.24	25.99 ± 6.13	27.76 ± 6.80*	+1.77 ± 1.22
Left side	21.99 ± 6.23	23.76 ± 6.72*	+1.77 ± 0.99	22.76 ± 6.22	24.53 ± 6.78*	+1.78 ± 1.12
Thickness of abdominal wall, cm						
Right side	1.46 ± 0.19	1.32 ± 0.25*	−0.15 ± 0.14	1.82 ± 0.20	1.66 ± 0.26*	−0.16 ± 0.11
Left side	1.40 ± 0.24	1.28 ± 0.26*	−0.13 ± 0.11	1.74 ± 0.24	1.63 ± 0.27*	−0.11 ± 0.09
Width of hernial defect, cm	12.29 ± 1.93	8.12 ± 2.18*	−4.17 ± 0.68	13.46 ± 2.06	8.32 ± 1.90*	−5.14 ± 0.75
Length of hernial defect, cm	12.37 ± 4.85	12.19 ± 4.87*	−0.18 ± 0.18	12.51 ± 4.64	12.36 ± 4.66*	−0.15 ± 0.11
Volume of abdominal cavity, cm^3	9502 ± 2976	9884 ± 2898***	+383 ± 374	9252 ± 2972	9621 ± 2910***	+370 ± 376
Volume of hernia sac, cm^3	457.8 ± 270.8	350.4 ± 226.7**	−107.3 ± 117.6	497.4 ± 271.2	385.9 ± 227.7***	−111.5 ± 118.4
Volume ratio, %	4.97 ± 3.55	3.70 ± 2.77**	−1.27 ± 1.08	5.59 ± 3.71	4.21 ± 2.88**	−1.38 ± 1.14

Note. The difference before and after BTA is statistically significant: * $p < 0.001$; ** $p < 0.01$; *** $p < 0.05$.

patients after BTA. The length of the hernial defect also changed, but this change was minimal.

According to E. B. Deerenberg et al., the lengthening of the muscles of the abdominal wall after BTA is from 2.5 to 4 cm, its thickness decreases by 6—10 mm, and the width of the hernial defect decreases to a maximum of 8.4 cm. The results obtained by us correspond to those of studies by other authors, even taking into account the use of a 2—3 times smaller dose of BTA (100 vs. 200—300 units) [5, 17, 21].

In both groups of patients, an increase in the volume of the abdominal cavity and a decrease in the volume of the hernial sac were observed after the administration of BTA. In patients with PVH, the volume of the abdominal cavity increased by an average of 382.6 ± 373.90 cm^3, and the volume of the hernia sac decreased by an average of 107.3 ± 117.6 cm^3, which was 4.5 % and 23.6 %, respectively, of the initial indicator. In patients with IH, the volume of the abdominal cavity increased by 369.6 ± 375.8 cm^3, and the volume of the hernia decreased by 111.5 ± 118.4 cm^3, which was 4.4 % and 21.4 %, respectively. According to A. Fafaj et al., the volume ratio (VR), which compares the volume of the hernia sac to the volume of the abdominal cavity, may have a prognostic value regarding the ability to close the fascial defect when suturing a large VH. At the same time, 25 % VR is the threshold, and with indicators below this value, the probability of complete closure of the hernia is high [7]. In our study, VR significantly decreased after BTA administration from 4.97 ± 3.55 % to 3.70 ± 2.77 % in patients with PVH and from 5.59 ± 3.71 % to 4.21 ± 2.88 % in patients with IH. It should be taken into account that the calculation of the volumes of the hernia and abdomen was performed on the basis of the obtained results of 3D modelling based on CT data Fig. 2. The examination was carried out in a state of rest and relaxation of the patient in a supine position, so it could not take into account the change in the size of the hernia and the abdominal cavity during muscle tension and when performing usual movements. Currently, there is no method in surgical practice that would allow simultaneous assessment of the real volumes of the above-mentioned structures at rest and standing, even without performing additional movements. Suggested by E. Y. Tanaka et al., the VR calculation method involved determining the volumes of the hernia and the abdominal cavity based on the sagittal, frontal, and vertical dimensions of these structures [16]. In our study, we used the calculation of volumes using a 3D model, which, in our opinion, is a more accurate method because it takes into account all the features and deformations of the hernia sac and abdominal cavity, but it is difficult and time-consuming to calculate by a radiologist. Therefore, we suggest using it as the method of choice for scientific research and not for routine use.

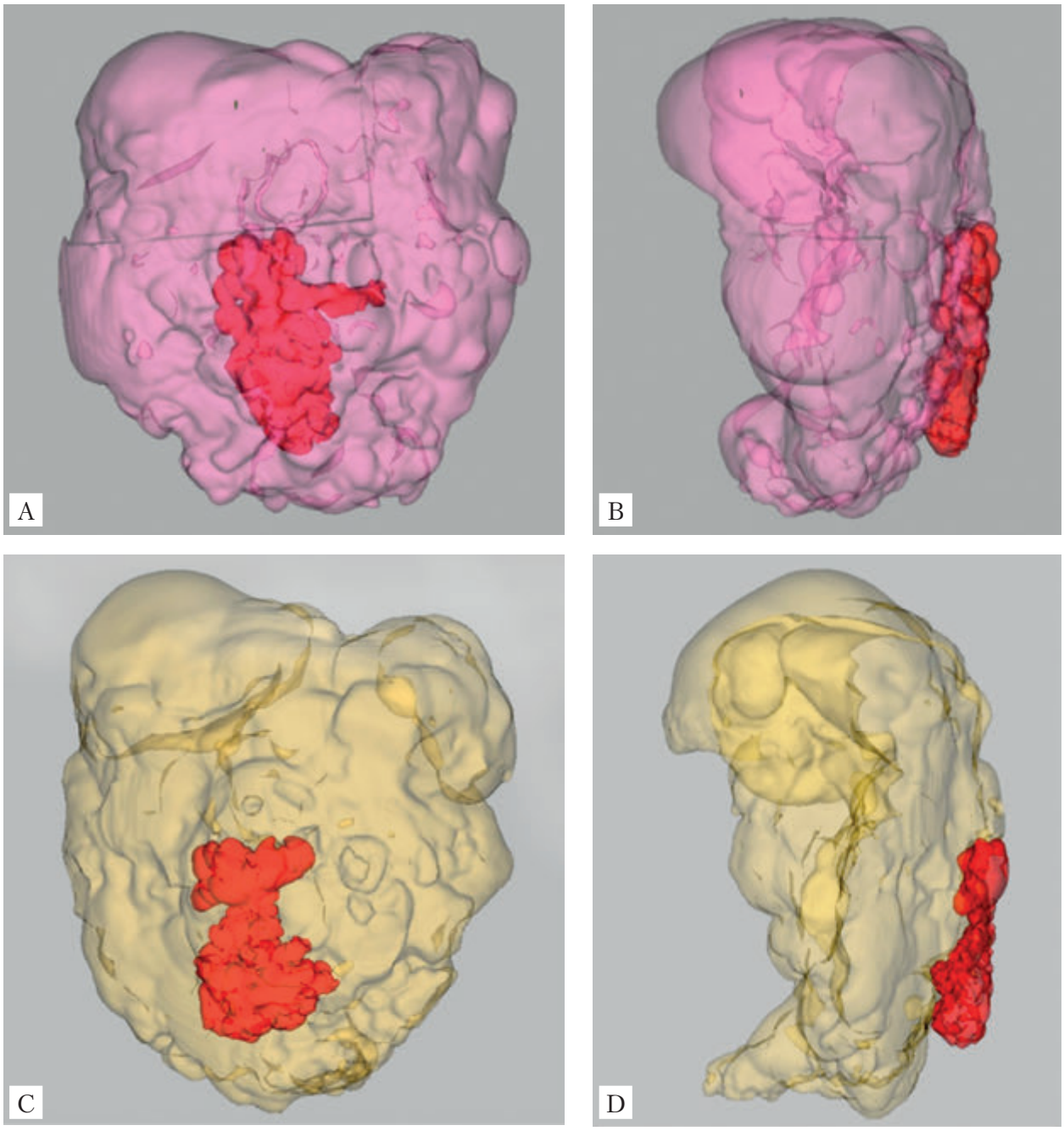

Figure 2. **3D modeling of the volumes of the patient's abdominal cavity and hernia sac (marked in red) based on the results of CT. Before BTA injection: direct (A) and side (B) projection; after BTA injection: direct (C) and side (D) projection**

It is also worth noting that the overall assessment of the effectiveness of the BTA injection technique can be technically difficult, as it requires the objectification of changes in the characteristics of the hernia and the abdominal cavity. Ultrasound does not allow for the evaluation of changes in the aforementioned indicators. The field of visualisation during ultrasound is limited by the characteristics of the linear sensor. In patients with large ventral hernias, the size of the hernial defect exceeds the length of the working surface of the sensor by several times. It is also impossible to evaluate the thickness of the muscles of the abdominal wall at comparable points before and after the introduction of BTA. Use of CT, including without intravenous contrast, allows to evaluate the parameters of the hernia and the abdominal wall in comparable sections. However, in order to evaluate changes in the volumes of the hernia sac and abdominal cavity, a radiologist must be able to use modelling tools to determine the volume of these structures. CT is a costly method that imposes a radiological burden on the patient. Therefore, in our

opinion, it can be used as a method of performance control at the initial stages of implementation of the BTA administration method but not as a routine research method. In our study, the BTA injection procedure was performed by one surgeon, ultrasound diagnostician, and CT assessment was performed by one expert radiologist in all patients.

After the introduction of BTA, all patients successfully underwent hernia repair without the separation of the anterior abdominal wall components. Currently, there is no unanimous opinion regarding the influence of BTA on the necessity of employing separation techniques. In some studies, this percentage increases compared to cases without BTA, while in others it varies widely from 14 to 57 %, without specifying the sizes of hernias included in the study or the presence of patients with loss of domain [5].

In 10 (15.2 %) cases, the hernial defect was open sutured, while in 56 (84.8 %) cases, it was addressed laparoscopically. The percentage of open hernioplasty was higher among patients with IH (17.9 %), compared to those with PVH (11.1 %), which may be due to the greater initial width of the hernial defect in patients with IH and its insufficient reduction for laparoscopic hernioplasty. Thus, out of 27 patients with PVH, 13 (48.2 %) had laparoscopic surgery using intraperitoneal onlay mesh technique (IPOM) and 11 (40.7 %) had laparoscopic IPOM+ with open aponeurosis defect suturing, and 3 (11.1 %) had open IPOM. Out of 39 patients with IH, 12 (30.8 %) had laparoscopic IPOM, 20 (51.3 %) had laparoscopic IPOM+ with open aponeurosis defect suturing, 4 (10.2 %) had open IPOM, and 3 (7.7 %) had open sublay hernia repair. Despite the development and variety of existing minimally invasive technologies for the treatment of uncomplicated primary ventral hernias, IPOM remains the go-to technique [20]. However, the use of laparoscopic IPOM in the case of surgical treatment of large size VH is not always possible, because when the width of the hernial defect is more than 10 cm, the tension between the edges of the aponeurosis increases and becomes excessive for reliable suturing of the hernia. According to the results of short- and long-term observations of M. Toffolo Pasquini et al., laparoscopic IPOM+ with open hernia suturing through a mini-access directly above the defect of the aponeurosis reduces recurrence and complications, compared to IPOM in patients with large hernias [18, 19]. Therefore, we consider it appropriate to use laparoscopic IPOM+ as an alternative to open surgery in patients with large ventral hernias, in which the width of the hernial defect has decreased to ≤ 10 cm after the introduction of BTA.

Our study's limitations include a small number of patients and a focus on evaluating the efficacy of a single dose of BTA. It is necessary to conduct further research on the introduction of BTA into different layers of the abdominal wall muscles via a single injection point, as well as the effectiveness of using different dosages of BTA, including the localisation of the introduction, with pronounced asymmetric deformations of the abdominal wall.

Conclusions

The administration of 100 units of botulinum toxin type A in the preoperative period consistently increases the length of the abdominal wall muscles, reduces the width of the hernial defect, and enhances the possibilities of further surgical treatment of large VH using laparoscopic technologies.

Declaration of interests

Authors have no conflicts of interest to declare.

Authors contributions

O. Y. Ioffe: work concept and design, critical review; T. V. Tarasiuk: work concept and design, data collection and analysis, statistical analysis, writing the manuscript; O. M. Chukanov: data collection and analysis; M. S. Kryvopustov: statistical analysis; O. P. Stetsenko: critical review.

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Оцінка ефективності та особливості методики введення ботулотоксину типу А при хірургічному лікуванні великих вентральних гриж

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Грижі передньої черевної стінки є однією з найпоширеніших хірургічних патологій у плановій та ургентній хірургії. Хірургічне лікування вентральних гриж великих розмірів (≥ 10 см) потребує застосування травматичних методик оперативного втручання для зведення країв грижового дефекту та відновлення цілісності передньої черевної стінки.

Мета — вивчити методику та ефективність застосування ін'єкцій ботулотоксину типу А (БТА) у м'язи передньої черевної стінки в пацієнтів із великими вентральними грижами в доопераційний період.

Матеріали та методи. Проведено проспективне когортне дослідження за участю 66 пацієнтів із великими вентральними грижами (первинними (ПВГ) та післяопераційними (ПОГ)). Усі пацієнти проходили лікування з червня 2017 р. до серпня 2024 р. та в доопераційний період отримали ін'єкції БТА 100 Од в м'язи передньої черевної стінки. Середній вік пацієнтів становив (58,98 ± 9,48) року. Чоловіків було 23 (34,8 %), жінок — 43 (65,2 %). Середня ширина грижового дефекту до введення БТА у пацієнтів із ПВГ становила (12,29 ± 1,93) см, у пацієнтів із ПОГ — (13,46 ± 2,06) см. Усім пацієнтам проведено оперативне втручання з приводу грижі через 4—5 тиж після ін'єкції БТА.

Результати. Ускладнень під час введення БТА та впродовж 4—5 тиж спостереження, до проведення оперативного втручання, не виявлено. Довжина м'язів передньої черевної стінки після ін'єкції з обох боків збільшилася в середньому на 1,7 см (мінімально — на 0,1 см, максимально — на 4,01 см). Ширина грижового дефекту зменшилася в середньому на (4,17 ± 0,68) см у пацієнтів із ПВГ та на (5,14 ± 0,75) см у пацієнтів із ПОГ ($p < 0{,}001$). Співвідношення об'ємів грижового мішка та черевної порожнини зменшилося після введення БТА з (4,97 ± 3,55) до (3,70 ± 2,77) % у пацієнтів із ПВГ ($p = 0{,}008$) та з (5,59 ± 3,71) до (4,21 ± 2,88) % у пацієнтів із ПОГ ($p = 0{,}008$).

Висновки. Введення БТА в дозі 100 Од у доопераційний період статистично значущо збільшує довжину м'язів черевної стінки, зменшує ширину грижового дефекту та розширює можливості подальшого хірургічного лікування великих вентральних гриж із використанням лапароскопічних технологій.

Ключові слова: післяопераційна грижа, вентральна грижа, герніопластика, ботулотоксин.

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Hemodynamic surgery of varicose veins of the lower extremities with the introduction of modern technologies

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Minimaly invasive and pathogenetically based methods are currently prevalent in phlebology, as they are in other fields of surgery. CHIVA (Cure conservatrice et hemodynamiy que de l'insuffisance veineuse en ambulatoire) hemodynamic surgery is one of these popular minimally invasive surgical procedures. The execution technique relies on the findings of a duplex ultrasound scan that is used to analyse the hemodynamics of the superficial venous network. The CHIVA strategy aims to preserve the venous material while also restoring normal distal venous pressure and venous function. However, this technique has a number of disadvantages, including the possibility of vein recanalisation and relapses, as well as the fact that the immediate cosmetic outcome is not always satisfactory.

Objective — to compare the outcomes of lower extremity varicose vein treatment based on the employed method: the CHIVA method executed via open surgery versus the CHIVA method combined with other minimally invasive methods (sclerotherapy, endovenous laser coagulation (EVLC)).

Materials and methods. A randomised prospective study was conducted on 52 patients with varicose veins of the lower extremities categorised as C1-C3 according to the CEAR classification. The patients were divided into 2 groups of 26 patients each, with one group undergoing the CHIVA procedure using the classic open technique, and the other group receiving a combination of CHIVA with EVLC and sclerotherapy. To evaluate the results, we used Hobb's criteria, measured the diameter of the great saphenous vein via ultrasound, analysed alterations in the Venous Clinical Severity Scoring (VCSS) , studied data from the Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ 20), and determined the incidence of relapses.

Results. After CHIVA and CHIVA+EVLC+ sclerotherapy, the normalisation of hemodynamics and interruption of the venous shunt led to a substantial reduction in the diameter of the great saphenous vein within 6 months after the operation ($p < 0.01$). Both groups had an improvement in VCSS 6 months after surgery. No statistical difference was observed between the treatment groups. All methods had a positive impact on the quality of life of patients, as shown by the CIVIQ 20 questionnaire. Of the 52 operated patients, there were 4 relapses (7.7 %). No relapses were noted in the group receiving CHIVA with EVLC and sclerotherapy ($p = 0.039$). As evaluated by Hobb's criteria, patients exhibited greater satisfaction with the outcomes of hemodynamic surgery combined with EVLC and sclerotherapy due to its better and faster aesthetic outcomes ($p = 0.012$ and 0.05).

Conclusions. All 52 patients exhibited favourable treatment outcomes, demonstrating a reduction in CVI symptoms during a comprehensive clinical assessment using ultrasound within 6 months and 1 year. The combination of CHIVA with EVLC and sclerotherapy showed distinct advantages in the treatment of varicose veins, yielding the most favourable cosmetic outcomes according to Hobb's criteria and achieving a reccurence rate of 0 %.

Keywords
chronic venous insufficiency, varicose veins, CHIVA, hemodynamic surgery, endovenous laser coagulation, sclerotherapy.

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Varicose veins in the lower extremities are a common manifestation of chronic venous insufficiency (CVI). The worldwide prevalence of varicose veins ranges from 5 % to 15 % among men and from 3 % to 29 % among women, depending on the age, sex, and ethnicity of the study population, survey methods, and how the disease is defined and measured [11, 20]. The spectrum of clinical manifestations of CVI

is huge, ranging from asymptomatic varicose veins and pigmentation to ulcers and scars. To identify, diagnose and treat CVI, it is necessary to understand the full spectrum of clinical manifestations, etiology and pathogenesis of the disease, as well as diagnostic methods [20]. Among diagnostic methods, the universally accepted gold standard is ultrasound with Doppler mapping [3, 6].

Minimally invasive techniques are prevalent not only in phlebology but in all areas of surgery. Currently, the method proposed by C. Franceschi in 1988 can claim the role of a less traumatic approach [5, 6]. The literature refers to the ambulatory conservative treatment of hemodynamic venous disorders (Cure conservatrice et hémodynamiy que de l'insuffisance veineuse en ambulatoire) as CHIVA. Unlike other operative methods of treating varicose veins, which are performed in accordance with an established protocol, the hemodynamic approach involves assessing individual venous hemodynamic characteristics using an ultrasound Doppler scan [3, 5]. Due to the complexity of such a personalised assessment, this technique is not very popular in our country. According to the literature, it is most often used in Italy and Spain, but recent publications show that this method is now being actively used in other countries throughout the world [2, 15, 21].

The CHIVA method is based on the concept of venous shunts, which are veins that divert venous blood from its normal flow, most often during muscle relaxation. The significance of the shunt is determined by the deflected flow, the starting point and the end point of the deflection [5]. The starting point is called the escape point and/or reflux point, while the endpoint is called the re-entry point (usually the re-entry perforator). There are several classifications of shunts. The most common is a type 1 shunt, which has an insufficient saphenofemoral junction as an escape point and a re-entrant perforator on the trunk of the great saphenous vein as the endpoint [10, 16].

The CHIVA strategy is conservative not only because it preserves venous material, which may be required for further arterial shunting, but also because it prevents the hemodynamic disorders associated with subcutaneous vein destruction [14]. Violation of the normal outflow of venous blood through superficial veins causes tissue damage, recurrence of varicose veins as a result of induced neoangiogenesis, and the formation of reticular varicose veins and telangiectasias in the areas of vein removal.This approach is hemodynamic because it restores normal distal venous pressure and venous function [2, 10]. Values are assigned to the adequate outflow of venous blood into the deep network. For this reason, limited venous interruptions are better than extensive ones, even if the immediate aesthetic outcomes are less satisfactory [19]. In fact, aesthetic outcomes improve over time, long-term outcomes are significantly better, and recurrences are far less common with fewer surgical interventions. However, any removal or occlusion of non-draining or redundant veins is not inconsistent with the CHIVA strategy [4, 13, 18].

Fragmentation of the venous pressure column and disconnection of venovenous shunts are usually performed by open surgery, but sclerotherapy (ST), endovenous laser coagulation (EVLC), or radiofrequency ablation may also be used. Only a few studies have compared the CHIVA method to other surgical approaches, mainly stripping [17]. Furthermore, there is insufficient research on the use of CHIVA principles in combination with other minimally invasive interventions and hardware techniques for varicose vein treatment [8, 12].

Objective — to compare the outcomes of lower extremity varicose vein treatment based on the employed method: the CHIVA method executed via open surgery versus the CHIVA method combined with other minimally invasive methods (sclerotherapy, endovenous laser coagulation (EVLC)).

Materials and methods

A prospective randomised controlled study included 52 patients. The majority of these patients were women — 38 (73.1 %).

The inclusion criteria:

1) the presence of varicose veins (C1-C3 class of varicose veins according to the CEAP classification);

2) age range: 18 to 65 years;

3) failure of the sapheno-femoral junction;

4) without previous surgical treatment in history;

5) patients with a capable deep venous system;

6) the patient's consent to participate in the study.

Exclusion criteria:

1) varicose vein complications (trophic ulcers, thrombophlebitis or phlebothrombosis, post-thrombophlebitic syndrome);

2) patients who previously underwent radical operations for varicose veins;

3) patients with severe concomitant pathology that may affect treatment course and outcome (diabetes, autoimmune diseases, oncological diseases, severe kidney, liver, heart system, and lung diseases);

4) patient refusal, lack of compliance regarding the use of compression therapy and its duration.

In addition to general clinical examinations, all patients underwent a duplex ultrasound scan (USDS) of the veins of the lower extremities in

the supine and standing positions, using the Paran and Valsalva tests, with detailed mapping of the hemodynamics of the lower extremities [3]. When conducting a detailed ultrasound, insufficiency of the saphenous-femoral junction and the re-entrant perforator on the trunk of the great saphenous vein was revealed in all patients. According to CHIVA terminology, patients had a type 1 shunt.

The study was conducted in accordance with the principles of the Declaration of Helsinki and the recommendations of the International Council for the Harmonisation of Good Clinical Practice.

The treatment method was chosen by randomising all patients into two groups of 26 patients each. The first group of patients was treated according to CHIVA's standard principles. These patients underwent an incision 3 cm below the inguinal fold and ligation of the sapheno-femoral junction, which served as the so-called «escape point». Drainage flow took place in the re-entry perforator on the great saphenous vein. Miniphlebectomy was used to remove varicose veins and nodes with no obvious anastomosis of discharge.

The second group included 26 patients whose hemodynamic picture was comparable to the first group. The CHIVA technique was used in combination with EVLC and sclerotherapy. This method involved an incision of up to 1.5 cm long at the saphenous-femoral junction, coagulation using EVLC of the proximal 7—10 cm of the great saphenous vein below the junction, and the injections of a foam sclerosant (1 % Ethoxysclerol) into venous branches of the 3—4 order, which lacked drainage anastomosis. These techniques were used to prevent recanalisation of the large subcutaneous vein in the proximal part, which is the most frequent cause of relapses after CHIVA with this type of shunt, and to ensure reliable closure of the tributaries of the great saphenous vein in the proximal part, thereby increasing the cosmetic outcome of the intervention by minimising the number of incisions necessary for miniphlebectomy.

All interventions were performed under local anesthesia with standard Klein's solution. In the case of combination with EVLC, Klein's solution was injected perivenously under ultrasound control [7]. In the post-procedural period, all patients received compression therapy, which included wearing medical compression stockings around the clock for the first three days, followed by daytime compression for the next three weeks.

The patients were thoroughly re-examined six months and a year after the intervention.

Relapse was considered the main endpoint of the study. During repeated visits, all patients underwent USDS of their lower extremity veins with detailed hemodynamic mapping. A recurrence was defined as the visible appearance of varicose veins in the intervention area, the restoration of reflux at the previously detected site, changes in the direction of blood flow through the saphenous-femoral junction, perforating veins or tributaries of the great saphenous vein. All relapses were divided into 5 hemodynamic types:

Relapse type 1 — relapse with resumption of reflux through the sapheno-femoral junction.

Relapse type 2 — restoration of reflux through the venous path that leaves the pelvis through veins located in the groin or perineum without restoration of the sapheno-femoral junction.

Relapse type 3 — restoration of reflux due to failed femoral perforating veins that were not detected during the initial procedure.

Relapse type 4 — restoration of reflux from the great saphenous vein to the tributaries of the second and third orders. This is the most typical type of relapse for the CHIVA method.

Relapse type 5 — varicose veins to a diameter of more than 5 mm in the area of intervention without «escape points», which can be detected by Doppler examination. This is a typical relapse with stripping and other interventions aimed at destroying the great saphenous vein and is atypical for CHIVA.

For objectification, the cross-sectional diameter of the great saphenous vein in the middle third of the thigh, approximately 20—25 cm from the saphenous-femoral junction, was determined in all patients during repeated USDS.

A score was calculated using Venous Clinical Severity Scoring (VCSS) (in accordance with the Clinical Practice Guidelines of the Society for Vascular Surgery and the American Venous Forum) [9].

Clinical evaluation of treatment outcomes after CHIVA and CHIVA modified methods was also carried out using Hobb's criteria, which were proposed by the authors of the method [5].

Hobb's criteria for evaluating the clinical outcome:

Objective criteria (assessed by a doctor)

Class A: no visible or palpable veins.

Class B: several visible or palpable veins less than 5 mm in diameter.

Class C: left or newly formed varicose veins with a diameter of more than 5 mm.

Class D: insufficiency of the main trunk of the great saphenous vein or perforator.

Subjective criteria (defined by the patient)

Class A: no complaints.

Class B: slight functional or cosmetic defect, but satisfied with the outome.

Class C: noticeable functional or cosmetic defect. Clinical evaluation of the outcomes as improvement, but dissatisfaction with the overall result.

Class D: complete absence of positive changes after treatment or worsening of the condition.

The treatment outcomes were classified into three groups:

- complete recovery (complete absence of varicose veins and symptoms of CVI);
- improvement (visible residual or newly formed varicose veins or nodes that have no or little clinical and hemodynamic significance);
- absence of positive changes (complete recurrence of varicose veins, recurrence of symptoms of CVI).

Satisfaction with treatment outcomes was also assessed using the Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ 20). In order to compare the average scores, the absolute scores were converted to a GIS index [1].

Statistical analysis

Statistical analysis was performed using Statistica 10 and MedStat. Data distribution normality was checked using the Shapiro-Uilk criterion. A comparison of the data between the groups was performed using the Wilcoxon two-sample test. Multiple comparisons were performed using the Rank Kruskal-Wallis test and Dunn's test, Scheeffe's method for multiple comparisons.

Results and discussion

Since hemodynamic interventions do not remove all varicose veins, the majority of research sources suggest that the CHIVA method produces superior long-term results than immediate ones. This impact is related to the time that is required for hemodynamic reconstruction of shunts. Therefore, the final outcomes were evaluated after half a year and a year of observation:

Recovery is the complete absence of varicose veins and CVI symptoms. Results after 6 months: CHIVA — 15 (57.7 %), CHIVA + EVLC + ST — 18 (69.2 %). Results after a year: CHIVA — 17 (65.4 %), CHIVA + EVLC + ST — 20 (76.9 %).

Improvements are visible residual or newly formed varicose veins or nodes that have no or little clinical and hemodynamic significance. Results after 6 months: CHIVA — 10 (38.5 %), CHIVA + EVLC + ST — 8 (30.8 %). Results after a year: CHIVA — 8 (30.8 %), CHIVA + EVLC + ST — 6 (23.1 %).

Without clinical changes — complete recurrence of varicose veins, presence of CVI symptoms. Results after 6 months: CHIVA — 1 (3.8 %), CHIVA + EVLC + ST — 0. Results after a year: CHIVA — 1 (3.8 %), CHIVA + EVLC + ST — 0.

A statistically significant difference between the groups was not found after half a year ($p = 0.348$) and after a year of observation ($p = 0.329$). The data show that any hemodynamic technique — standard or supplemented with modern technologies — provides a favourable clinical outcome.

Objective — data, including the diameter of the great saphenous vein in the middle third of the thigh, VCSS scale, and data obtained using CIVIQ 20 before treatment, 6 months and 1 year after surgery, are shown in Table 1.

Hemodynamic methods in classical execution, or supplemented by modern technologies, give a good clinical result. No statistically significant difference was found between the groups depending on the treatment method ($p > 0.05$). According to the data of the clinical assessment and the questionnaire, a statistically significant difference was found between the values before treatment and 6 months after treatment ($p < 0.01$). Normalisation of hemodynamics and interruption of the venous shunt leads to a significant decrease in the diameter of the great saphenous vein already 6 months after the operation ($p < 0.01$). There was no statistically significant difference in the indicators after 6 months and after a year.

Analysis of the data presented in Table 2 reveals that, based on the objective assessment, there was no statistically significant difference in clinical treatment outcomes between the CHIVA group and the

Table 1. **Data of objective examination methods before and after treatment**

Indicator	CHIVA			CHIVA + EVLC + ST		
	Before	After 6 months	After 1 year	Before	After 6 months	After 1 year
Diameter of the great saphenous vein, mm	7.3 ± 1.7	4.2 ± 0.9	3.9 ± 1.1	7.2 ± 1.9	4.1 ± 0.8	4.2 ± 1.3
VCSS, points	8.9 ± 2.4	1.3 ± 2.1*	1.5 ± 7.2*	8.5 ± 2.8	0.6 ± 0.9*	0.5 ± 1.2
CIVIQ 20 (GIS)	71.44 ± 8.67	97.6 ± 5.4	95.8 ± 8.7*	74.13 ± 8.75	98.8 ± 1.6*	99.3 ± 1.4

* $p < 0.01$ compared to data obtained before treatment.

Table 2. **Evaluation of clinical outcomes according to Hobb's criteria**

Class	After 6 months		After 1 year	
	CHIVA	CHIVA + EVLC + ST	CHIVA	CHIVA + EVLC + ST
Objective assessment				
A	14 (53.8 %)	18 (69.2 %)	16 (61.5 %)	20 (76.9 %)
B	8 (30.8 %)	8 (30.8 %)	5 (19.2 %)	6 (23.1 %)
C	2 (7.7 %)	0	4 (6.2 %)	0
D	1 (3.9 %)	0	1 (6.2 %)	0
Subjective assessment				
A	12 (46.2 %)	18 (69.2 %)	15 (68.8 %)	20 (76.9 %)
B	3 (11.5 %)	8 (30.8 %)	3 (11.5 %)	6 (23.1 %)
C	10 (38.4 %)	0	7 (26.9 %)	0
D	1 (3.8 %)	0	1	0

CHIVA group supplemented with additional technologies after 6 months ($p = 0.147$) and after one year ($p = 0.131$), respectively. A statistically significant change was seen after 6 months ($p = 0.012$) and after a year ($p = 0.05$) based on the subjective assessment. Therefore, patients expressed more satisfaction with the outcomes of hemodynamic surgery supplemented with EVLC and sclerotherapy because it provided better and faster aesthetic outcomes.

There were 4 relapses (7.7 %) among 52 operated patients, indicating a favourable outcome. No recurrence was seen in the group receiving CHIVA in combination with EVLC and ST ($p = 0.039$).

All relapses were classified into hemodynamic types. Relapses of type 2 and type 5 were not detected. There were 2 cases of type 4 relapses, one case of type 1 relapse with restoration of reflux through the sapheno-femoral junction, and one case of type 3 relapse.

Currently, there is a shift in the methodology of surgical intervention for varicose veins from radical techniques to minimal and justified procedures, supported by the principles of minimally invasive and outpatient surgery. The use of USDS, which allows for comprehensive mapping of varicose veins, facilitates the identification of the sources and prevalence of venous reflux, as well as hemodynamic correction options for each type of lesion [2, 4, 22]. Now in the arsenal of surgeons, there is a sufficient number of minimally invasive methods that can be used to achieve this goal. The combination of minimally invasive technologies with a hemodynamic approach provides optimal cosmetic outcomes by reducing both the number and length of incisions. Varicose vein sclerotherapy, combined with CHIVA, improves immediate cosmetic outcomes. Ablation of the proximal part of the great saphenous vein effectively facilitates reliable closure of the confluence of many tributaries and prevents recanalisation, thereby significantly impacting the incidence of relapses [8].

Conclusions

Hemodynamic methods, including standard CHIVA or CHIVA supplemented with modern technologies such as EVLC and sclerotherapy, ensured favourable clinical outcomes. Clinical assessment and questionnaire data revealed a statistically significant difference between values before treatment and 6 months after treatment ($p < 0.01$). The normalisation of hemodynamics and interruption of the venous shunt led to a substantial reduction in the diameter of the great saphenous vein within 6 months after the operation ($p < 0.01$).

According to Hobb's criteria, no statistically significant difference was observed between the treatment groups on the objective assessment scale. However, a statistically significant difference was noted on the subjective assessment scale after 6 months ($p = 0.012$) and after a year ($p = 0.05$) due to the fact that the patients achieved better and faster aesthetic outcomes.

Hemodymic procedures resulted in a low incidence of varicose vein relapses, with just 7.7 % reported among all patients. Notably, no recurrences were observed in the group when CHIVA was combined with EVLC and sclerotherapy ($p = 0.039$).

The study found that no approach has a clear advantage over others. It is important to select the optimal technique for each patient based on their venous system's haemodynamics, technical and economic capabilities, and desire for a quick cosmetic outcome.

Declaration of interests

The authors have no conflicts of interest to declare.

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Ethics approval and written informed consent statements

The assessment and usage of all clinical data was approved and permitted before the study by the ethics committee of

Bogomolets National Medical University. The study protocol conformed to the ethical guidelines of the «World Medical Association (WMA) Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects» adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, South Korea, October 2008. Written informed consent was obtained from all individual participants included in the study.

Authors contributions

I. V. Kolosovych: work concept and design, critical review; K. O. Korolova: work concept and design, data collection and analysis, statistical analysis, writing the manuscript.

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Гемодинамічна хірургія варикозного розширення вен нижніх кінцівок із застосуванням сучасних технологій

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Нині у флебології, як і в інших галузях хірургії, трендовими є малоінвазивні та патогенетично обґрунтовані методики. Гемодинамічна хірургія CHIVA є малоінвазивною хірургічною процедурою. Техніка виконання ґрунтується на результатах ретельного аналізу гемодинаміки поверхневої венозної мережі за допомогою дуплексного сканування. Стратегія CHIVA спрямована на збереження венозного матеріалу, а також на відновлення правильного дистального венозного тиску та правильної венозної функції. Проте ця методика має низку недоліків, зокрема ризики реканалізації вен та рецидивів, а також не завжди дає задовільний безпосередній косметичний результат.

Мета — порівняти результати лікування варикозної хвороби нижніх кінцівок залежно від використаного методу лікування: CHIVA за допомогою відкритої операції або CHIVA у комбінації з іншими малоінвазивними методиками (склеротерапія, ендовенозна лазерна коагуляція (ЕВЛК)).

Матеріали та методи. У дослідження було залучено 52 пацієнти з варикозною хворобою нижніх кінцівок, С1–С3 клас за CEAP класифікацією. Пацієнтів розподілили на дві однакові за кількістю групи, в одній виконано CHIVA за класичною відкритою методикою, в іншій застосовано комбінацію CHIVA з ЕВЛК та склеротерапією. Для оцінки результатів використовували критерії Хобса, визначення діаметра великої підшкірної вени за допомогою ультразвукового дослідження, оцінку за шкалою Venous Clinical Severity Scoring (VCSS), дані опитувальника Chronic Venous Insufficiency quality of life Questionnaire (CIVIQ 20), кількість рецидивів.

Результати. Після CHIVA та CHIVA+ЕВЛК+склеротерапія нормалізація гемодинаміки та переривання венозного шунта сприяла суттєвому зменшенню діаметра великої підшкірної вени вже через 6 міс після операції ($p < 0,01$). В обох групах зареєстровано поліпшення оцінки за VCSS через 6 міс після операції. Статистично значущої різниці між групами не виявлено. Обидві стратегії позитивно впливали на якість життя пацієнтів за опитувальником CIVIQ 20. Зареєстровано лише 4 (7,7 %) рецидиви (усі в групі CHIVA) ($p = 0,039$). Пацієнти були більше задоволені результатами гемодинамічної хірургії, доповненої ЕВЛК та склеротерапією, при оцінці за суб'єктивними критеріями Хобса, оскільки застосування такої стратегії дало кращий і швидший естетичний результат ($p = 0,012$ та $p = 0,05$).

Висновки. Хороший результат лікування зі зменшенням симптомів хронічної венозної недостатності при комплексній клінічній оцінці з використанням ультразвукового дуплексного сканування через 6 міс та 1 рік зареєстрували в усіх пацієнтів. Комбінація CHIVA з ЕВЛК та склеротерапією мала переваги: найбільша косметичність за суб'єктивними критеріями Хобса та відсутність рецидивів (0 %).

Ключові слова: хронічна венозна недостатність, варикозне розширення вен, CHIVA, гемодинамічна хірургія, ендовенозна лазерна коагуляція, склеротерапія.

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Efficacy of the ERAS strategy in patients with type III–IV paraesophageal hernias

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ERAS (Enhanced Recovery After Surgery) protocols have demonstrated efficacy across numerous surgical specialties; however, their effectiveness has not been evaluated in patients with paraesophageal hernias (PEH).

Objective — to determine the efficacy of the ERAS strategy in patients with type III—IV PEH undergoing laparoscopic surgery.

Materials and methods. The study was conducted at the Department of General Surgery No 2 of Bogomolets National Medical University from 2017 to 2023, involving 114 patients who underwent laparoscopic hernioplasty for Type III—IV PEH. The ERAS strategy was applied in 96 patients (main group — Group M) and not applied in 18 patients (comparison group — Group C). The efficacy of the ERAS protocol was evaluated by comparing average hospital stay, hunger, thirst, general weakness, and depression levels using a 10-point visual analogue scale (0 = «no concern,» 10 = «severe concern»), as well as the frequency of nausea, vomiting, abdominal distention, passage of gas, and bowel movement within the first postoperative day.

Results. Group M showed lower average scores for «general weakness», «hunger», and «thirst» by factors of 1.43, 1.35, and 1.34, respectively, compared to Group C. The application of the ERAS protocol positively influenced bowel function recovery: on the first postoperative day, the proportion of patients with gas passage was higher in Group M than in Group C (78.1 % vs. 55.6 %), while the incidence of abdominal distention was lower (2.1 % vs. 16.7 %). Bowel movement was observed in 51.0 % of patients in Group M compared to 27.8 % in Group C. These positive outcomes associated with the ERAS protocol contributed to a reduced average hospital stay of 1.72 ± 0.76 days compared to 2.33 ± 0.91 days in the control group.

Conclusions. The use of the ERAS protocol in patients undergoing laparoscopic surgery for type III—IV paraesophageal hernia demonstrated significant advantages in the early postoperative period. Patients reported significantly less «general weakness», «feeling of hunger», and «feeling of thirst» compared to the control group. Improved bowel function recovery was recorded, evidenced by a higher proportion of patients with gas passage and bowel movements and a significantly lower proportion of patients with abdominal distension, as well as a reduced average length of hospital stay. The obtained results confirm the feasibility of implementing the ERAS protocol to improve postoperative recovery and reduce postoperative complications in patients with type III—IV paraesophageal hernia.

Keywords
type III—IV paraesophageal hernia, surgical treatment, laparoscopic approach, ERAS protocol, outcomes.

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The ERAS (Enhanced Recovery After Surgery) protocol is a modern approach to perioperative patient management aimed at accelerating recovery, reducing complications, and shortening hospital stay duration [8, 10, 16, 20]. This protocol includes a series of evidence-based strategies and recommendations to optimize all aspects of surgical care [7, 22, 18].

ERAS protocols were developed by a group of European surgeons in 2001 [4]. The main aspects of the concept include a multidisciplinary team working with the patient, a multimodal approach to addressing issues that delay recovery and cause complications, an evidence-based approach to protocols, and changes in management utilizing interactive and continuous feedback [9].

The ERAS strategy has been implemented as a primary focus in the care of surgical patients across all stages of treatment (in outpatient clinics, preoperative departments, operating rooms, postoperative recovery departments, and wards).

ERAS protocols have proven effective in many surgical specialties, including in the surgical treatment of giant ventral hernias [5], colorectal surgery [1, 11], pancreatic surgery [14], gynecology [2, 15], urology [17], bariatric surgery [19], and others. They contribute to better treatment outcomes, reduce complications, and shorten hospital stays, which decreases overall healthcare costs. However, the effectiveness of the ERAS strategy has not been evaluated for patients with paraesophageal hernias (PEH), who are characterized by a higher average age, a greater prevalence of chronic vascular, heart, lung, kidney, and gastrointestinal diseases, and, in most cases, excess body weight and obesity.

Objective — to determine the effectiveness of the ERAS strategy in patients with type III—IV PEH who underwent laparoscopic surgery.

Materials and methods

The study was conducted at the Department of General Surgery No 2 of Bogomolets National Medical University from 2017 to 2023, involving 114 patients who underwent laparoscopic hernioplasty for type III—IV PEH. The ERAS strategy was applied in 96 patients (main group).

The following measures were included in the main principles of the ERAS protocol for patients with PEH:

- informing the patient about the specifics of the surgical procedure, postoperative period, and dietary behavior after surgery;
- use of minimally invasive methods (laparoscopic access);
- avoidance of mechanical bowel cleansing;
- pain prevention using multimodal analgesia (Table 1) and local infiltration anesthesia in the area of trocar access points;
- gastroprotection using proton pump inhibitors;
- absence of abdominal cavity drainage;
- reduction of stress response through the use of glucocorticoids;
- prevention of infectious complications (antibiotic prophylaxis, antiseptic washing of trocar wounds);
- prevention of thromboembolic complications (LMWH);
- early patient mobilization — verticalization within 1—2 h after surgery;
- prevention of nausea and vomiting, particularly through the planned administration of ondansetron on the first postoperative day;
- nutrition: intake of a carbohydrate mixture 2 h before surgery and postoperative sipping 6 h after;
- discharge from the hospital at the earliest possible time.

Before surgery. No later than 2 h before the operation, all patients received 200 ml of warm, boiled water with 5 g of glucose to:

- reduce the preoperative fasting period, as well as feelings of hunger and thirst;
- alleviate preoperative anxiety;

Table 1. **Multimodal anesthesia scheme for patients with type III—IV Paraesophageal hernias**

Time of administration, duration	Drug	Dosage, route of administration
30—45 min before surgery	Atropine	0.5—1.0 mg intramuscularly
	Dimedrol	10 mg intramuscularly
	Acetaminophen	1000 mg IV over 15 min
20 min before tracheal intubation	Dexamethasone	8 mg intravenously
After tracheal intubation to the first incision	Bupivacaine 0.25 %	10—30 ml local infiltration anesthesia
During surgery	Sevoflurane	Inhalation, 1 L/min
20—30 min before the end of surgery	Acetaminophen	1000 mg intravenously
After surgery		
1st—3rd day	Acetaminophen	1000 mg intravenously 4 times daily
1st—3rd day	Dexketoprofen	50 mg intravenously as needed
5 days	Diclofenac	50—100 mg once daily rectally
1st—2nd day (for high-intensity pain)	Nalbuphine	10—20 mg intravenously

• decrease the risk of postoperative insulin resistance;
• avoid anesthesia-related risks (regurgitation), as this amount of liquid completely leaves the stomach within 2 hours;
• enhance the anabolic effect in the early postoperative period by reducing postoperative nitrogen loss and protein depletion, as well as maintaining postoperative body weight and muscle function.

In the early postoperative period, 2 hours after extubation, the patient begins to drink water, and after 6 hours, postoperative sipping is initiated (the patient was given a protein mixture of 125 ml). This mixture is high in protein — 18 g per 125 ml — and has a high caloric value of 306 kcal per 125 ml. It also contains vitamins and trace elements (including selenium, chromium, etc.), is fiber-free, and is gluten-free.

Criteria for evaluating treatment outcomes

The effectiveness of ERAS protocol implementation was evaluated based on the average length of hospital stay and the total score according to the Clavien-Dindo classification, as well as feelings of hunger, thirst, general weakness, and depression, assessed on a 10-point visual analogue scale (0 points — «does not bother», 10 points — «bothers significantly»). Additional factors included the frequency of nausea, vomiting, abdominal distension, gas passage, and the presence of bowel movements on the first postoperative day.

Basic methods of mathematical statistics were used for statistical analysis of the study results: descriptive statistics and paired comparisons. Distribution normality was checked for deviations using the Shapiro-Wilk test (when $n < 30$) or the Pearson chi-square test (when $n \geq 30$). For paired comparisons, parametric tests (Student's t-test and Fisher's F-test) were applied if the distribution was normal; if the distribution differed from normal, a non-parametric test (Mann-Whitney U test) was used. The Pearson chi-square test was applied to compare frequencies of qualitative variables, with a significance level of < 0.05.

For quantitative indicators, the arithmetic mean (M) and standard deviation (± SD) were used, and for qualitative indicators, percentages were reported. Statistical analysis was performed using IBM SPSS Statistics 22.

Results

Patients in groups O and P did not differ statistically significantly in terms of average age, body mass index (BMI), gender, nature, and frequency of complaints (Table 2).

Table 2. **Characteristics of patients in groups**

Indicator	Comparison group (n = 18)	Main group (n = 96)
Average age, years	50.3 ± 11.9	54.1 ± 10.1
Men Women	44.4 % 55.6 %	35.4 % 64.6 %
BMI, kg/m^2	26.5 ± 2.8	27.4 ± 2.7
Disease duration, months	58.9 ± 40.6	59.3 ± 53.7
Heartburn	9 (50.0 %)	51 (53.1 %)
Chest pain	10 (55.6 %)	40 (41.7 %)
Belching	6 (33.3 %)	41 (42.7 %)
Nausea	9 (50.0 %)	55 (57.3 %)
Hoarseness	12 (66.7 %)	45 (46.9 %)
Cough	7 (38.9 %)	24 (25.0 %)
Dysphagia	5 (27.8 %)	32 (33.3 %)
Hiccups	2 (11.1 %)	21 (21.9 %)
Odynophagia	3 (16.7 %)	13 (13.5 %)
Vomiting	3 (16.7 %)	19 (19.8 %)
Feeling of fullness after eating	5 (27.8 %)	36 (37.5 %)
Weight loss	3 (16.7 %)	25 (26.0 %)
Shortness of breath	5 (27.8 %)	28 (29.2 %)

Note. All $p > 0.05$.

One or more comorbidities were present in 124 (79.0 %) patients, including 14 (77.8 %) in group P and 78 (81.3 %) in group O ($p = 0.732$), (Table 3).

There were no statistically significant differences between the study groups regarding the nature and frequency of individual comorbidities (all $p > 0.05$).

No statistically significant differences were also found between the groups in instrumental study indicators (Table 4).

According to intraoperative data, the mean values of the area and width of the esophageal hiatus (EH) were greater in patients in the main group (Table 5).

In the main group, cruroplasty was performed in 25 (26.0 %) patients, cruroplasty reinforcement with a mesh implant in 71 (74.0 %); Nissen fundoplication was performed in 79 (82.3 %) patients, and Toupet fundoplication in 17 (17.7 %). In all cases, patients in group P underwent cruroplasty and Nissen fundoplication.

During the perioperative period, patients in the main group had a statistically significantly lower frequency of complications of grade I and

Table 3. **Nature and Frequency of comorbidities in groups**

Indicator	Comparison group (n = 18)	Main group (n = 96)
Ischemic heart disease	9 (50.0 %)	41 (42.7 %)
Heart failure	7 (38.9 %)	38 (39.6 %)
I degree	5 (71.4 %)	28 (73.7 %)
IIA degree	2 (18.6 %)	10 (26.3 %)
Heart rhythm disorders	4 (22.2 %)	34 (35.4 %)
Hypertension	9 (57.4 %)	50 (52.1 %)
I stage	3 (33.3 %)	10 (20.0 %)
II stage	6 (66.7 %)	40 (80.0 %)
Overweight	10 (55.6 %)	66 (68.8 %)
Obesity	2 (11.1 %)	10 (10.4 %)
Chronic bronchitis	7 (38.9 %)	38 (39.6 %)
Chronic obstructive pulmonary disease	2 (11.1 %)	14 (14.6 %)
A stage	1 (50.0 %)	8 (57.1 %)
B stage	1 (50.0 %)	6 (42.9 %)
Feeling of fullness after eating	5 (27.8 %)	36 (37.5 %)
Weight loss	3 (16.7 %)	25 (26.0 %)
Shortness of breath	5 (27.8 %)	28 (29.2 %)

Note. All p > 0.05.

Table 4. **Main Indicators of endoscopic and radiological studies**

Indicator	Comparison group (n = 18)	Main group (n = 96)
Endoscopic examination		
Esophagitis	13 (72.2 %)	58 (60.4 %)
Erosive esophagitis, stage*	9 (50.0 %)	53 (55.2 %)
A	3 (33.3 %)	6 (11.3 %)
B	3 (33.3 %)	21 (36.9 %)
C	2 (22.2 %)	20 (37.7 %)
D	1 (11.1 %)	6 (11.3 %)
Erosive gastritis	5 (27.8 %)	19 (19.8 %)
Duodenal ulcer	1 (5.6 %)	8 (8.3 %)
Radiological examination		
Reducibility		
Irreducible hernia	14 (77.8 %)	80 (83.3 %)
Partially reducible hernia	4 (22.2 %)	16 (16.7 %)
Hernia volume		
Cardiofundal	11 (61.1 %)	66 (68.8 %)
Subtotal	7 (38.9 %)	27 (28.1 %)
Total gastric	0	3 (1.6 %)
Hernia		
III type	17 (94.4 %)	87 (90.6 %)
IV type	1 (5.6 %)	9 (9.4 %)

Note. All p > 0.05.
* Los Angeles classification.

Table 5. **Results of intraoperative measurement of EH parameters**

EH Parameters	Comparison group (n = 18)	Main group (n = 96)
Area, mm^2	86.8 ± 18.2 (53—161)	95.6 ± 23.2 (51—212)*
Width, mm	29.3 ± 3.3 (24—38)	31.1 ± 3.7 (24—43)*
Length, mm	54.8 ± 5.4 (46—65)	54.9 ± 7.0 (44—74)

Note. Minimum and maximum values are shown in parentheses.
* p < 0.05.

II according to the Clavien-Dindo classification (p = 0.009), with no grade III or IV complications observed in either group (Table 6).

On the first day after surgery, there was a significant difference between the groups in several studied indicators. The application of the ERAS protocol improved the perioperative period. Specifically, a statistically significant difference was found in the assessment of such important parameters as «feeling of hunger» and «feeling of weakness», which are factors that hinder the quick restoration of patients' quality of life after surgery and negatively impact the duration of hospital stay. In the main group, there was a higher proportion of patients with low scores on these indicators and a lower proportion with high scores (Fig. 1, 2). In this group, the average scores for «general weakness» and «feeling of hunger» were lower than in group P by 1.43 times (2.41 ± 0.67 and 3.44 ± 1.09 points) and 1.35 times (3.13 ± 1.3 and 4.22 ± 1.26 points), respectively (Table 7).

The patients in both groups also showed a statistically significant difference (p = 0.001) in the distribution of the «feeling of thirst» score. In the main group, there was a higher proportion of patients with low3 scores and a lower proportion with high scores (Fig. 3), and the average score for this parameter was 1.34 times lower than in group P (1.51 ± 0.38 and 2.11 ± 0.90 points) (see Table 7).

Table 6. **Distribution of patients in study groups by complication grade according to the Clavien-Dindo classification [3]**

Complication	Comparison group (n = 18)	Main group (n = 96)
Total	5 (27.8 %)	7 (7.3 %)*
I grade		
Myocardial ischemia episode (intraoperative)	1 (5.6 %)	1 (1.0 %)
Intraoperative episode of systolic blood pressure drop < 70 mm Hg	1 (5.6 %)	2 (2.0 %)
Bundle branch block	1 (5.6 %)	1 (1.0 %)
Paroxysm of atrial fibrillation	1 (5.6 %)	2 (2.0 %)
II grade		
Exudative pleuritis not requiring drainage	1 (5.6 %)	1 (1.0 %)

Note. * The difference in indicators is statistically significant (p = 0.009).

Table 7. **Comparative characteristics of survey results on the first postoperative day in the study groups**

Indicator	Comparison group (n = 18)	Main group (n = 96)
General weakness, points	3.44 ± 1.09	2.41 ± 0.67*
Feeling of hunger, points	4.22 ± 1.26	3.13 ± 1.30*
Feeling of thirst, points	2.11 ± 0.90	1.51 ± 0.38*
Gas passage	10 (55.6 %)	75 (78.1 %)**
Bowel movement	5 (27.8 %)	49 (51.0 %)
Abdominal distension	3 (16.7 %)	2 (2.1 %)**F
Nausea/vomiting	2 (11.1 %)	3 (3.1 %)

Note. * p = 0.001; ** p < 0.05. F Fisher's exact test.

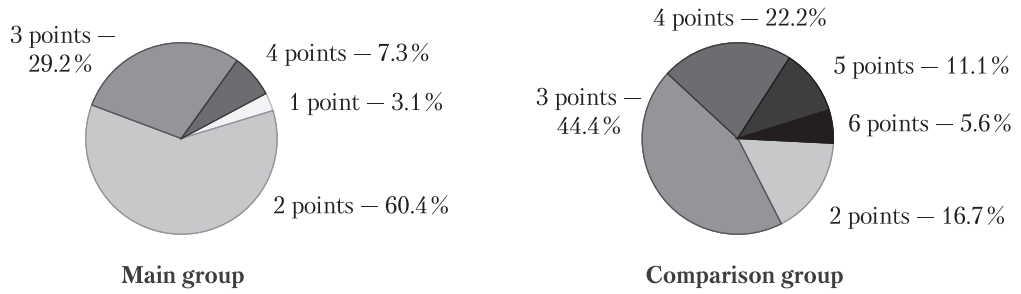

Figure 1. **Distribution of patients by general weakness score (p = 0.001)**

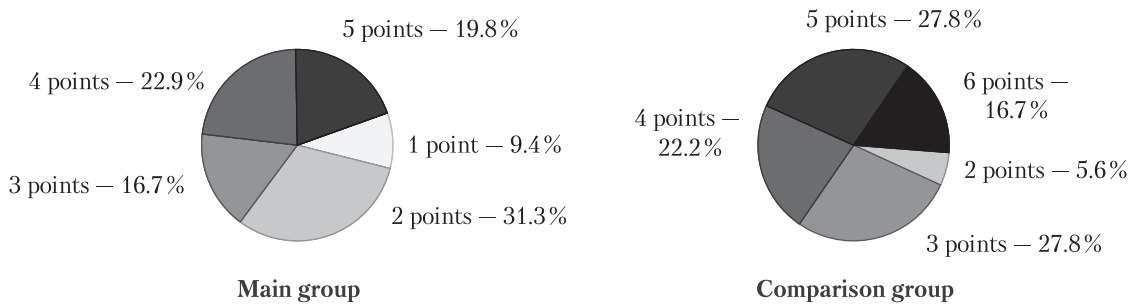

Figure 2. **Distribution of patients by hunger score (p = 0.001)**

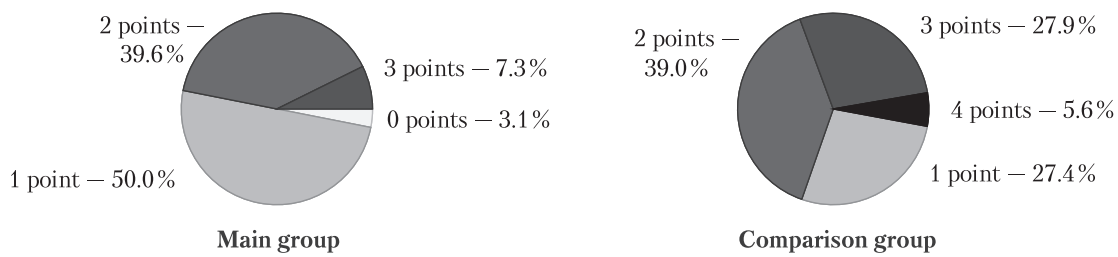

Figure 3. **Distribution of patients by thirst score (p = 0.001)**

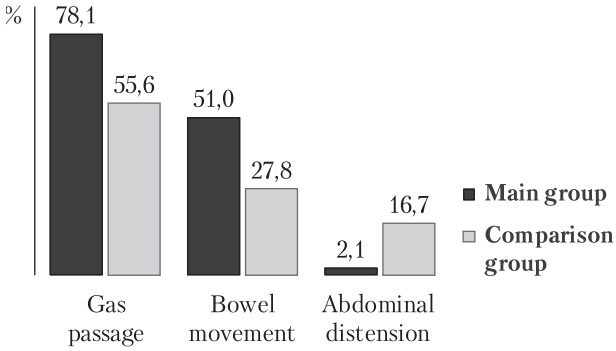

Figure 4. **Frequency of indicators characterizing bowel function recovery**

The use of the ERAS protocol in patients of the main group also had a positive impact on indicators characterizing the recovery of bowel function. In this group, on the first postoperative day, there was a higher proportion of patients who experienced gas passage — 78.1 % compared to 55.6 % ($p = 0.044$), bowel movement — 51.0 % compared to 27.8 % ($p = 0.070$), and a lower proportion of patients with abdominal distension — 2.1 % compared to 16.7 % ($p = 0.027$) (Fig. 4).

The positive effects of the ERAS protocol contributed to a reduction in the average length of hospital stay in the main group (1.72 ± 0.76 days) compared to group P (2.33 ± 0.91 days, $p = 0.003$).

Discussion Over the last decade, Enhanced Recovery After Surgery (ERAS) protocols have gained significant popularity due to their effectiveness in optimizing treatment outcomes [18, 20]. Currently, there are 24 core elements of patient care in the ERAS protocol, all supported by scientific evidence. In recent years, there has been a growing body of research dedicated to the application of ERAS protocol principles in the surgical treatment of abdominal diseases [1, 6, 14, 15, 19, 21], but there is a lack of data on their use in the surgical treatment of paraesophageal hernias (PEH).

The success of PEH repair depends on multiple factors (choice of access, use of mesh in cruroplasty, method of fundoplication, surgical technique). In addition to these surgeon-dependent factors, preoperative and postoperative care factors also significantly influence treatment outcomes. Patients with PEH often have excess body weight (in our study, the average body mass index in the main group was 27.4 ± 2.7 kg/m^2) and a high prevalence of chronic diseases: ischemic heart disease (42.7 %), cardiac arrhythmias (35.4 %), hypertension (52.1 %), chronic bronchitis (39.6 %), chronic obstructive pulmonary disease (14.6 %), erosive esophagitis (55.2 %), erosive gastritis (19.8 %), etc. This creates significant potential for improving outcomes by optimizing adverse factors in PEH patients prior to elective surgery.

Our study focused on assessing the effectiveness of ERAS strategy in the early postoperative period despite the fact that its philosophy aims not only at short-term goals, such as reducing hospital stay duration, but also at patient recovery in the long-term postoperative period.

To minimize the impact of open surgical access, only patients who underwent laparoscopic surgery were included in the study. On the first postoperative day, patients treated according to the ERAS protocol recorded significantly lower average scores for «general weakness», «feeling of hunger», and «feeling of thirst» (1.43, 1.35, and 1.34 times lower, respectively) compared to patients in the control group.

In addition, the use of the ERAS protocol had a positive impact on the recovery of bowel function: on the first postoperative day, the proportion of patients with gas passage was higher—78.1 % versus 55.6 %, bowel movement was observed in 51.0 % versus 27.8 %, and the proportion of patients with abdominal distension was lower—2.1 % versus 16.7 %.

These positive effects of the ERAS protocol contributed to a reduction in the average hospital stay to 1.72 ± 0.76 days compared to 2.33 ± 0.91 days in the control group.

Conclusions

The use of the ERAS protocol in patients undergoing laparoscopic surgery for type III—IV PEH demonstrates significant advantages in the early postoperative period, specifically with patients reporting significantly less «general weakness», «feeling of hunger», and «feeling of thirst» compared to the control group. Additionally, there were better indicators of bowel function recovery, as evidenced by a higher proportion of patients with gas passage and bowel movement and a significantly lower proportion of patients with abdominal distension.

The positive effects of the ERAS protocol contributed to a reduced average hospital stay.

The results obtained confirm the feasibility of implementing the ERAS protocol to improve postoperative recovery and reduce postoperative complications in patients with type III—IV PEH.

Declaration of interests

The authors declare no conflict of interest.

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Authors contributions

Concept and design of the study — O. Y. Ioffe, T. A. Tarasov; data collection and analysis — O. P. Stetsenko, T. A. Tarasov; statistical analysis — L. Y. Markulan, T. A. Tarasov; manuscript writing— O. P. Stetsenko, T. A. Tarasov; critical review — O. Y. Ioffe, L. Y. Markulan, T. A. Tarasov.

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Ефективність стратегії ERAS у хворих з параезофагеальними грижами III—IV типу

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ERAS (Enhanced Recovery After Surgery)-протоколи довели ефективність у багатьох хірургічних спеціальностях, але її не було оцінено для хворих з параезофагеальними грижами (ПЕГ).

Мета — визначити ефективність стратегії ERAS у хворих із ПЕГ III—IV типу, яким проведено лапароскопічне втручання.

Матеріали та методи. Дослідження проведено на базах кафедри загальної хірургії № 2 Національного медичного університету імені О. О. Богомольця в 2017—2023 рр. із залученням 114 хворих, яким було виконано лапароскопічну герніопластику з приводу ПЕГ III—IV типу. У 96 хворих застосували стратегію ERAS (основна група — група О)), у 18 — не застосовували (група порівняння — група П)). Оцінку ефективності впровадження ERAS-протоколу проводили за середніми значеннями ліжко-дня, відчуттям голоду, спраги, загальної слабкості, депресії за 10-бальною візуальною аналоговою шкалою (0 балів — «не турбує», 10 балів — «сильно турбує»), частотою нудоти, блювання, здуття живота, відходження газів, наявністю випорожнення в першу добу після операції.

Результати. В групі О зареєстрували середні бали за показниками «загальна слабкість», «відчуття голоду» та «відчуття спраги», які були відповідно в 1,43, 1,35 та 1,34 разу меншими порівняно з такими в групі П. Застосування ERAS-протоколу позитивно вплинуло на відновлення функцій кишечника: в першу добу після операції частка пацієнтів із відходженням газів була більшою, ніж у групі П (78,1 та 55,6 % відповідно), а частка пацієнтів зі здуттям живота — меншою (2,1 і 16,7 %), випорожнення кишечника зафіксували в 51,0 та 27,8 % пацієнтів відповідно. Ці позитивні ефекти використання ERAS-протоколу сприяли скороченню середнього терміну перебування в стаціонарі до (1,72 ± 0,76) доби порівняно з (2,33 ± 0,91) доби у контрольній групі.

Висновки. Застосування ERAS-протоколу в пацієнтів, яким виконували лапароскопічні операції з приводу ПЕГ типу III—IV, продемонструвало значні переваги в ранній післяопераційний період. Пацієнти відзначили значно менше «загальної слабкості», «відчуття голоду» та «відчуття спраги» порівняно з контрольною групою. Зареєстровано кращі показники відновлення функцій кишечника, про що свідчила більша частка пацієнтів із відходженням газів і випорожненням кишечника та значно менша частка пацієнтів зі здуттям живота, а також зменшення середньої тривалості перебування в стаціонарі. Отримані результати підтверджують доцільність впровадження ERAS-протоколу для поліпшення відновлення після операцій та зменшення післяопераційних ускладнень у пацієнтів із ПЕГ типу III—IV.

Ключові слова: параезофагеальна грижа III—IV типу, хірургічне лікування, лапароскопічний доступ, ERAS-протокол, результати.

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Severity of pain syndrome, functional activity, and quality of life in male patients with inguinal hernias in the preoperative period

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According to the European Hernia Society (EHS) and the Hernia Surge Group (HSG), males with inguinal pain syndrome make up the majority of candidates for planned inguinal hernia surgeries. Chronic groin pain in the preoperative stage typically has a negative impact on such patients' functional activity and quality of life. It is therefore considered a significant indication for planned surgery. According to recent research, appropriate functional outcomes, such as improved physical activity and patient quality of life, are as important as an accurate anatomical restoration of the inguinal region after planned inguinal hernia surgery.

Objective — to assess the severity of preoperative inguinal pain syndrome, functional activity, and quality of life in male patients with inguinal hernias.

Materials and methods. The study focuses on the preoperative clinical examination of 50 patients (males) with primary unilateral inguinal hernias. The patients were treated in the surgical department of the State Scientific Institution «Centre for Innovative Medical Technologies of the National Academy of Sciences of Ukraine» between 2018 and 2024. A questionnaire method was employed to assess the functional activity, quality of life, and severity of pain syndrome in patients before surgery. This method involved the use of the modified Carolinas Comfort Scale (MCCS), the European Questionnaire for the Assessment of Quality of Life (EQ-5D-3L), and the Visual Analogue Scale (VAS).

Results. The average pain severity index on the VAS was 2.1 ± 0.9 points. The MCCS was used to assess patients' functional activity, resulting in an average total score of 33.7 ± 12.1 points, which corresponded to 44.9 %, classifying the patients as «not satisfied» in the clinical group. The EQ-5D-3L descriptive system was used to assess patients' quality of life. We found that 30 % reported moderate mobility limitations, 18 % reported moderate self-care issues, and 34 % reported limitations in their daily activities. 24 % of patients exhibited moderate anxiety or depression-related symptoms. At the same time, all patients noted the presence of pain syndrome, with 76 % experiencing moderate pain and 24 % suffering severe pain.

Conclusions. The «symptomatic» group of males with inguinal hernias exhibits a high level of local pain syndrome in the area of the hernia protrusion (2.1 ± 0.9 on the VAS, and 24 % of patients reported a significant degree of pain severity before planned surgical intervention (> 3 points) according to the EQ-5D-3L system). In the vast majority of cases, it significantly impairs their functional activity and quality of life (66 % of patients are not satisfied with their quality of life (32.4 ± 5.6 points on the MCCS)). Effective local pain management is an important objective in the planned surgical treatment of inguinal hernias. This necessitates further investigation into surgical technique selection and procedure adjustments.

Keywords
inguinal hernia, quality of life, chronic pain, functional status.

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According to the most recent data from the European Hernia Society (EHS) and Hernia Surge Group (HSG), the majority of patients who require planned surgical intervention for inguinal hernias experience symptoms, with men being the predominant group. A wait-and-see strategy may be appropriate for only one-third of the individuals who have a «minimally symptomatic» or asymptomatic progression of the disease [12]. At the same time, the presence of pain syndrome in the area of

the hernia protrusion is one of the primary reasons patients seek medical assistance, as well as the indication for planned surgical intervention. The onset of pronounced local pain indicates a higher risk of an incarcerated hernia, which increases the incidence of perioperative complications and reduces the effectiveness of surgical therapy [4, 14].

It should be noted that persistent groin pain at the preoperative stage negatively impacts the functional activity and quality of life for a specific group of patients. This serves as a compelling reason to proceed with planned surgery [2, 6].

The severity of preoperative pain is one of the important starting «points of reference», which serves as an original marker of the specified indicator's perioperative dynamics. It provides a more objective assessment of the effectiveness and quality of surgical treatment for inguinal hernias. Furthermore, it facilitates the comparison of various surgical techniques and modifications, thereby optimising their selection [10].

Modern perspectives on the outcomes of planned inguinal hernia reconstruction emphasise not only the reliability of morphological abdominal wall reconstruction in preventing hernia incarceration but also the importance of achieving adequate functional outcomes. This, in turn, becomes practically impossible without eliminating or significantly reducing the severity of preoperative inguinal pain syndrome, as well as improving related markers of physical activity and quality of life in patients after surgical treatment [8].

Nevertheless, this task remains unsolved at present.

Given the foregoing, preoperative assessment of inguinal pain syndrome, functional activity, and quality of life in the described patient population is unquestionably significant and relevant.

Objective —to assess the severity of preoperative inguinal pain syndrome, functional activity, and quality of life in male patients with inguinal hernias.

Materials and methods

The study focuses on the preoperative clinical examination of 50 patients (males) with primary unilateral inguinal hernias. The patients were treated in the surgical department of the State Scientific Institution «Centre for Innovative Medical Technologies of the National Academy of Sciences of Ukraine» between 2018 and 2024. This study was carried out in compliance with all measures to ensure safety for the health of patients, respect for their rights, human dignity, and moral and ethical norms (minutes of the meeting of the committee on the ethics of scientific research No 3 dated 09/21/2023).

The study's inclusion criteria were as follows: male sex, primary unilateral inguinal hernias with a symptomatic course, the absence of indications and the need for simultaneous surgical interventions on the abdominal cavity and/or the abdominal wall organs, and the patient's informed consent to participate in the study.

The study's exclusion criteria were as follows: women, patients with recurrent and bilateral inguinal hernias, patients requiring simultaneous surgical interventions on the abdominal cavity and/or the abdominal wall organs, patients with a history of radiation therapy to the area of the small pelvis, patients with hypogastric sensitivity disorders of any etiology, patients with severe concomitant cardiovascular, renal, or other systemic pathologies, and patients who did not give written consent to participate in the study.

All study participants underwent a thorough examination during the preoperative phase, which included anamnesis, survey administration, and a range of physical, clinical, laboratory, and instrumental procedures.

The anamnesis data collection process necessitated documentation of each individual patient's disease course. It included a mandatory description of inguinal hernia symptoms and their severity, the presence of an incarcerated hernia in the anamnesis, and the exclusion of criteria that would prevent the patient from participating in the study.

The physical examination included a comprehensive assessment and palpation of the patient's inguinal areas and the pubic symphysis area in both vertical and horizontal positions while at rest, as well as during straining. We also conducted a bilateral adductor test and elicited the cough impulse.

The mandatory laboratory tests included a complete blood count, a comprehensive urinalysis, a biochemical blood analysis (total protein, albumin, total bilirubin and its fractions, ALT, AST, urea, creatinine, glucose, C-reactive protein), a coagulogram (prothrombin index, prothrombin time, international normalised ratio, fibrinogen), a determination of blood group and Rhesus factor, a Wasserman reaction, and a blood test for viral hepatitis B and C markers (HbSAg, anti-HCVAg IgM and IgG).

A dynamic ultrasound examination of the inguinal areas, as well as the Valsalva test, were performed on the patients in both horizontal and vertical positions to identify the presence of a hernia, which is common in professional athletes.

The ultrasound criteria used to diagnose a hernia in professional athletes were protrusion of the posterior wall of the inguinal canal and an increase in the height of the inguinal space.

We performed pelvic magnetic resonance imaging (MRI) to address controversial physical and ultrasound signs of a hernia, which is common in professional athletes, and to conduct a thorough differential diagnosis of potential causes of groin pain (adductor muscle syndrome, pubic osteitis, hip joint pathology, etc.).

The diagnostically relevant MRI criteria for a hernia that is commonly found in professional athletes included:

- amplification of the MR signal from the upper branch of the pubic bone, along with signs of increased hydrophilicity in the inguinal canal structures;
- enhancement of the MR signal originating from the inguinal canal;
- increase in the height of the inguinal space (secondary criterion).

During the preoperative period, patients' pain syndrome at rest was assessed using the Visual Analogue Scale (VAS). The results were evaluated on a 10-point scale (0—10), with 0 indicating no pain and 10 indicating extremely severe pain.

Preoperative functional activity was assessed using an eight-question modified Carolinas Comfort Scale (MCCS) questionnaire. Each question independently assessed pain syndrome during physical exertion and at rest, as well as mobility limitation during physical exertion (with the exception of one question, which only assessed pain syndrome). The absence of a question about the subjective experience of having a mesh implant set this questionnaire apart from the standard Carolinas Comfort Scale (CCS) questionnaire. The MCCS questionnaire included five-point ratings for each question. The minimum score for each question is 0 points, indicating the absence of pain syndrome or mobility limitation during physical exertion. The maximum score is 5 points, representing extremely severe pain syndrome or mobility limitation during physical exertion. The minimum score for each question is 0 points, and the maximum score is 10 points (except for one question, where the maximum score is 5 points). Assessed questions: pain while lying down, pain and mobility limitation when bending forward, pain and mobility limitation while sitting, pain and mobility limitation during regular daily activities (e.g., getting out of bed, bathing, and dressing), pain and mobility limitation during coughing, sneezing, and deep breathing, pain and mobility limitation while walking or standing, pain and mobility limitation when climbing or descending stairs, pain and mobility limitation during physical exercises unrelated to the primary job. The total score was calculated by adding the scores from each of the eight questions, which could range from 0 to 75 points. All scores obtained were converted into percentages of the maximum possible score for the questionnaire. To simplify further analysis and the formation of clinical groups based on the level of satisfaction with functional results, the MCCS scores were stratified by symptoms severity. Patients were classified into four groups: very satisfied (J 5 %), generally satisfied (> 5 % ≤ 30 %), not satisfied (> 30 % ≤ 60 %), and very dissatisfied (> 60 %).

An assessment of the quality of life of patients with inguinal hernias was conducted prior to surgery using the European Questionnaire for the Assessment of Quality of Life (EQ-5D-3L), which consists of five questions. The findings of the EQ-5D-3L system were assessed on a question-by-question basis, with each question being assigned a score ranging from 1 to 3. A score of 1 indicated the absence of any complaints, a score of 2 indicated the presence of specific complaints, and a score of 3 indicated the presence of pronounced complaints. The following criteria were assessed: mobility, self-care, daily activities, pain or discomfort, and anxiety or depression.

Statistical analysis

We statistically processed the data using several variational and descriptive statistics approaches, along with the additional statistical analysis tool SPSS Statistics: An IBM Company, Version 23. The study includes descriptive statistics indicators such as the mean (M) and standard deviation (SD) for normal distribution, as well as the Pearson correlation coefficient (rxy).

Results

The age range of the patients in the study was 20 to 85 years. The average age was 62.1 ± 15.1 years.

The pain severity throughout the preoperative period was measured by the VAS, with an average value of 2.1 ± 0.9 points.

At the preoperative stage, the MCCS descriptive system was used to assess patients' functional activity, resulting in an average total score of 33.7 ± 12.1 points, which corresponded to 44.9 %, classifying the patients as «not satisfied» in the clinical group (> 30 % ≤ 60 %). The lowest score was 15 points, and the highest was 66. In a more detailed breakdown by group, 9 patients (18 %) with an average score of 19.2 ± 2.2 points were included in the «generally satisfied» category (> 5 % ≤ 30 %), which corresponded to an average of 25.6 %; 33 patients (66 %) with an average score of 32.4 ± 5.6 points fell into the «not satisfied» category (> 30 % ≤ 60 %), which corresponded to an average of 43.2 %; 8 patients (16 %)

Table 1. **Characteristics of functional activity of patients at the preoperative stage based on data from MCCS questionnaire**

Patient satisfaction	Number of patients	Average score
Very satisfied	0	–
Generally satisfied	9 (18 %)	19.2 ± 2.2
Not satisfied	33 (66 %)	32.4 ± 5.6
Very dissatisfied	8 (16 %)	55.5 ± 6.9
Total	50	33.7 ± 12.1

with an average score of 55.5 ± 6.9 points fell into the «very dissatisfied» category, which corresponded to an average of 75.0 %. None of the patients in the study reported being «very satisfied» (≤ 5 %).

Characteristics of functional activity of patients at the preoperative stage based on data from MCCS questionnaire are presented in Table 1.

The EQ-5D-3L descriptive system was used to assess patients' quality of life. We found that 15 patients (30 %) reported moderate mobility limitations, while the rest of the patients did not report any mobility limitations. 9 patients (18 %) reported moderate self-care issues, while the remaining patients did not report any difficulties in self-care. 17 patients (34 %) reported limitations in their daily activities, while only one patient (2 %) complained about the complete impossibility of doing daily routine tasks. All patients noted the presence of pain syndrome, with 38 patients (76 %) experiencing moderate pain and 12 patients (24 %) suffering severe pain. 12 patients (24 %) exhibited moderate anxiety or depression-related symptoms, whereas severe symptoms were observed in 2 patients (4 %).

Characteristics of patients' quality of life at the preoperative stage based on data from the EQ-5D-3L questionnaire are presented in Table 2.

The methodological aspects of administering the survey were consistent for all patients. We provided each participant with the same explanations and detailed instructions on how to complete each of the questionnaires.

Discussion

According to current research and recommendations, all individuals with symptomatic inguinal hernias should undergo scheduled surgical treatment. Emergency surgeries for incarcerated hernias are associated with increased risks of intra- and postoperative complications, higher mortality rates, and a significant increase in economic costs [1, 3].

At the same time, it is worth noting that, even in the absence of complications, a considerable percentage of patients with inguinal hernias experience a severe limitation of functional activity, as well as a deterioration in quality of life [2].

Modern herniology has advanced significantly, particularly in terms of optimising candidate selection for surgery, actively implementing minimally invasive surgical interventions, and modern approaches to perioperative management and patient rehabilitation. It allowed for significant progress in improving patients' quality of life and restoring functional activity after surgery.

It has become a compelling argument for expanding the indications for planned surgical procedures for inguinal hernia.

This study included anamnesis, instrumental studies, and a survey to assess quality of life, functional activity, and preoperative inguinal pain syndrome in males with inguinal hernias. We used the VAS, EQ-5D-3L, and MCCS questionnaires.

The original version of the CCS questionnaire was designed to assess the quality of life in postoperative patients who underwent anterior abdominal wall hernia repair. Since this scale is well validated for the targeted patient population, it is regarded as the preferred tool for assessing quality of life and has advantages over the traditional SF36 questionnaire, which is not specific [13]. In our study, we employed a modified version of the questionnaire to assess patients' quality of life during the preoperative period. The study found that most patients were not satisfied with their quality of life and functional capacities (32.4 ± 5.6 points).

According to the preliminary summary of the survey data, the pain syndrome was shown to be the most important factor affecting patients' quality of

Table 2. **Characteristics of patients' quality of life at the preoperative stage based on data from EQ-5D-3L questionnaire (n = 50)**

Score	Mobility	Self-care	Daily activities	Pain/Discomfort	Anxiety/Depression
1	35 (70 %)	41 (82 %)	32 (64 %)	0	36 (72 %)
2	15 (30 %)	9 (18 %)	17 (34 %)	38 (76 %)	12 (24 %)
3	0	0	1 (2 %)	12 (24 %)	2 (4 %)

life and functional activity during the preoperative period. Such findings were obtained during the survey using the EQ-5D-3L questionnaire. This questionnaire was chosen based on research indicating that it has higher construct validity and sensitivity in patients with chronic pain than the SF36 [9]. As a result, to some extent, all study patients reported having inguinal pain syndrome, the severity of which, when compared to the findings of the MCCS and VAS questionnaires, had a direct correlation with the patients' quality of life (rxy = 0.81 for the MCCS questionnaire).

The accurate identification of the etiology and nature of the pain syndrome in patients with inguinal hernias is an important component in predicting the development of chronic inguinal pain and, as a result, the quality of life of these patients in the postoperative period. This is supported by data from Forester et al.'s 2021 multivariate regression analysis of 960 individuals who underwent inguinal hernia repair [5]. The study conducted by Romain et al. in 2022 yielded comparable results, where 36.5 % of patients with chronic postoperative groin pain were diagnosed with pain syndrome persistence prior to surgery [11].

Thus, the results obtained during the study patient analysis were generally comparable to the data of foreign authors [7].

Conclusions

The «symptomatic» group of males with inguinal hernias exhibits a high level of local pain syndrome in the area of the hernia protrusion (2.1 ± 0.9 on the VAS, and 24 % of patients reported a significant degree of pain severity before planned surgical intervention (> 3 points) according to the EQ-5D-3L system). In the vast majority of cases, it significantly impairs their functional activity and quality of life (66 % of patients are not satisfied with their quality of life (32.4 ± 5.6 points on the MCCS)).

Effective local pain management is an important objective in the planned surgical treatment of inguinal hernias. This necessitates further investigation into surgical technique selection and procedure adjustments.

Prospects for further research

Further randomised clinical trials are required to determine the impact of preoperative inguinal pain syndrome on the development of chronic inguinal pain, as well as the dynamics of quality of life and functional activity in patients with inguinal hernias.

Declaration of interests

The author declares that there are no conflicts of interest.

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Виразність больового синдрому, функціональна активність та якість життя чоловіків із пахвинними грижами в доопераційний період

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За даними European Hernia Society (EHS) та Hernia Surge Group (HSG), серед кандидатів на планові операції з приводу пахвинних гриж домінують чоловіки із больовим синдромом у пахвинній ділянці. Хронічний пахвинний біль на доопераційному етапі зазвичай негативно впливає на функціональну активність і якість життя пацієнтів, що є важливим аргументом на користь планової операції. За сучасними уявленнями, досягнення задовільних функціональних результатів (поліпшення показників фізичної активності) та якості життя пацієнтів після планової хірургії пахвинних гриж є таким самим важливим елементом, як і надійність анатомічної реконструкції пахвинної ділянки.

Мета — провести оцінку доопераційного пахвинного больового синдрому, функціональної активності та якості життя чоловіків із пахвинними грижами.

Матеріали та методи. Проаналізовано результати доопераційного клінічного обстеження 50 пацієнтів (чоловіків) з первинними однобічними пахвинними грижами, що перебували на лікуванні в хірургічному відділенні Державної наукової установи «Центр інноваційних медичних технологій НАН України» у період із 2018 до 2024 р. Для оцінки функціональної активності, якості життя та больового синдрому на доопераційному етапі застосовували анкетування із використанням modified Carolinas comfort scale (MCCS), Європейського опитувальника оцінки якості життя (EQ-5D-3L) та візуальної аналогової шкали (ВАШ).

Результати. Середній показник виразності больового синдрому за ВАШ становив (2,1 ± 0,9) бала. При оцінці функціональної активності пацієнтів за MCCS середній сумарний бал становив 33,7 ± 12,1, що при перерахунку становило в середньому 44,9 % та відповідало клінічній групі пацієнтів «не задоволені». При оцінці якості життя пацієнтів за EQ-5D-3L помірне обмеження мобільності відзначили 30 % пацієнтів, помірні труднощі при догляді за собою — 18 %, обмеження при заняттях повсякденною діяльністю — 34 %. Помірний рівень тривоги чи депресивних ознак виявлено в 24 % пацієнтів. Усі пацієнти відзначали наявність больового синдрому, зокрема помірний біль — 76 %, а виразний — 24 %.

Висновки. «Симптомна» група чоловіків із пахвинними грижами до виконання планового оперативного втручання характеризується значущим рівнем локального больового синдрому в ділянці грижевого випинання (2,1 ± 0,9 за ВАШ та, відповідно, 24 % пацієнтів (> 3 балів) за EQ-5D-3L)), що в більшості з них суттєво знижує функціональну активність і якість життя (66 % пацієнтів не задоволені якістю життя ((32,4 ± 5,6) бала за MCCS)). Корекція локального болю є важливим завданням планового хірургічного лікування пахвинних гриж, що потребує пошуку та оптимізації вибору методик і модифікацій операцій.

Ключові слова: пахвинна грижа, якість життя, хронічний біль, функціональний статус.

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Optimisation of bronchoalveolar lavage technique for isolating alveolar macrophages in mice

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Bronchoalveolar lavage (BAL) is a widely used technique to collect immune cells from the lungs, with alveolar macrophages (AMs) being the most prevalent cells in BAL fluid. AMs are vital for maintaining lung homeostasis and providing immune defence against airborne pathogens. However, in murine models, BAL procedures usually yield low numbers of AMs, thus limiting experimental design, especially when high cell counts are needed.

Objective — to optimise BAL techniques in mice to maximise AM recovery.

Materials and methods. Young and older BALB/c mice were used in the study. Bronchoalveolar lavage was performed following the method of Luckow and Lehmann (2021) with modifications. Statistical analysis was done using the Mann-Whitney U test, with a significance level set at $p < 0.05$.

Results. Female BALB/c mice of different ages were chosen due to the frequency of their use as models of pulmonary diseases. A simplified method described by Luckow and Lehmann (2021), which avoids tracheotomy by using peroral cannula insertion, was employed. The protocol was modified by securing the cannula with a ligature to prevent BAL fluid leakage in older mice. To reduce mechanical stress on alveoli, a buffer volume of 0.6 mL was used, and the study compared two buffer variants: one at room temperature without EDTA, and another heated to 37°C with EDTA. The pre-heated buffer with EDTA significantly increased BAL cell yields in all mice groups, confirming the importance of these optimisations for higher cell recovery.

Conclusions. Our modified bronchoalveolar lavage protocol includes securing the trachea with a ligature to prevent BAL fluid leakage, reducing lavage volume to 0.6 mL to minimise lung damage, and using a 37°C solution with EDTA for improved AM recovery rates. Further studies are needed to explore the significance of other buffer components for BAL protocol optimisation, the possible age-related differences in AM isolation in male BALB/c mice, and the strain-specific features of the BAL technique.

Keywords
bronchoalveolar lavage, alveolar macrophages, aging.

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Bronchoalveolar lavage (BAL) is used to isolate immune cells and soluble substances from the lungs [4]. Under normal conditions, alveolar macrophages (AMs) are the predominant cell type collected in BAL fluid [27]. In addition to homeostatic functions, i.e., removal of lung surfactant and cellular debris, this population of macrophages is important for the protection of the host from airborne pathogens. They can recognise pathogens and destroy them through phagocytosis, as well as provide the necessary stimuli to engage adaptive immunity in a fight against infection [16]. In light of the aforementioned, research

on AMs is vital for improving host resistance to infections spread by aerosol transmission, including emerging virus variants with epidemic and pandemic potential, such as SARS-CoV-2 [7], as well as research on the role these cells play in the pathogenesis of non-infectious lung diseases [19].

Mice are commonly used in laboratories because they are easy to handle and care for, share a high degree of similarity with humans, and reproduce quickly [2]. Animal models, including murine ones, are the pillar of pulmonary research since they reproduce the numerous complex physiological processes, multiorgan interplay, and disease phenotypes. Murine models are widely used for preclinical experiments concerning emerging infectious diseases, asthma, chronic obstructive pulmonary diseases, lung cancer, etc. [25]. Pulmonary macrophages, including AMs, are the principal object in such models. In these experiments, mice's age is one of the crucially important factors, on which depends the translational potential of the experimental study [9]. Animal sex also plays a crucial role, especially in studies that focus on immune reactivity and consider sex-dependent characteristics of immunity [6]. All of these factors require the incorporation of cell isolation techniques in the study design, considering animal age and sex characteristics.

BAL usually yields a relatively low number of AMs per mouse, often less than $1 \cdot 10^5$ [15, 28], which may significantly limit experimental design. Using more mice to address this issue contradicts the «4Rs» principle of animal research, which mandates limiting the animal count to the bare minimum required for dependable data [11].

Objective — to optimise the BAL technique in mice to maximise the collection of AMs.

Materials and methods

Ethical statement. Young (6—12 weeks old) BALB/c mice of both sexes and older (8—10 months old) female BALB/c mice were used in experiments. Animals were euthanised by injecting an overdose of anesthetic (sodium thiopental 200 mg/kg) into the peritoneal cavity. The animal procedures received approval from the Bioethics Committee of the Educational and Scientific Centre «Institute of Biology and Medicine» at Taras Shevchenko National University of Kyiv.

Bronchoalveolar lavage. The method recently described by Luckow and Lehmann (2021) was used with modifications [14]. Briefly, the skin on the ventral side of the neck is disinfected using ethanol, and an incision is made with scissors to reveal the salivary glands that lie over the trachea. The salivary glands are carefully removed with forceps to expose the trachea. A 1 ml syringe filled with buffer is attached to a rigid straight 23G olive tip cannula (J0156A; Jorgensen Laboratories, LLC, USA). The olive on the tip is polished and smooth, free from sharp edges. The syringe with the cannula is then inserted through the mouth directly into the trachea, ensuring that the esophagus is not entered. Once the cannula is correctly positioned, it is tied by ligature placed posterior to the olive tip. Then, 0.6 ml of lavaging solution (saline warmed to 37 °C and supplemented with 2 mM EDTA) is gradually introduced into the lungs and then slowly aspirated. The fluid is collected in a tube after detaching the syringe from the cannula. BAL was then repeated 3 times, with the cannula staying inside the trachea.

Statistical analysis. Mann-Whitney U test was used for comparisons between groups. The significance level was set at $p < 0.05$.

Results and discussion

The BALB/c strain was chosen for these experiments due to its common use in preclinical models of pulmonary diseases [25]. Additionally, we have used female mice of different ages considering their frequent use in models of chronic obstructive pulmonary disease and asthma — diseases with sex-dependent prevalence [10, 18].

The majority of the described BAL methods involve performing a tracheotomy with the subsequent insertion of a cannula into the trachea [4]. The cannula is also fixed with a surgical knot to prevent it from sliding out of the trachea and reduce leakage of BAL fluid. Due to the small size of mice, this procedure is quite complex and may require a lot of trained personnel when high numbers of AMs are needed for study. Therefore, we chose a simplified protocol recently published by Luckow and Lehmann (2021), which is based on the peroral insertion of a cannula and thus does not require tracheotomy [14].

According to Luckow and Lehmann (2021), the olive tip of the cannula has a larger diameter than the internal lumen of the murine trachea. Therefore, the tracheal muscles ensure consistent fixation of the cannula, thus preventing the leakage of BAL fluid. The authors applied their technique on adult animals with weights ranging from 15 to 35 g [14]. Although suitable for the majority of experiments on mice, this method may fail in ageing studies. Since mice grow bigger with age, the diameter of their tracheal lumen may proportionally increase [5, 13]. Additionally, the contractile properties of smooth muscle cells, including tracheal muscles, can deteriorate with ageing [1]. This may explain frequent BAL fluid leaking, which

was observed in our pilot studies on older mice. Hence, we modified this method by placing a ligature around the trachea posterior to the olive tip, thus firmly securing the inserted cannula (Fig. 1).

One of the important parameters of the BAL procedure is the volume of the instilled buffer. 1 mL is frequently used as a fixed one-time volume of the lavage buffer that is repeatedly injected into the lungs. According to Lai and Chou, total lung capacity and functional residual capacity in mice are 1.05 ± 0.04 and 0.25 ± 0.01 mL, respectively [12]. Consequently, the infusion of 1.0 mL buffer in one go during BAL fluid collection could impose mechanical stress on the alveoli, potentially causing harm to macrophages [17, 24]. These assumptions were confirmed by Sasaki et al. They compared 3 different fixed volumes of injection buffer (0.55 mL, 0.75 mL, and 1 mL, instilled 10 times each) and found that an infusion of 1mL leads to the highest percentages of CD11b-CD11c-SiglecF-cells (presumably alveolar epithelial cells) in BAL fluid compared to two other studied volumes. Moreover, detrimental effects were observed in AMs isolated with 1mL of injection buffer, including reduced cell viability during culture and impaired functionality, particularly in response to stimulation with fine particles. Notably, the authors did not register a significant influence of lavaging fluid volume on recovery efficiency [22]. In light of the aforementioned factors, a fixed injection volume of 0.6 mL was chosen for our studies.

EDTA is a chelating agent that is often used in the laboratory to detach adherent cells. It chelates calcium and magnesium, leading to cadherin misfolding and disruption of lateral cell junctions [21]. It is sometimes added into injection buffer to facilitate detachment of AMs from alveoli [8, 20], but other researchers do not use it [23]. The temperature of the lavaging fluid also varies in different reports: some authors use pre-cooled buffer (4 °C) [15], while others heat it to 37 °C [8, 26]. Busch et al. have found that both the addition of EDTA and pre-warming of lavage buffer to 37 °C yield more AMs than cold buffer without EDTA [3].

In our study, 2 variants of lavage buffer were compared:

1) Room temperature without EDTA (buffer No 1);

2) heated to 37 °C and supplemented with EDTA (buffer No 2).

Buffer No 1 yielded a maximum of $3 \cdot 10^5$ cells in all studied groups of mice, while buffer No 2 increased the numbers up to $5 \cdot 10^5$ cells in young animals of both sexes and more than $10 \cdot 10^5$ cells in old female BALB/c mice (Fig. 2). Overall, our observations show that using a pre-heated injection buffer containing EDTA resulted in significantly higher BAL cell numbers in BALB/c mice regardless of age and sex. Our results confirm the findings of Busch et al., which suggest that pre-warming and EDTA supplementation are important optimisations that lead to significantly higher BAL cell numbers in mice.

Conclusions

Our BAL protocol variant features several important developments:

1) Securing the trachea with a ligature prevented BAL fluid leakage in older mice, thereby expanding Luckow and Lehmann's technique (2021) to bigger and older animals.

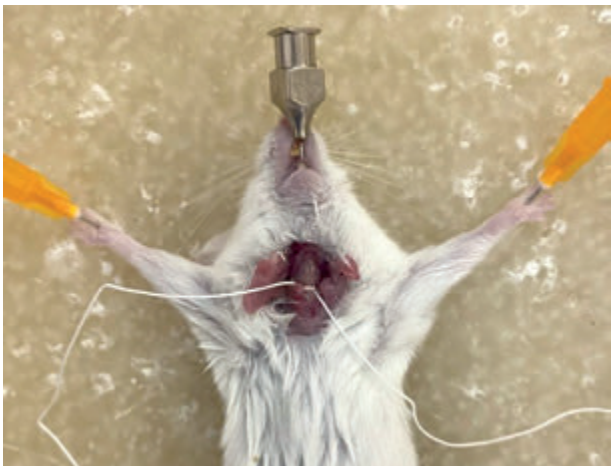
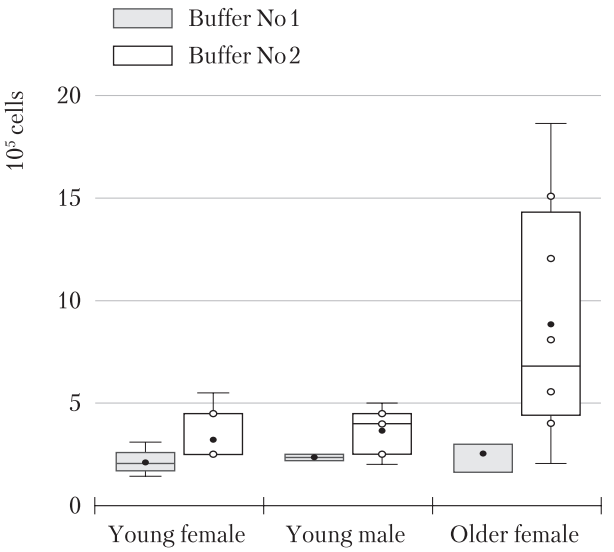


Figure 1. **Ligature securing cannula inside the trachea**



The difference between buffer No 1 and buffer No 2 is statistically significant for all three groups ($p < 0.05$).

Figure 2. **Comparison of cell numbers yielded by buffer No 1 and buffer No 2 in young female, male, and older female BALB/c mice**

2) The reduction of the one-time lavage volume to 0.6 mL minimised mechanical strain on lung alveoli and, thus, prevented AM damage.

3) The use of a pre-heated 37 °C lavage solution containing EDTA significantly enhanced AM recovery rates, particularly in older mice.

More studies are warranted to explore the role of other potential lavage buffer components, such as fetal bovine serum, as well as to further adjust its volume, EDTA concentration, and other parameters. Assessing age-related features in AM isolation using BAL is needed in male BALB/c animals. Moreover, one cannot exclude strain-specific features of the BAL technique.

Declaration of interests

The authors declare no competing interests.

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Authors contributions

Conception and design, critical review: L. Skivka; data collection: R. Dovhyi, M. Rudyk, A. Dvukhriadkina, K. Ostrovska; data analysis and interpretation: R. Dovhyi, T. Serhiichuk, Y. Yumyna, N. Senchylo; drafting the manuscript: R. Dovhyi.

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Оптимізація методики бронхоальвеолярного лаважу для виділення альвеолярних макрофагів у мишей

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Бронхоальвеолярний лаваж (БАЛ) є широко використовуваною методикою для виділення імунних клітин легень, при цьому альвеолярні макрофаги (АМ) є найбільш численними клітинами БАЛ. АМ відіграють ключову роль у підтримці гомеостазу легень та імунному захисті від патогенів, що передаються повітряним шляхом. Однак при проведенні БАЛ на мишах зазвичай вдається отримати відносно малу кількість АМ, що значно обмежує можливості дизайну дослідження, особливо коли потрібно отримати велику кількість клітин.

Мета — оптимізувати методику БАЛ у мишей для отримання максимальної кількості АМ.

Матеріали та методи. У дослідженні використовувалися молоді та старші миші лінії BALB/c. БАЛ отримували за методикою Luckow and Lehmann (2021) з модифікаціями. Статистичний аналіз виконували за допомогою U-тесту Манна — Уїтні, при рівні значущості $p < 0,05$.

Результати. Для досліджень було обрано самиць мишей лінії BALB/c різного віку у зв'язку з частим використанням таких тварин для моделювання захворювань легень. Використовувався спрощений метод, описаний Luckow and Lehmann (2021), який уникає застосування трахеотомії завдяки пероральному введенню канюлі. Протокол було модифіковано шляхом закріплення канюлі лігатурою для запобігання витоку рідини БАЛ у старших мишей. Для зменшення механічного навантаження на альвеоли використовували об'єм буфера 0,6 мл. В даному дослідженні порівнювали два варіанти буфера: один кімнатної температури без ЕДТА, а інший — підігрітий до 37 °C з ЕДТА. Застосування попередньо підігрітого буфера з ЕДТА значно збільшувало кількість клітин БАЛ у всіх групах мишей, що підтверджує важливість такої оптимізації протоколу для збільшення кількості АМ.

Висновки. Наш модифікований протокол бронхоальвеолярного лаважу включає закріплення трахеї лігатурою для запобігання витоку рідини БАЛ, зменшення об'єму лаважу до 0,6 мл для мінімізації пошкодження легень, і використання розчину, підігрітого до 37 °C з ЕДТА для збільшення кількості АМ. Потрібні подальші дослідження з метою вивчення значення інших компонентів буфера для оптимізації протоколу БАЛ, можливих вікових відмінностей у виділенні АМ у самців мишей лінії BALB/c, а також особливостей застосування техніки БАЛ на мишах різних ліній.

Ключові слова: бронхоальвеолярний лаваж, альвеолярні макрофаги, старіння.

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Bifocal endometriomas involving a Pfannenstiel incision. Clinical case

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Endometrioma of the anterior abdominal wall (EAAW) is a rather rare variant of extragenital endometriosis, which in most cases occurs after obstetrical and gynecological procedures. EAAW presented predominantly as a single tumour-like mass, and multiple ectopias were observed in only 1.9—5.6 % of cases, exclusively after Pfannenstiel laparotomy.

Here we present a clinical case of a 37-year-old patient who complained of the large tumour-like nodules along the postoperative anterior abdominal wall scar, accompanied by severe cyclic, catamenial pain. Additionally, the patient noted an increase in tumour size during menstruation. Thirty-three months ago, she underwent an elected cesarean section for obstetric indications. Based on ultrasonography and computed tomography scans, the presence of two EAAW in the corners of the postoperative scar was established: 46 × 32 × 31 mm and 14 × 18 × 13 mm, respectively. Both lesions were excised out without damaging their integrity. The fascial defect was replaced by synthetic polypropylene mesh. The diagnosis of EAAW was finally confirmed based on pathological (presence of endometrial glands and cytogenic stroma) and immunohistochemical (positive membrane expression of CD10 in cytogenic stroma, intense cytoplasmic expression of CK7 in endometrial glands, marked nuclear expression of progesterone (PR) and estrogen (ER-α) receptors in endometrial glands and cytogenic stroma, proliferative activity index Ki-67 — 2 %) studies. At a follow-up after 19 months, the patient was asymptomatic; according to physical examination and ultrasound scan, there was no evidence of recurrence.

Abdominal wall endometriosis is a rare condition. Clinicians should be aware of this pathology, especially in women presenting with a painful mass near the scar of a previous obstetrical and gynecological surgery. Surgery is the best treatment modality for endometrioma, whereas its optimal volume is considered to be R0 resection with preservation of endometriomas' integrity. The final diagnosis of EAAW requires pathological and immunohistochemical confirmation.

Keywords
extrapelvic endometriosis, scar endometriosis, abdominal wall endometriosis, caesarean section.

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Endometrioma of the anterior abdominal wall (EAAW) is a rather rare and specific variant of extragenital endometriosis [6, 12], with a frequency of 0.4 % to 3 % in the structure of endometriosis in women of reproductive age [3, 12]. In most cases, EAAW occurs after obstetric and gynecologic surgical interventions (cesarean section, myomectomy, hysterectomy, laparoscopy) [2, 6, 7, 12—14]; however, cases of condition after general surgical procedures also have been described [3, 11], as well as sporadic observations of spontaneous EAAW have been published [3, 5, 6, 9, 10].

EAAW presented predominantly as a single tumour-like mass, and multiple ectopias were observed in only 1.9—5.6 % of cases, exclusively after Pfannenstiel laparotomy [4, 15]. Due to the rarity of multiple EAAW, we present our own clinical observation with emphasis on the diagnosis and surgical treatment of this condition.

Case report

A 37-year-old patient (G3P3) complained of tumour-like masses in the area of the anterior abdominal wall postoperative scar, accompanied by marked cyclic, catamenial pain. Additionally, the patient noted an increase in tumour-like masses during menstruation. The length of the disease was 12 months when the above-described phenomena first appeared. Menarche at 13 years, menstrual cycle of 28 days, menstruation of 4—5 days, painless. Thirty-three months ago, she had an elected cesarean section for obstetric reasons. Two previous pregnancies ended in timely deliveries through natural labour.

On examination, the patient has Class II obesity (BMI — 36.05 kg/m^2). In the area of the left corner of the Pfannenstiel incision, a moderately mobile and slightly painful tumour-like mass approximately 5 cm in size is detected. On the right end of Pfannenstiel's incision, a second tumour-like mass about 2 cm in diameter, mobile and somewhat painful, is determined. The skin over both masses was unchanged.

On ultrasonography (USG) in the left iliac region, directly under the postoperative scar, a solid (38.1 mm) hypogenic mass of oval shape with a cellular texture and a clear hyperechogenic contour was detected. In Doppler mapping, peripheral and central blood flow (degree of vascularization — 2) and the presence of an afferent vessel with a diameter of 3 mm are determined in the mass. On the right side, a hypogenic mass (26.4 mm) with a hyperechogenic contour was visualized in the subcutaneous tissue of the anterior abdominal wall; unexpressed peripheral blood flow was detected at Dopplerography.

A computed tomography (CT) scan was performed on the second day after menstruation to determine the prevalence of tumour-like masses of the anterior abdominal wall. In the right iliac region, a solid mass measuring 14 × 18 × 13 mm is located in the subcutaneous tissue; on the left, a solid mass (46 × 32 × 31 mm) with a clear and irregular contour involving subcutaneous tissue, fascia, and left rectus abdominis muscle (Fig. 1). A preoperative diagnosis of multiple endometriomas of the anterior abdominal wall after cesarean section was established.

The surgical intervention was planned and performed in the middle of the patient's menstrual cycle. Revision on the left side revealed a tumour-like mass with involvement of subcutaneous tissue, fascia and rectus abdominal muscle. Excision of the tumour-like nodule en bloc within healthy tissues was performed; the fascial defect was replaced with polypropylene mesh. The tumour-like mass on the right was excised within the subcutaneous tissue. Both anterior abdominal wall masses were removed without compromising their integrity. The surgery was completed with layer-by-layer suturing of the anterior abdominal wall tissues.

In section, the gross specimens are represented by multiple microcavities with hemorrhagic contents (Fig. 2). Microscopic examination of both masses noted the presence of endometrial glands and cytogenic stroma (Fig. 3).

Immunohistochemical study (Fig. 4, 5) revealed positive membrane expression of CD10 in cytogenic stroma, intense cytoplasmic expression of CK7 in endometrial glands, marked nuclear expression of progesterone (PR) and estrogen (ER-α) receptors in endometrial glands and cytogenic stroma, and proliferative activity index (Ki-67) — 2%. Thus, pathomorphologic findings fully confirmed the diagnosis of anterior abdominal wall endometriomas.

The postoperative period was uneventful, and the patient was discharged from the hospital on the third postoperative day. At the follow-up

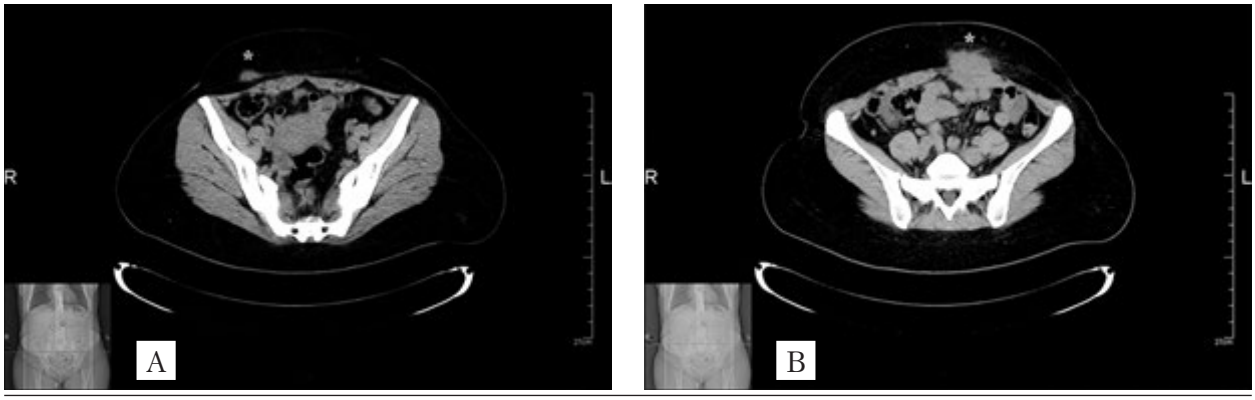

Figure 1. **Axial computed tomography: solid mass in the subcutaneous tissue of the right iliac region (A); solid mass of the left iliac region, involving the subcutaneous tissue, fascia, and left rectus abdominis muscle (B)**

* Solid mass (endometrioma)

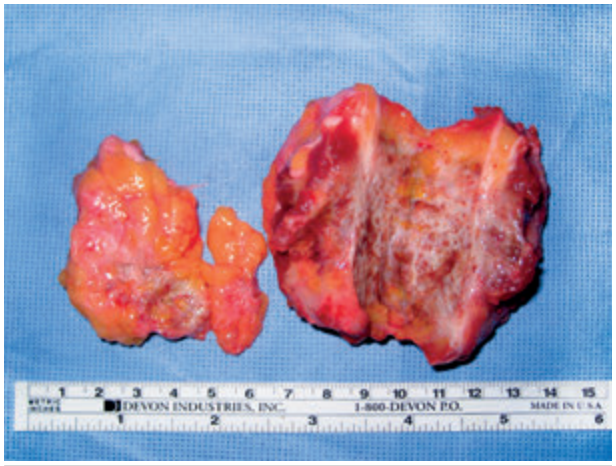

Figure 2. **Macroscopic appearance of abdominal wall endometriomas**

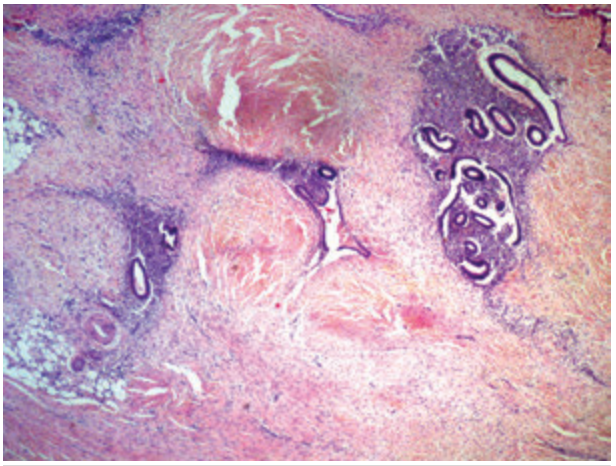

Figure 3. **Microscopic examination: endometrial glands and cytogenic stroma.** H&E staining, ×40

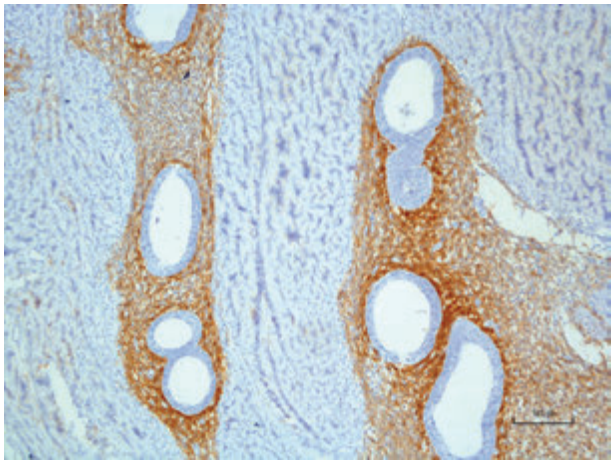

Figure 4. **Immunohistochemistry: diffuse CD10 expression in cytogenic stroma.** DAB × 100

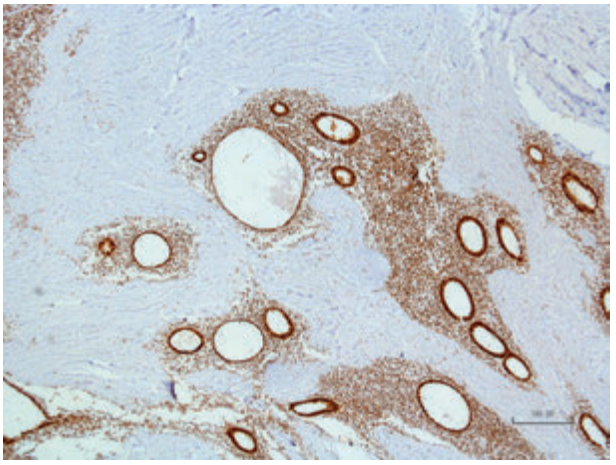

Figure 5. **Immunohistochemistry: diffuse expression of PR in endometrial glands and cytogenic stroma.** DAB ×40

examination after 19 months, the patient was asymptomatic, and according to the results of the physical examination and ultrasound scan, there was no evidence of recurrence.

Discussion

Since the first description of EAAW by Meyer R. in 1903, less than 1000 cases have been published in the specialized literature [11]. The age of patients with EAAW ranged from 21 to 49 years [2—4, 7, 8, 11, 12, 14, 15], and the average time from the primary surgical intervention to diagnosis of EAAW was 28.3—38.6 months [1, 6, 15], although in a number of studies this index varied quite widely, from 5 to 20 years [2, 3, 8, 9, 14].

The etiopathogenesis of EAAW has not been definitively studied to date [1, 6, 13]. However, autotransplantation of endometrium during surgical interventions on pelvic organs is believed to be the most probable trigger in the occurrence of EAAW — the so-called implantation theory [2, 4, 8]. At the same time, the assumption of possible hematogenous and lymphatic spread, as well as the concept of metaplasia of primitive polypotential mesenchymal cells, are the basis for justifying the occurrence of spontaneous EAAW [1, 4, 6].

It has been noted that one of the potential factors associated with EAAW is increased body weight (BMI ≥25 kg/m^2) in operated women [2, 3, 13], which is usually explained by additional technical difficulties in performing surgical interventions in this category of patients, namely, inadequate hysterorrhaphy and tissue contamination of the anterior abdominal wall [2].

The vast majority of cases (from 59 % to 100 %) of EAAW were observed after cesarean section [2, 3, 6—9, 11—15], and in view of the global growth of cesarean section, an increase in this pathology should be expected [1, 8]. However, the current

incidence of EAAW after cesarean section is quite low and is estimated to be between 0.21—1.3 % [1, 8], which presumably should be explained by the potentially large number of undiagnosed cases [2].

To date, there are no evidence-based studies on the prevention of EAAW after cesarean section [1], but some publications recommend the following measures: (1) use of wound protectors/retractors; (2) use of separate suture materials when suturing the uterus and the anterior abdominal wall; (3) avoiding contact of gauze swabs used inside the uterine cavity with the soft tissues of anterior abdominal wall, or even complete renouncement from their use; (4) changing gloves and surgical instruments after suturing the uterine wall; and (5) performing thorough cleaning of subcutaneous tissue and fascia, especially at the corners of the Pfannenstiel wound, at the final stage of surgery [2, 7, 15].

Classically, EAAW is characterized by a symptomatic triad: catamenial pain, palpable mass within the anterior abdominal wall, and history of obstetric-gynecological interventions [1, 2, 6, 7]. However, these signs may not always be identified. Thus, cyclic (catamenial) pain is observed in 51.0—86.9 % of EAAW cases [2, 3, 7, 8, 11—13, 15], and an anterior abdominal wall mass is recognized on palpation in only 32.5—66.7 % of observations, which depends on depth of its location within the anterior abdominal wall, i.e., in subcutaneous tissue, fascia, rectus abdominis muscle, or peritoneum [2, 3, 7]. External catamenial bleeding from EAAW has been described as a rare symptom (1.25—9.1 %) [11, 13]. As a result of the low specificity of symptoms, the diagnosis of endometrioma is often difficult, and initially EAAW are treated as hernias, lipomas, granulomas, desmoid tumours, etc. [1, 3, 4, 7, 9, 11].

When EAAW is suspected before surgery, it is advisable to use medical imaging studies in order to clarify the size and spread of mass within the anterior abdominal wall tissues and, if aponeurosis is involved, to anticipate the necessity of replacing the fascial defect using synthetic meshes [3, 6]. Currently, USG is considered the first-line diagnostic method of EAAW, and its informativity is 78.3—97.0 % [1—3, 6, 11-]. EAAW has been visualized as a hypogenic mass with a hyperechoic contour and varying degree of vascularization from the periphery toward the centre according to Doppler USG [2, 6].

Magnetic resonance imaging (MRI) and CT are preferred tools for diagnosis and planning the extent of surgical procedure for deep and widespread EAAW, as well as for nonpalpable masses of the anterior abdominal wall [1—3, 6, 11—14]. EAAW, according to MRI on T1W (with and without fat suppression) and T2W images, is visualized as a hyperintense heterogeneous mass in the area of the postoperative scar as a result of catamenial hemorrhages in endometrial ectopia. With prolonged conservation of EAAW, its radiological characteristics change due to progressive hemosiderin deposition and pronounced fibrosis; this determines low signal intensity on T2W images [1, 4]. On CT, EAAW is visualized as a solid mass in the area of the postoperative anterior abdominal wall scar [2, 9]. Possible radiologic appearance depends on the menstrual cycle phase, ratio of stromal and glandular elements, amount of hemorrhagic imbibition of ectopia, and degree of inflammation and fibrosis in the surrounding tissues [9].

In most cases, EAAW is located directly in the thickness of the postoperative scar after Pfannenstiel laparotomy, predominantly in the left corner (66 %), and in rare cases, ectopias at a 5—6 cm away from the former incision line have been described [3, 13]. According to the localization in layers of the anterior abdominal wall, EAAW are divided into: superficial — placed in subcutaneous tissue (above the aponeurosis); intermediate — with infiltration of fascia and rectus abdominal muscle sheet; and deep — when ectopia is located in the thickness of the rectus abdominis or involved peritoneum [2]. As maintained by E. Piriyev et al., out of 80 cases of EAAW, ectopias were localized predominantly epifascial (72.5 %) and in 27.5 % — subfascial or with involvement of all anterior abdominal wall layers [13]. According to a number of studies, involvement of fascia in endometrial ectopia was noted in 60.0—71.4 % of EAAW cases [3, 13, 15].

EAAWs are mostly located in the corners of the postoperative scar after Pfannenstiel laparotomy [11]. A similar pattern was noted in the study of P. Zhang et al. (2019), where localization of endometriomas in the ends of scars after Pfannenstiel laparotomy was observed in 83 % of cases and after midline laparotomy — in 84.2 %. Moreover, the authors suggested that Pfannenstiel laparotomy is more predisposed to EAAW formation compared to midline laparotomy [15]. The mean size of EAAW in published clinical series was 22—42 mm [2, 3, 7—9, 11, 13], and in few reports, the size of endometrial ectopia reached 14 cm [4].

Fine-needle aspiration biopsy is used by some authors to clarify the diagnosis of EAAW and to exclude malignancy [3, 6, 8, 11, 14]. However, the use of this method for diagnosis of EAAW is rather controversial due to potential implantation along the puncture channel, and therefore, its excision is considered mandatory during subsequent surgery [1, 4, 6].

Actually, the use of hormonal drugs is not considered an independent method for EAAW treatment

as the severity of symptoms decreases only while taking the drugs and recovers after discontinuation of treatment [1, 3, 6]. According to current recommendations, hormones are used in patients who refuse surgery, as well as in premenopausal women or within the postoperative period to prevent recurrence [6, 11].

Surgical excision is the mainstay of treatment for symptomatic EAAW [1, 2, 4, 6]. The generally recognized principles of surgery for EAAW include excision of endometriomas together with surrounding fibrosis within healthy tissue (R0 resection) and thorough preservation of mass integrity to prevent re-implantation of endometrial cells [2, 6]. Therefore, a number of studies recommend maintaining a distance of 5—10 mm from the edges of endometrioma [1, 8].

In cases of aponeurosis excision during surgical removal of EAAW, further approach depends on size of the formed fascial defect. Thus, small defects are sutured according to the tension free principles [1, 2, 6], and polypropylene meshes are recommended to replace aponeurosis defects larger than 3 cm [1, 2, 6, 14]. The frequency of anterior abdominal wall reconstruction using synthetic grafts in different series of patients with EAAW ranged from 6.7 % to 36.4 % of cases [2, 3, 6—8, 11].

In cases where EAAW is located in the rectus abdominis with spread to the peritoneum, the use of laparoscopic techniques for surgical ablation of endometrial ectopias in the anterior abdominal wall and pelvic peritoneum is recommended [2, 3, 6]. It should be noted that concomitant pelvic endometriosis (adenomyosis) in patients with EAAW can be diagnosed in 8.7—96.2 % of cases [3, 9, 12, 13].

Various percutaneous ablation options have been proposed as an alternative to surgical treatment of EAAW, including: (1) USG-controlled sclerotherapy with alcohol, polidocanol; (2) Chemical cauterization with silver nitrate; (3) Laser vaporization; (4) Cryoablation; and (5) High-intensity focused ultrasound [1, 5]. The common disadvantage of the mentioned methods is the inability to confirm diagnosis pathomorphologically and to exclude malignancy [11].

Histopathologic examination of the removed anterior abdominal wall masses is considered to be the final stage of EAAW diagnosis and includes detection of endometrial glands surrounded by cytogenic stroma with foci of hemorrhages (hemosiderin) and characteristic signs of hormonal transformation in the secretory or proliferative phases [4, 7, 9, 11]. Immunohistochemistry with positive expression in cytogenic stroma (CD10, PR, ERα) and endometrial glandular structures (CK7, PR, ERα, Ki67) is a desirable additional method of EAAW diagnosis [4, 7, 13].

Malignant transformation of EAAWs is a rare phenomenon, with an incidence of less than 1 %, and its main histopathological variants are represented by clear cell carcinoma and endometrioid adenocarcinoma [7, 10, 14]. G. Liu et al. (2021), based on a systematic review of the literature, stated that there are currently no standardized treatment protocols for malignant EAAW [10].

Although no recurrence of EAAW has been observed in most studies [2, 4, 8], however, few publications indicate that its incidence can be as high as 3.3—15.4 % at follow-up times ranging from 12 to 36 months [7, 11, 12].

Conclusions

Thus, the presence of a tumour-like mass in the postoperative scar after obstetric and gynecological interventions, accompanied by catamenial pain and its increase in volume during menstruation, is characteristic for EAAW. Surgery remains the leading method for EAAW treatment, and its optimal volume is considered R0 resection with preservation of endometrioma integrity. The final diagnosis of EAAW requires pathomorphologic and immunohistochemical confirmation.

Declaration of interests

The authors declare that they have no conflicts of interest and that they have no financial ties to disclose.

Ethics approval and written informed consents statements

Oral and written informed consent was obtained from the patient to publish the patient-related data in anonymized form.

Authors contributions

A. E. Mishina: project development, management, manuscript writing; E. V. Gutu: data collection, manuscript editing; I. V. Mishin: project development, data collection, manuscript editing; and S. E. Gutu: data collection, manuscript editing. All authors read and approved the final manuscript.

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Біфокальні ендометріоми з розрізом Пфанненштиля. Клінічний випадок

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Ендометріома передньої черевної стінки (ЕПЧС) — досить рідкісний варіант екстрагенітального ендометріозу, який у більшості випадків виникає після акушерсько-гінекологічних маніпуляцій. ЕПЧС представлявся переважно як одна пухлиноподібна маса, а множинні ектопії спостерігалися лише в 1,9—5,6 % випадків, виключно після лапаротомії за Пфанненштилем.

Представлено клінічний випадок пацієнтки віком 37 років, яка скаржилася на великі пухлиноподібні вузли вздовж післяопераційного рубця на передній черевній стінці, що супроводжуються сильним циклічним катаменіальним болем. Крім того, пацієнтка відзначила збільшення розмірів пухлини під час менструації. Тридцять три місяці тому їй зробили плановий кесарів розтин за акушерськими показаннями. За даними ультразвукового дослідження та комп'ютерної томографії встановлено наявність у кутах післяопераційного рубця двох ендометріом передньої черевної стінки розмірами 46 × 32 × 31 та 14 × 18 × 13 мм. Обидва вогнища були вирізані без порушення їхньої цілісності. Фасціальний дефект заміщено синтетичною поліпропіленовою сіткою. Діагноз ЕПЧС був остаточно підтверджений на основі патологічних (наявність ендометріальних залоз і цитогенної строми) та імуногістохімічних (позитивна мембранна експресія CD10 в цитогенній стромі, інтенсивна цитоплазматична експресія CK7 в ендометріальних залозах, помітна ядерна експресія прогестерону (PR) і естрогену (ER-α) рецепторів в ендометріальних залозах і цитогенній стромі, дослідження індексу проліферативної активності Ki-67 — 2 %). Під час контрольного обстеження через 19 міс пацієнтка була безсимптомною. За даними фізикального обстеження та ультразвукового сканування не виявлено жодних ознак рецидиву.

Ендометріоз черевної стінки є рідкісним захворюванням. Клініцисти повинні знати про цю патологію, особливо у жінок з хворобливою пухлиною біля рубця після попередньої акушерської та гінекологічної операції. Найкращим методом лікування ендометріоми є хірургічне втручання, оптимальним його обсягом вважають резекцію R0 зі збереженням цілісності ендометріоми. Остаточний діагноз ЕПЧС потребує патологічного та імуногістохімічного підтвердження.

Ключові слова: позатазовий ендометріоз, рубцевий ендометріоз, ендометріоз черевної стінки, кесарів розтин.

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Endoscopic transluminal necrosectomy in the complex treatment of a patient with acute infected necrotizing pancreatitis. Clinical case

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This study presents a clinical case of acute pancreatitis treatment, which manifested as infected walled-off necrosis in a 49-year-old obese woman. Diagnosis and treatment were provided by a multidisciplinary team comprising surgeons, anesthesiologists, interventional radiologists, and endoscopists. The treatment strategy followed a «step-up approach,» a modern technique involving gradual progression from less to more invasive methods, thereby reducing the physiological stress on the patient. This approach has demonstrated efficacy in numerous studies.

In Western countries, endoscopic transluminal necrosectomy is gaining popularity, and our clinic has been implementing it successfully since 2021. Despite its effectiveness, clinicians still encounter challenges when opting for endoscopic transluminal interventions over other minimally invasive methods. Key issues include determining the timing and frequency of interventions, choosing debridement techniques and antiseptics for walled-off necrosis, and establishing criteria for transitioning to more invasive procedures. Today, researchers handle these nuances on a case-by-case basis, relying on the expertise and proficiency of a specific specialized department, which necessitates further research.

In this case the patient achieved complete debridement of a localized fluid/necrosis collection through a step-wise approach. Initial management involved ultrasound-guided percutaneous drainage and lavage, followed by four sessions of endoscopic transluminal necrosectomy as the final minimally invasive intervention. We assess the unfavorable long-term outcomes, 2.5 years post-treatment, as negligible.

Keywords
acute pancreatitis, acute necrotizing pancreatitis, acute infected pancreatic necrosis, walled-off necrosis, endoscopic transluminal/transgastric necrosectomy, direct endoscopic necrosectomy.

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Acute pancreatitis is one of the most common gastrointestinal disorders requiring acute hospitalization [22]. In most cases, AP is a relatively mild, self-limiting condition that can be managed with supportive care and has few long-term consequences. [5]. Acute necrotizing pancreatitis (ANP), a severe form of AP, affects 10–20 % of AP patients and is characterized by extended hospitalization, multiple organ failure, infection, the need for extensive therapy and surgical interventions, complications, and repeated hospital admissions. The mortality rate associated with ANP ranges from 15 % to 39 %, depending on the presence

of infection in the necrotic area [7]. Currently, minimally invasive treatment methods for acute necrotizing pancreatitis form the basis of surgical tactics, reducing mortality and the number of complications, and, in most cases, allowing for the avoidance or postponement of open surgery [8].

Clinical case

Patient P., 49 years old woman, was delivered on November 14, 2021, by the emergency medical care team to the Kyiv City Clinical Emergency Hospital with a diagnosis of AP? perforation of a hollow organ? Upon admission: complaints of intense pain in the epigastrium, nausea, repeated vomiting of food, severe abdominal distension, lack of bowel movement and passing of gases, dryness in the oral cavity.

Medical history: according to the patient, stomach ache appeared within a day, gradually intensified, and an emergency medical team was called; the pain attack developed after alcohol and fatty food consumption. Concomitant diseases: IHD, stage 2 hypertension, class III obesity (height 172 cm, weight 118 kg); in anamnesis — extirpation of the uterus with appendages in 2016.

Objectively: the general condition of the patient is of medium severity; pulse 88 bpm, blood pressure — 200/100 mm Hg, body temperature — 37.1 °C. On palpation, the abdomen is soft, swollen, painful in the epigastric and mesogastric regions, symptoms of peritoneal irritation are weakly positive. Auscultation reveals absent bowel sounds. ASA Physical Status Classification System — 3. Total blood count: leukocytes $13.6 \cdot 10^9$/l, hemoglobin — 161 g/l. Biochemistry blood test: chylous blood. X-ray of abdominal organs: free gas, horizontal fluid levels were not detected. X-ray of the organs of the chest cavity: the pulmonary pattern is enhanced, deformed in all lung fields, the roots of the lungs are compacted, the heart is not enlarged, the sinuses are free. Ultrasound examination (ultrasound): there is free fluid in the suprahepatic space of 24 mm, in Morrison's pouch of 7 mm, between the loops of the intestine of 15 mm in certain areas; the liver: right/left lobes — 152/80 mm, respectively, echogenicity is increased, heterogeneous, liver steatosis, the pancreas is not visualized. Esophagogastroduodenoscopy (EGD): impaired gastric and duodenal motility according to the hypotonic type; no signs of perforation were detected; a nasojejunal feeding tube was installed.

Preliminary diagnosis: AP of moderate severity. Considering the severity of the patient's condition due to acute pain syndrome and local complications such as free fluid in the abdominal cavity and unstable hemodynamics, the patient was admitted to the general intensive care unit. During the first day of hospitalization, the rule of «four catheters» by Y. M. Susak [1] was applied: the left subclavian vein and the epidural space ThIX–ThX were catheterized a nasojejunal feeding tube was installed during EGD, and a diagnostic laparocentesis with abdominal drainage was performed: about 1000 ml of brown contents were obtained (α-amylase — 849 g/h/l. On the first day of hospitalization, 5 l of crystalloid solutions were administered by intravenous infusion. On the first day, the patient's condition was stabilized (pain syndrome reduced, hemodynamics normalized to 140/90 mm Hg). The patient was then transferred to an on-call surgical department. 300—100 ml of brown, then serous fluid was secreted from the abdominal cavity drainage every day; once the debit of secretions had decreased to less than 50 ml/day, the drainage was removed on day 45.

Ultrasound as of November 24, 2021: signs of diffuse changes in the liver parenchyma characteristic of fatty hepatosis, moderate hepatomegaly, chronic calculous cholecystitis, acute necrotizing pancreatitis, parapancreatitis, free fluid in the omental bursa, infiltration of retroperitoneal tissue relative to the left lateral canal.

November 26, 2021 — drainage of the omental bursa under ultrasound control with pigtail drainage 9 Fr — 220 mm: 400 ml of brown cloudy liquid was released at one time — taken for the bacteriological examination; the cavity was washed with a 2 % betadine solution. During hospitalization, the drain was washed several times a day with a saline solution and a 2 % betadine solution up to 50 ml to clean the necrotic area and ensure drainage patency; the nature of the drainage content — detritus, pus, washing liquid up to 150—50 ml/day.

November 30, 2021 — the result of the microbiological examination of a punctate from the omental bursa: *Acinetobacter baumannii*, insignificant growth, sensitive to gentamicin, tobramycin.

November 29, 2021 — the abdominal CT-scan with contrast: destructive pancreatitis, pronounced parapancreatic infiltration with spread to the root of the mesentery, the omental bursa, the splenic hilum and part of the liver, along the greater curvature of the stomach, to the epigastric region and duodenum, covering the colon under the anterior abdominal wall, Gerot's fascia more on the left, paracollar tissue more on the left, and along the flanks of the abdominal cavity to the small pelvis, with the presence of free fluid infiltration along the course of 10—27 mm, including in the pelvic cavity; the state after drainage. Ascites. Calculous cholecystitis.

Infiltration of the anterior abdominal wall along the midline with a limited fluid component.

On December 3, 2021, the patient was transferred to the specialized department of surgery of the liver, bile ducts and pancreas (surgical department No 2) of the Kyiv City Clinical Emergency Hospital with a diagnosis of AP of moderate severity. Marshall Organ Failure Score at admission — 1 point (creatinine 156 μmol/l).

On December 10, 2021, taking into account complaints of difficulty breathing, the frequency of respiratory movements of 18/min, a puncture of the left pleural cavity was performed under ultrasound control. 250 ml of translucent yellowish exudate was obtained, after which an improvement in respiratory function was observed; the frequency of respiratory movements was 12/min.

December 15, 2021 — the abdominal CT-scan with contrast: the state after drainage of a fluid/necrosis collection under ultrasound control for acute necrotizing pancreatitis with extrapancreatic necrosis with the formation of multiple fluid collectors in the abdominal cavity and retroperitoneal space, taking into account the clinical pattern — with infection. Late phase. Balthazar Severity Index 4(E) Ascites. Left-sided pneumohydrothorax. Splenic infarction (Fig. 1).

December 15, 2021 — a puncture of the right and left pleural cavity under ultrasound control; 150 and 300 ml of translucent yellowish exudate were obtained, respectively, after which an improvement in respiratory function was observed. Conservative treatment was continued.

December 16, 2021 — the result of repeated microbiological examination of secretions from the omental bursa: *Acinetobacter baumanii*, sensitive to tobramycin.

December 17, 2021 — the drainage of the omental bursa was replaced with a new one, with a larger diameter of 12 Fr. The daily three-time washing of the cavity of the necrotic collection with a saline solution and a 2 % betadine solution up to 50 ml was continued to clean up the necrotic focus and ensure patency of the drainage. Debit through the drainage was 150—50 ml/day of detritus with washing liquid.

Since the patient refused the proposed open necrosectomy, conservative treatment was continued, during which the patient's condition was relatively stable.

January 10, 2022 — abdominal CT scan with contrast: the state after drainage of a fluid/necrosis collection under ultrasound control for acute necrotizing pancreatitis with extrapancreatic necrosis spreading to the root of the mesentery, gastro-omental pouch, along the anterior layer of the renal fascia, perirenal space on the left. In comparison with the abdominal CT scan as of December 15, 2021, the size of the necrotic collector increased and CT signs of infection appeared. Ascites. Left-sided hydrothorax. Infarction of the spleen. GSD: gallstones (Fig. 2).

January 10, 2022 — EGD: moderate compression of the stomach from the outside along the back wall from the cardia to the antrum, more pronounced in the antrum, erythematous gastropathy.

Clinical diagnosis: acute infected necrotic pancreatitis, walled-off necrosis (Atlanta 2012), a course of moderate severity.

The patient was offered an alternative minimally invasive treatment — endoscopic transluminal

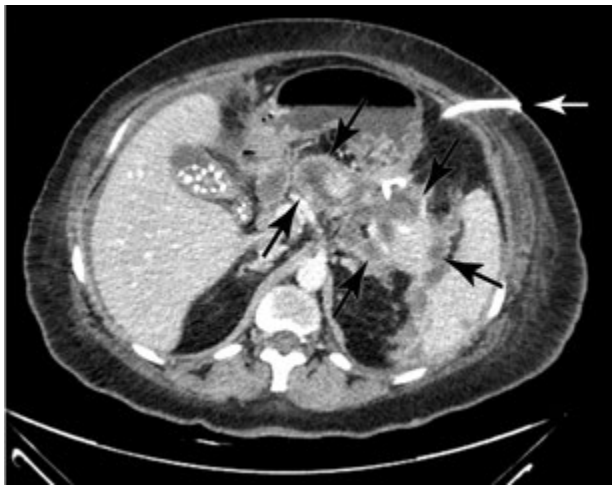

Figure 1. **Abdominal CT scan with contrast on December 15, 2021: a fluid/necrosis collection is indicated by the black arrows; a pigtail-type percutaneous drainage is visualized in the cavity of the collection and indicated by the white arrow; the formation of the delineation and walls of the collection**

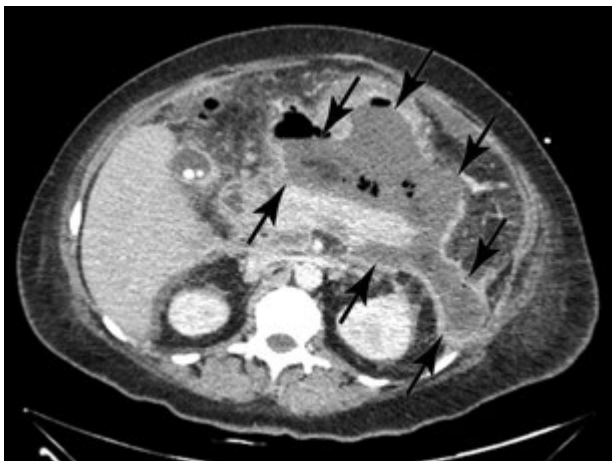

Figure 2. **Abdominal CT scan with contrast on January 10, 2022: a fluid/necrosis collection is indicated by the black arrows; the delineation and the wall of the collection are clearly visualized**

necrosectomy — and the patient consented to the operation.

January 13, 2022 — endoscopic transgastric necrosectomy (Fig. 3), debridement and drainage of the WON cavity with No 2 plastic double pigtail stents 10 Fr — 5 cm were performed under general anesthesia. After the operation, a noticeable reduction in pain syndrome was observed, the respiratory rate normalized to 14/min, and the maximum daily body temperature gradually decreased from 38–39° to 37.5°C.

January 17, 2022 — a puncture of the right pleural cavity under ultrasound control; 200 ml of translucent yellowish exudate was evacuated.

January 19, 2022 — repeated endoscopic transgastric necrosectomy (session No 2) under general anesthesia. The postoperative period was uneventful, and the patient's condition was stable.

January 26, 2022 — repeated endoscopic transgastric necrosectomy (session No 3) under general anesthesia. Moderately positive dynamics was noted after the operation.

February 1, 2022 — repeated endoscopic transgastric necrosectomy (session No 4, Fig. 4—6) under general anesthesia. At the end of the procedure, the plastic stents installed during the first session were replaced with a new, identical stent No 1. The positive dynamics were noted after the operation: the temperature gradually decreased to 37°C, appetite and sleep normalized, and stools were regular and well-formed; subjectively, the patient felt stronger, began to get out of bed more frequently; discharge from the percutaneous drainage of the localized necrotic collection cavity significantly decreased (less than 50 ml/day), and was removed. Fig. 7 depicts the blood leukocyte count during endoscopic transgastric necrosectomy sessions.

During the entire period of treatment, infusion therapy was carried out taking into account the patient's body weight, tolerance and hematocrit; antibiotic therapy according to the principle of escalation (empirically — levofloxacin 500 mg and metronidazole 500 mg IV twice a day; after bacteriological examination — tobramycin 80 mg IV infusion in saline solution; ceftriaxone 1000 mg + metronidazole 500

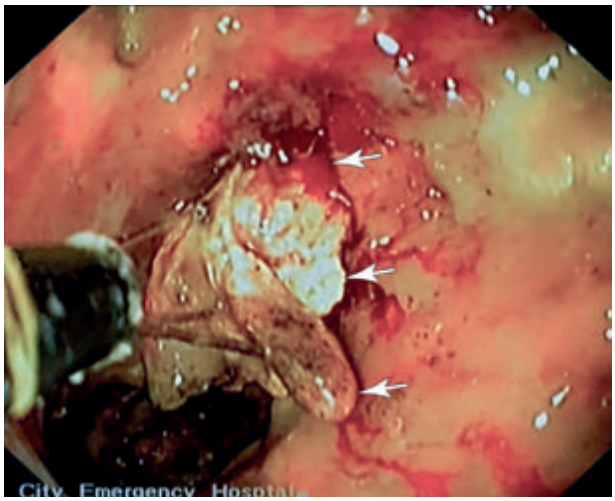

Figure 4. **Session No 4, endoscopic transluminal necrosectomy using an endoscopic tripod; necrotic sequestration is indicated by arrows**

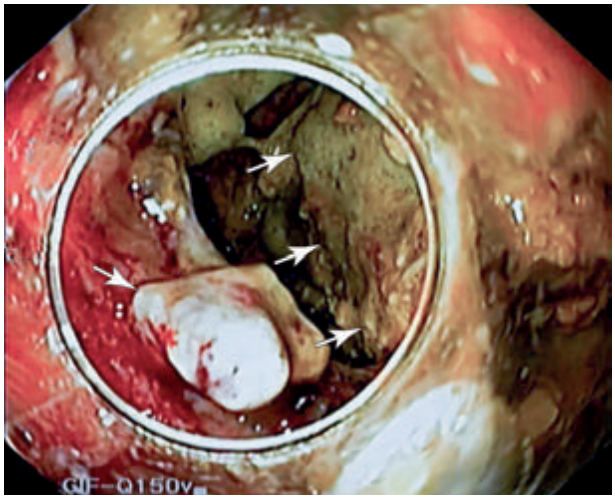

Figure 3. **Session No 1, the view of the WON cavity during the first endoscopic transluminal necrosectomy: a large number of necrotic sequestrations and pus are visualized, as indicated by arrows; on the walls of the cavity, loose granulations under fibrin, pronounced contact bleeding**

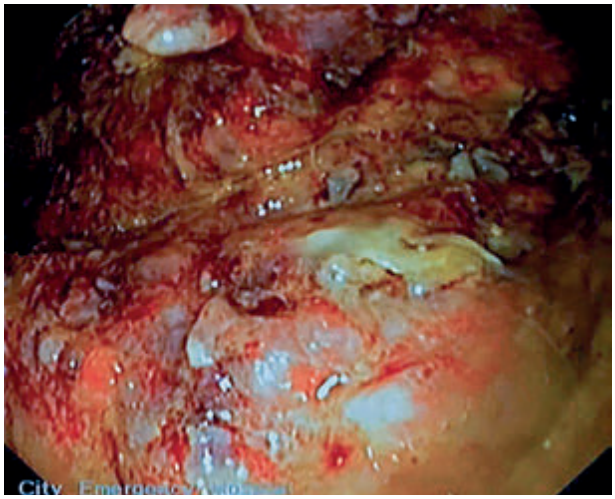

Figure 5. **Session No 4, the view of the WON cavity at the end of the 4th session of endoscopic necrosectomy: sequestrations and pus are absent, granulations have increased on the walls, and the amount of fibrin and bleeding has significantly decreased**

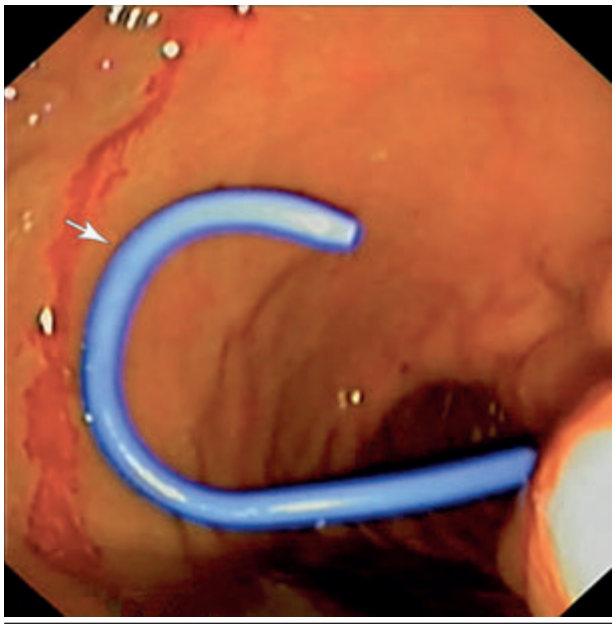

Figure 6. **Session No 4, a plastic double pigtail stent ∅ 10 Fr — 5 cm installed transgastrically in the WON cavity, as indicated by the white arrow**

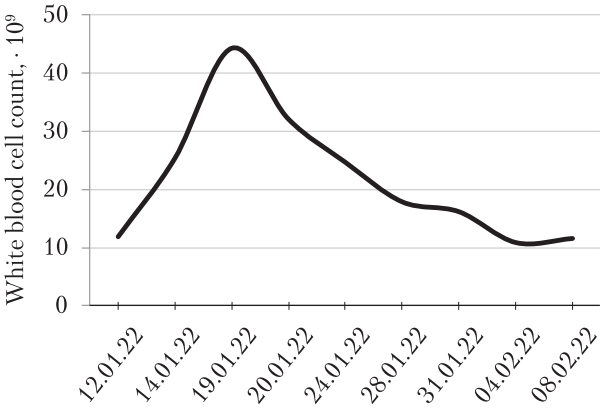

Figure 7. **Blood leukocyte count during endoscopic transgastric necrosectomy sessions**

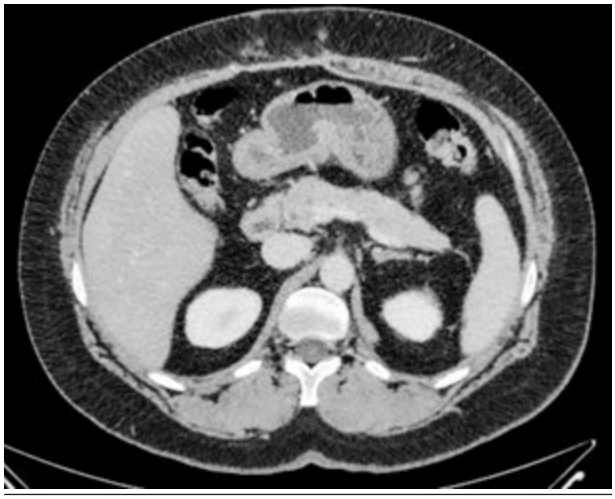

Figure 8. **Abdominal CT scan with contrast on August 28, 2024**

mg IV twice a day; meropenem 1000 mg + amoxil-K 1200 mg IV twice a day; cefosulbin 1000 mg + metronidazole 500 mg + levofloxacin 500 mg IV twice a day; epidural anesthesia with bupivacaine solution 5 mg/ml — 3.0 ml up to 10 ml in saline solution every 3 hours for 10 days, depending on the intensity of the pain syndrome; for enteral feeding, a saline solution was administered through the nasojejunal tube at a dose of 800 ml per day and lactulose at a dose of 80 ml per day for the first three days. Subsequently, enteral feeding mixtures, broths, and compote were provided. The transition to independent feeding was carried out as the patient developed an appetite and showed no signs of nausea.

The period from the onset of the disease to the puncture of the fluid collection in the omental bursa was 12 days; the period from the onset of the disease to the first transgastric endoscopic necrosectomy was 61 days. Bed days — 95. She was discharged for outpatient treatment in a satisfactory condition on February 16, 2022. After 2.5 years, we managed to contact the patient; she did not have any complaints related to the disease. She was asked to perform an abdominal CT scan with contrast for her follow-up.

August 28, 2024 — abdominal CT scan with contrast: the state after treatment of pancreatic necrosis with signs of infection (2021); at the time of examination, signs of pancreatitis, fluid collections in the abdominal and pleural cavities were not detected (Fig. 8).

Additionally, in September 2024, the patient underwent the SF-36 score test for assessing health-related quality of life [19]:

Physical functioning	90 %
Role limitations due to physical health	50 %
Role limitations due to emotional problems	67 %
Energy/fatigue	65 %
Emotional well-being	84 %
Social functioning	88 %
Pain	100 %
General health	50 %
Health change	100 %

Discussion

Early diagnosis, early fluid resuscitation, dynamic assessment of the clinical picture, and the selection of optimal tactics are critical aspects in the management of patients with acute pancreatitis. In the case of moderate and severe forms of AP, early enteral nutrition, antibiotic therapy for acute infected pancreatic necrosis, and the ability to perform the necessary range of minimally invasive interventions are also important. Early diagnosis is critical in order to begin infusion treatment with crystalloid solutions in an appropriate

amount as soon as possible (up to 24 hours). Among infusion solutions in AP, the Ringer-lactate solution demonstrated the greatest effectiveness up to 24—48 hours after the onset of a pain attack, lowering C-reactive protein levels (CRP), reducing persistent manifestations of systemic inflammatory response syndrome (SIRS), and organ failure [16], and is recommended as the drug of choice for primary fluid resuscitation in AP [22]. To ensure the most effective therapy, individuals with AP should be admitted to a specialized department immediately. Furthermore, in circumstances where the department's therapeutic capacities are restricted, transferring a patient with severe necrotizing pancreatitis to a specialized center with the necessary minimally invasive treatment methods should be considered [6]. The updated classification of acute pancreatitis — Atlanta 2012 [5] should be used at the time of clinic admission and in the future to determine the severity of the disease, the morphological form, and the presence/absence of acute infected pancreatic necrosis. CT/MRI and ultrasound should be conducted dynamically.

Although many patients with ANP may be managed conservatively (intensive therapy, combined use of antimicrobial drugs, nutritional support, with or without drainage), about 26—38 % may require necrosectomy or other surgeries owing to complications [13]. Walled-off necrosis (WON) is one of the most severe complications of acute pancreatitis, with distinct borders, the presence of a wall, and fluid-necrotic contents. Secondary infection of the WON is associated with a poor patient condition and increases the risk of complications and mortality [21], necessitating antibiotic therapy and early invasive procedures [2]. Currently, there is no one accepted marker for the presence of acute infected pancreatic necrosis [20]. The presence of infection should be assessed comprehensively, taking into account the clinical picture (deterioration of the patient's state), imaging techniques (CT, MRI), microbiology of aspirate from peri-/pancreatic collections, and laboratory markers. Percutaneous fine needle aspiration (FNA) of peri-/pancreatic collections is not recommended as a routine procedure, but should be performed only when there is a suspicion of infection, an uncertain clinical picture, and unclear (non-informative) imaging results [3]. C-reactive protein, creatinine, prothrombin time, and lactate dehydrogenase show the strongest correlations with acute infected pancreatic necrosis [20]. Other indicators, such as interleukin-6 and procalcitonin, also correlate with acute infected pancreatic necrosis but are less frequently available.

The treatment of severe forms of AP is long-term and requires significant resources. A multidisciplinary step-up approach is currently the best recommended strategy for the treatment of acute necrotizing pancreatitis [3]. It involves a gradual transition from less invasive techniques to more invasive ones to cause the least possible stress on the patient's body. There are convincing clinical data that the «step-up approach» leads to a significant reduction in the number of complications, negative long-term consequences, and mortality in acute necrotizing pancreatitis [8].

Today, surgical treatment options for complicated forms of AP include percutaneous, endoscopic transluminal, laparoscopic, and open interventions [7, 17]. Over the past 20 years, new minimally invasive techniques have appeared, including video-assisted retroperitoneal debridement (VARD) and endoscopic transluminal necrosectomy (synonyms in the English-language literature: direct endoscopic necrosectomy, DEN, endoscopic transgastric necrosectomy) as more favourable approaches. The optimal interventional tactics for patients with suspected or proven infected pancreatic necrosis are percutaneous drainage of the necrotic collection under the control of imaging techniques (ultrasound) or endoscopic transluminal drainage followed, if necessary, by endoscopic or surgical necrosectomy [22].

Among the minimally invasive interventions for complicated forms of AP, endoscopic transluminal interventions are becoming more and more frequently used [3], and since 2021 they have been successfully implemented in our clinic. The results of endoscopic transgastric necrosectomy are encouraging. A systematic review of 10 studies of endoscopic necrosectomy found complete resolution of walled-off necrosis in 76 % of cases, with a total long-term adverse event rate of 27 % and mortality of 5 %, although patient characteristics varied between studies [9]. The Bakker randomized controlled trial showed the advantages of endoscopic transgastric necrosectomy over surgical necrosectomy with a lower risk of recurrent episodes of organ failure (0 % vs. 50 %), fewer pancreatic fistulas (10 % vs. 70 %), and lower post-procedural interleukin-6 levels ($p = 0.03$) [4]. A retrospective study by Tan confirmed that endoscopic transgastric necrosectomy had a lower complication rate and shorter hospital stay compared to surgical necrosectomy [18].

The limitations of the endoscopic approach include the necessity for multiple interventions, an inadequate endoscopic evaluation of the quantity of necrotic collections, the difficulties associated with the removal of numerous necrotic collections, the restricted feasibility of endoscopic transgastric necrosectomy in instances of retroperitoneal spread of the necrotic process, and the challenges

or impossibility of debridement of distal left-sided necrotic collections [8]. This method has technical limitations due to the lack of specialized tools, the challenge of achieving a stable confluence between the necrotic collection cavity and the hollow organ, and the difficulty of preventing damage to vital structures, such as blood vessels, within the necrotic cavity [8].

Today, there are two approaches to endoscopic transluminal interventions for walled-off necrosis: DEN, which involves performing necrosectomy during the first few sessions, regardless of the clinical course of acute pancreatitis, and the step-up approach, which involves performing DEN after primary transluminal drainage using a transluminal stent fails. Several studies [11, 14, 15] have demonstrated the advantage of the step-up approach in avoiding unnecessary DEN, showing that 20—90 % of patients with WON can be treated only with endoscopic drainage using plastic stents or a fully covered wide-diameter metal stent SEMS (self-expandable metal stent), including a specialized stent for these operations LAMS (lumen-apposing metal stent). Factors that may hinder the effectiveness of drainage-only tactics include the large size of WON, the small diameter of the stent, and the large number of solid sequestrations in the WON cavity [11, 14, 15]. Limitations in the choice of metal stents include a greater risk of bleeding compared to plastic ones; are subject to mandatory removal after resolution of the WON cavity (plastic stents can be left for a long time, if necessary, especially in the case of «disconnected pancreatic duct» syndrome); the high cost of such a stent (~500—1500 Euro).

In our clinic, an Olympus TJF-150 duodenoscope is used for transluminal access and transluminal stent installation. If necrosectomy is necessary, an Olympus GIF-Q150 gastroscope with a distal cap is used under general anesthesia with tracheal intubation to protect the airways from potential aspiration of infected WON cavity contents. The patient's position during the procedure is supine, which allows localizing the topographical position of WON in relation to the stomach according to imaging methods of diagnosis (CT or MRI). Depending on the WON attachment site, a cystotome is used to puncture the gastric or duodenal wall under endoscopic control for transluminal drainage. Then No. 2 plastic double pigtail stents with a diameter of 10 French — 5 cm are installed along the guidewire. If imaging diagnostic procedures reveal dense necrotic collections in the WON cavity, a direct necrosectomy is performed through the confluence between the gastric/duodenal cavity and the WON cavity, created by a dilatation endoballoon with a diameter of 15—20 mm. Direct necrosectomy can also be performed through a SEMS stent. Removal of sequestrations and detritus is carried out with the help of a tripod, a loop, a catch basket, and lavage of the WON cavity with antiseptic solutions. In our clinic, a 2 % betadine solution and a 1 % hydrogen peroxide solution are used for lavage of the WON cavity. There is still no evidence in the literature regarding the effectiveness and benefits of specific antiseptics. Installing transnasal drainage parallel to the stents into the WON cavity for long-term lavage is one of the options for completing the procedure.

Indications for endoscopic transluminal interventions at our clinic include a localized necrotic peri-/pancreatic collection identified on abdominal CT with contrast or abdominal MRI and situated adjacent to the stomach and/or duodenum; the duration of the illness from the first painful episode is i 4 weeks; evidence of external compression of the stomach and/or duodenum as per EGD findings. 50—60 % of patients with WON experience compression of the stomach/duodenum from the outside [8], which manifests as an obvious protrusion into the lumen and topographically correlates with the area of walled-off necrosis next to the corresponding hollow organ. If there is no evidence of severe portal hypertension, we can perform endoscopic transluminal interventions at the protrusion site without an endosonoscope (endoscopic ultrasound, EUS) [10, 23]. The use of an endosonoscope is preferable since it facilitates the visualization of large blood vessels within the tissues, reducing the risk of bleeding. Furthermore, if the WON cavity is located within the EUS visualization, EUS technology can reach it in up to 100 % of cases, allowing WON cavity achievement when there is no typical bulging into the stomach [3], and may shorten the procedure duration.

To achieve sanitation of the WON cavity from necrotic masses, 3 to 6 endoscopic transluminal sessions are necessary [7]. The number of sessions depends on the volume of WON, the extent of the necrotic process, and the consistency of the content. In some cases, the contents of the WON cavity are almost homogeneous, «cheesy», and can be easily washed out. However, in most cases, in addition to fluid, there are large sequestrations that spread in the form of honeycombs, can be attached quite tightly, and require gradual removal over several sessions as they detach into the lumen of the WON cavity. Aggressive removal of sequestrations can cause massive bleeding. To date, there are no unequivocal criteria regarding the number of necessary sessions for debridement and the time periods between

interventions. In the study by Qing Liu [12], no significant correlation was found between the interval of endoscopic necrosectomy and the following parameters, including general information about the patient, etiology of pancreatitis, biochemistry blood test (leukocyte count, neutrophil percentage, C-reactive protein), preoperative fever, distribution and size of WON, type and number of stents, and initial (empirical) necrosectomy. However, there were significant differences between necrosectomy interval and Modified CT Severity Index (MCTSI) ($p < 0.001$), WON solid/liquid ratio ($p < 0.001$) before intervention, postoperative fever ($p = 0.038$), increased C-reactive protein ($p = 0.012$) and fever before re-intervention ($p = 0.024$) [12]. In the clinical case presented by us, repeated interventions (sessions) were carried out with an interval of 6—7 days and were justified by the presence of the dense sequestrations, which could not be removed in the previous endoscopic transgastric necrosectomy session, and by the lack of significant improvement in the patient's general condition, hyperthermia, and leukocytosis. Today, it remains uncertain which cases should continue with endoscopic transluminal procedures to achieve complete debridement of WON, and which ones should transition to more invasive methods such as laparoscopic procedures. These decisions are made individually in each specific case, taking into account the clinical picture and the experience of the medical center.

We successfully achieved complete debridement of WON during 4 sessions of endoscopic transluminal necrosectomy in the clinical case we presented. We generally assessed the long-term negative consequences 2.5 years after endoscopic minimally invasive treatment of acute infected pancreatic necrosis in this patient as insignificant, using the «SF-36 score» test as our guide.

Declaration of interests

The authors declare that they have no conflicts of interest.

Authors contributions

Conception and design — N. V. Puzyr; acquisition of data — A. Y. Tkachenko, M. V. Maksymenko, V. V. Volkovetskii; drafting the article — N. V. Puzyr; critical revision of the article — A. Y. Tkachenko, L. O. Pererva, Y. M. Susak.

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Ендоскопічна транслюмінальна некрозектомія у комплексному лікуванні пацієнтки з гострим інфікованим некротичним панкреатитом. Клінічний випадок

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Представлено клінічний випадок лікування гострого панкреатиту, що набув морфологічної форми інфікованого обмеженого некротичного скупчення у жінки віком 49 років з ожирінням. Для діагностики та лікування застосовано мультидисциплінарний підхід із залученням лікарів-хірургів, анестезіологів-реаніматологів, радіологів, інтервенційних лікарів УЗД, інтервенційних ендоскопістів. У тактиці хірургічного вибору використано «step-up approach» — сучасний покроковий підхід, що передбачає поступовий перехід від менш інвазивних методів до більш інвазивних для якнайменшого стресу для організму пацієнта. Його ефективність доведено в численних дослідженнях.

Ендоскопічну транслюмінальну некрозектомію нині дедалі частіше виконують у західних країнах. Із 2021 року її успішно впроваджено в нашій клініці. Невирішеними залишаються питання щодо вибору ендоскопічних транслюмінальних втручань серед інших малоінвазивних методів, часових інтервалів між втручаннями, їх кількості, способу та режиму промивання порожнини обмеженого некротичного скупчення, вибору антисептика для промивання, критеріїв переходу до інвазивніших методів лікування, що потребує подальших досліджень. Нині для вирішення цих питань застосовують індивідуальний підхід із урахуванням можливостей та досвіду певного спеціалізованого відділення. У наведеному клінічному випадку в пацієнтки вдалося досягти повної санації обмеженого рідинно-некротичного скупчення комбінацією черезшкірного дренування під ультразвуковим контролем із лаважем (перший етап) та чотирьох сесій ендоскопічної транслюмінальної некрозектомії як основного методу малоінвазивного лікування. Віддалені негативні наслідки через 2,5 року після лікування у цієї пацієнтки оцінені нами в цілому як несуттєві.

Ключові слова: гострий панкреатит, гострий некротичний панкреатит, гострий інфікований панкреатичний некроз, обмежене некротичне скупчення, ендоскопічна транслюмінальна/трансгастральна некрозектомія, пряма ендоскопічна некрозектомія.

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Evolution of the doctrine of Zollinger-Ellison syndrome. Literature review

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Zollinger–Ellison syndrome (ZES) is a rare pathology that does not have specific clinical manifestations and is not always diagnosed in time. This is attributed to doctors' insufficient awareness of this pathology and the limited availability of the necessary examination methods. Foreign literary sources on this problem are analysed. Historical data regarding the discovery of this pathology and the origin of the syndrome's name are provided. The epidemiology of the disease is highlighted. The most characteristic clinical manifestations and possible complications of ZES are described in detail. The characteristic changes in gastric acid production associated with this pathology and their diagnostic value (sensitivity and specificity) are presented. At the same time, indicators of both basal and maximal stimulated gastric acid production are significantly increased. The most important stage in the examination of patients with suspected ZES is the determination of blood gastrin levels. At the same time, it is shown that it is not always possible to make definitive judgements in support of ZES based on gastrin indicators. An absolute criterion in favor of ZES is fasting gastrin values of 1000 pg/ml or more. When gastrin levels are less than this indicator, tests using secretin or calcium gluconate have significant diagnostic value. In these circumstances, tests with secretin or calcium gluconate are mandatory. The information on the possible localization of gastrin, the incidence of malignant transformation, and the mechanism of metastasis is given. Methods of determining gastrin localization, sensitivity, and specificity are described in detail. Based on the findings, a differentiated treatment strategy for patients with ZES is provided. Indications and contraindications for surgical and medical treatment of patients with ZES are given. The prospects of a new treatment direction - the use of targeted radiotherapy - are shown. These patients require constant monitoring by a gastroenterologist and a surgeon and periodically undergo the necessary examinations.

Keywords
Zollinger-Ellison syndrome, treatment tactics, gastrin, examination algorithm.

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Zollinger-Ellison syndrome (ZES) is a relatively rare and difficult-to-diagnose disease with no clear pathognomonic clinical manifestations.

In 1955, Robert M. Zollinger and Edwin Ellison (R. Zollinger and E. Ellison), American surgeons at Ohio State University Medical Centre, published a report on two patients who had recurrent multiple duodenal ulcers in the intestine that were resistant to antiulcer treatment and standard surgical interventions. Pronounced hypersecretion of hydrochloric acid and non-beta-cell pancreatic tumours were also reported. These authors were the first to associate gastric hypersecretion of hydrochloric acid and recurrent peptic ulcers with pancreatic islet non-beta-cell tumours [76]. Since then, this pathology has been referred to by the names of these scientists. ZES is characterised by the above-mentioned triad of symptoms.

Later, R. Gregory et al., 1960 [24] established a cause-and-effect relationship between the clinical manifestations of ZES and hyperproduction of gastrin, which is produced by a specific tumour — gastrinoma — and leads to pronounced hypersecretion of hydrochloric acid by the stomach. This publication marked the beginning of the investigation into this pathology. Many professionals, including geneticists and pathophysiologists, gastroenterologists, endocrinologists, surgeons, and oncologists, contributed their scientific and practical expertise

to this issue. The interest in ZES by specialists from various fields of medicine and biology indicates that this pathology is becoming more relevant in the global medical community. This, in turn, contributed to a more in-depth study of the pathology's etiology and pathogenetic mechanisms, as well as the development and implementation of new diagnostic methods and treatment technologies [24].

Gastrinoma is the second most common neuroendocrine tumour (NET) after insulinoma. In most cases, gastrinomas are sporadic (not familial, not hereditary). However, in approximately half of the cases, they are associated with the syndrome of multiple endocrine neoplasia type 1 (MEN 1). Various samples reveal that 20—61 % of patients with MEN 1 syndrome have gastrinoma with ZES, while 30—38 % of all gastrinoma patients have MEN 1 syndrome [6, 19].

Epidemiology. Gastrinoma is the second most common neuroendocrine neoplasia after insulinoma. In most cases, gastrinomas are sporadic (not familial, not hereditary). However, in approximately half of the cases, they are associated with the syndrome of multiple endocrine neoplasia type 1 (MEN 1). Thus, according to different samples, gastrinoma is found in 20—61 % of patients with MEN 1 syndrome, and conversely, MEN 1 syndrome is found in 30—38 % of all patients with gastrinomas [6, 19].

Gastrinoma is caused by genetic mutations that lead to the uncontrolled proliferation of hormonally active cells. At the same time, multipotent stem cells are the source of gastrin-producing NET development [11].

Among patients with idiopathic peptic ulcer disease of the stomach and duodenum, ZES, as the cause of ulcer formation (that is, this ulcer is essentially a symptomatic ulcer), is diagnosed in 0.1—1 %, and among patients with recurrent postoperative ulcers, in 2 % of cases [55].

The annual incidence of ZES is 0.3—4 cases per 1 million of the global population. According to the literature, sporadic gastrinomas (ZES) are usually detected at the age of 41 to 55 years. However, observations of these diseases are also described both in children aged 7 years and in elderly people aged 70—80 years [17].

Gastrinomas in MEN 1 (hereditary gastrinomas) usually occur in younger patients as multiple microgastrinomas with a predominant localization in the duodenum [15].

According to some authors, this pathology occurs more often in men than in women (ratio 3 : 2) [32].

However, there is another opinion according to which this pathology is diagnosed more often in women than in men [17].

According to other data, ZES is equally often diagnosed in both men and women [38].

Features of the clinical course. ZES lacks pathognomonic clinical manifestations that would allow for an unambiguous diagnosis of this pathology. However, the presence of some non-specific symptoms and clinical manifestations makes it possible to suspect ZES.

According to the literature, common nonspecific symptoms include abdominal pain (73—98 %), diarrhea (73—75 %), heartburn (44—56 %), and weight loss (7—53 %) [41]. Other symptoms are nausea, vomiting, and intestinal malabsorption [22].

In almost all cases, the initial clinical symptoms of ZES are mainly due to gastric hypersecretion of hydrochloric acid and hyperchlorhydria, leading to severe peptic ulceration and, in some cases, malabsorption and diarrhea [22].

What is more, with ZES, unlike ulcers caused by *Helicobacter pylori* or non-steroidal anti-inflammatory drugs, they often have atypical localization — the distal parts of the colon, the proximal part of the jejunum, the esophagus, as well as possible multiple ulcers of different localization, which are characterized by quite frequent complications — perforation, bleeding, penetration, stenosis [10].

Diarrhea is the second most common symptom of ZES after abdominal pain. In 3—10 % of cases, diarrhea can be the first and only manifestation of ZES. The development of chronic diarrhea in ZES is also based on hyperproduction of hydrochloric acid, which neutralizes pancreatic enzymes, accompanied by malabsorption [56].

Heartburn and episodes of vomiting with acidic stomach contents at the height of pain are also a characteristic clinical sign of ZES, which can lead to its reduction and some relief. In the future, this can also lead to the development of gastroesophageal reflux disease (GERD). According to the Los Angeles classification, the severity of GERD with ZES can vary from mild (A or B) grade to severe (C or D) grade, potentially leading to the development of complications such as esophageal stricture, Barrett's esophagus, esophageal-tracheal, or even esophageal-aortic fistula [43, 52].

Robinson A. M. et al. (2023) described two cases of esophageal perforation in patients with ZES, in which peptic stricture and esophageal ulcer developed as a result of gastroesophageal reflux. One of them developed an esophageal-aortic fistula, which led to a fatal outcome [52].

Despite the improvement of diagnostic techniques and increased awareness of doctors, it is not always possible to recognize ZES in time. It can take 4—8 years from the moment of the first symptoms to

the establishment of a diagnosis. At the same time, in connection with the widespread use of PPIs, the percentage of early diagnosis of ZES decreased by 62 % compared to the time when PPIs were prescribed much less often [36]. This is because PPIs mask the clinical picture of ZES, and these patients are often misdiagnosed as having irritable bowel syndrome or reflux disease [20].

A number of diagnostic techniques are used for timely recognition of this pathology. The study of gastric acid production indicators has enabled the establishment of specific parameters inherent in ZES, since almost all clinical manifestations of this pathology arise from the hypersecretion of hydrochloric acid due to constant stimulation by hypergastrinemia. Namely, the assessment of basal gastric acid output (BAO) and maximum stimulated gastric acid output (MAO) and their ratio was carried out according to the method developed by A. W. Kay [34].

In patients with ZES, the BAO level was increased by 4—6 times, and in some patients by more than 10 times compared to the norm. At the same time, an increased level of MAO was also observed [16].

Patients with sporadic ZES without previous acid-reducing surgical interventions (gastric resection, vagotomy) had a BAO level of ≥ 15 mEq/h. The sensitivity of this criterion is 90—98 % [39].

In patients after acid-reducing operations, the sensitivity for BAO ≥ 5 mEq/h was 81—100 %, for BAO ≥ 14.4 mEq/h — 73 %, and 37 % for BAO ≥ 19.2 mEq/h, respectively. At the same time, the specificity for the BAO criterion ≥ 5 mEq/h was 85 %, while for the other two aforementioned criteria, it was 100 % [54].

In practice, the BAO criterion of ≥ 15 mEq/h for patients without previous acid-reducing surgery, with a sensitivity of 91 %, and ≥ 5 mEq/h for patients with a history of such surgery, with a sensitivity of 100 %, is most often used to diagnose ZES [39].

The MAO criterion of ≥ 25 mEq/h in patients without acid-reducing surgery and ≥ 10 mEq/h after acid-reducing surgery had a sensitivity of 90 %. Moreover, such a criterion as the BAO/MAO ratio ≥ 0.6 had a sensitivity and specificity of over 80 % [41].

The following criteria were determined during the study of indicators of gastric acid production by the method of intragastric pH-metry. In patients with ZES after previous acid-reducing interventions on the stomach, the pH values ranged from 0.83 to 1.99 ($M = 1.14 \pm 0.04$), and in patients with an unoperated stomach, from 0.32 to 1.14 ($M = 1.05 \pm 0.06$). Moreover, the sensitivity of these indicators in both groups was 99 % [54].

The ratio of BAO/MAO indicators also has its own peculiarity in ZES. In particular, when the value of this ratio is ≥ 0.6, the sensitivity reaches 89 % with the same percentage of specificity [54].

The next criterion for assessing the secretory function of the stomach was the study of the volume of gastric output over a certain period of time. In patients with ZES, the volume of gastric acid production was 3—8 times greater than in patients with idiopathic duodenal ulcers or in the control group.

In particular, in patients with previous acid-reducing surgical interventions, the volume of gastric secretion was 247 ± 25 ml/h, and without gastric interventions, it was 314 ± 10 ml/h [8].

In patients with ZES, in the presence of diarrhea, peptic stricture of the esophagus, or cicatricial stenosis of the pyloric department, significantly higher rates of gastric acid production were observed compared to patients who did not have these symptoms. The presence or absence of abdominal pain, as well as symptoms such as heartburn, nausea, vomiting, weight loss, and bleeding, did not correlate with acid production [54].

Without a doubt, the main diagnostic criterion for the diagnosis of ZES is the determination of the level of gastrin in the blood serum. At the same time, it should be taken into account that the upper physiological level of fasting gastrin, according to various authors, can range from 100 pg/ml to 200 pg/ml. The content of gastrin from 300 pg/ml to 1000 pg/ml with the corresponding clinical picture is a reason to suspect ZES. And a level of more than 1000 pg/ml indicates the presence of a gastrinoma, provided that it is recorded in patients with peptic ulcer disease or hyperchlorhydria [2, 17].

Intermediate values of gastrin (200—1000 pg/ml) occur in 60 % of patients with ZES. At the same time, other potential causes of hypergastrinemia should be excluded. In particular, the secretion of gastrin in a normal physiological state is stimulated by distension of the antral part of the stomach, vagal stimulation, or hypercalcemia. However, it is inhibited by acidic gastric pH (negative feedback), secretin, somatostatin, vasointestinal polypeptide, glucagon, or calcitonin. Hypergastrinemia can also occur in other pathological conditions. Specifically, with hypochlorhydria or achlorhydria, chronic atrophic gastritis, pernicious anemia, or *Helicobacter pylori* infection [22].

Long-term use of proton pump inhibitors can also lead to hypergastrinemia. Therefore, before determining the level of gastrin, you should stop taking drugs in this group for at least 1 week, and H_2 histamine receptor antagonists — for 48 hours [54].

In 1972, J. I. Isenberg et al. established that in patients with ZES, there is a paradoxical increase in the level of gastrin in blood serum after intravenous injection of secretin [29].

Since then, this test has been widely implemented in practice and has acquired the status of a provocative secretin test. This test is indicated in controversial situations and for patients with suspected ZES when the fasting gastrin level does not exceed 1000 pg/ml [8].

Secretin is administered as a bolus intravenously (for 30 seconds) at a dose of 2 units/kg of body weight. Blood samples were tested for gastrin content fasting and 2.5, 5, 7.5, 10, 15, and 30 minutes after administration of secretin [22].

Different cut-off levels of gastrin increase have been proposed for evaluating the secretin test. In particular, the secretin test was considered positive with an absolute increase in gastrin concentration (by 110—200 pg/ml or more) or by 50 % of its fasting content. However, further studies revealed that an increase in serum gastrin of 120 pg/ml or more demonstrated high-test sensitivity (94 %) and 100 % specificity [22].

At the same time, false-negative results were observed in 6—20 % of patients, and false-positive results were observed in 15—39 % of cases. This could be due to the presence of pernicious anemia in patients or to their long-term use of proton pump inhibitors (PPIs). In 10 % of cases, the results of the secretin test in patients who have been taking proton pump inhibitors for a long time could be both false-positive and false-negative [57].

As an alternative to the secretin test, a test with intravenous infusion of calcium gluconate solution at a dose of 5 mg/kg/h over 3 hours was proposed. Blood samples for determination of gastrin concentration were examined before and after every 30-minute interval for 4 hours from the start of the infusion. The test results were considered positive when the gastrin level increased by 20 % or more compared to its fasting level [54].

The diagnostic value of indicators of general neuroendocrine markers (chromogranin-A, neuron-specific enolase, synaptophysin) is also limited by the fact that their specificity does not exceed 40—50 % [44].

However, the results of these techniques can be both false negative and false positive. Therefore, some difficulties in the evaluation of specific tumour markers in patients with gastrinoma require additional examination methods.

At the beginning of the study of ZES, it was considered that almost all sporadic gastrinomas are localized in the pancreas [28].

However, at the beginning of the 90s of the last century, systematic data on the localization of gastrin in the wall of the duodenum appeared. According to these sources, gastrinomas are three times more common in the pancreatic duct than in the pancreas [66, 76].

Characteristically, in 70—85 % of cases, duodenal gastrinomas are localized in the first and second portions of the duodenum. Duodenum gastrinomas are usually less than 1 cm in size, often multiple, and account for approximately 50—88 % of sporadic ZES-associated gastrinomas and 70—100 % of MEN 1 associated gastrinomas [49].

In 50 % of cases, gastrinoma is localized in the mucosa or submucosa of the duodenum [70].

Diametrical changes in the view of gastrin localization over the last few decades are certainly related to the improvement of instrumental diagnostic methods [31].

Given that gastrinomas of the duodenum were often small in size, mobilization of the duodenum, duodenotomy, and intraoperative transillumination of the duodenum are used for their careful search [18, 27, 64].

Characteristically, duodenal and pancreatic gastrinomas differ in their biological essence. In particular, pancreatic gastrinomas, unlike duodenal gastrinomas, have a much higher rate of liver metastases, which is one of the main factors in long-term survival, resulting in patients with pancreatic gastrinomas having a worse prognosis. Duodenal gastrinomas often metastasize to regional lymph nodes [13, 50, 67].

The results of further studies showed that about 80 % of gastrinomas are localized in an anatomical area called the gastrinoma triangle. Its vertices are the junction of the vesical and common bile ducts, the point of intersection of the middle and lower thirds of the duodenum, and the projection of the zone between the head and body of the pancreas [60].

Later, information appeared about the localization of gastrin in the lymph nodes of the abdominal cavity (primary lymphonodular gastrinoma). In particular, J. A. Norton et al. [49, 50] claimed that in 10—15 % of cases, primary gastrinomas are localized in peripancreatic and periduodenal lymph nodes. The possibility of primary localization of gastrin in lymph nodes is confirmed by the results of studies that report long-term (up to 20 years) recurrence-free survival after removal of only the lymph node in patients with sporadic ZES compared to patients after resection of primary duodenal or pancreatic gastrinoma [5, 12]. Primary sporadic gastrinomas can be localized not only in the pancreas, duodenum, and lymph nodes. In 5 % of cases, they were located in the ovaries, liver, biliary tract, stomach, kidneys, jejunum, and esophagus [13, 69].

According to the literature, primary localization of gastrin in the liver was observed only in 35 patients. Moreover, it is characteristic that in most of

the registered cases, there were single gastrinomas, and only 5 (14 %) had multiple tumours [25].

As a rule, gastrinoma metastasizes to the liver, regional lymph nodes, and bones. Metastases in the spleen, peritoneum, and mediastinum are less common. An important predictor of the presence of metastases in the liver is the localization of the tumour in the liver with a size of more than 3 cm [31].

Further diagnostic procedures are aimed at localization with gastrin. An important stage in the examination of a patient with ZES is the topical diagnosis of gastrinoma, which can be quite difficult.

Esophagogastroduodenoscopy (EGD) is used to visually assess the condition of the esophagus, stomach, and duodenum and to identify symptomatic ulcers of various locations and their possible complications. Duodenoscopy can also provide information about duodenal gastrinomas [17].

According to the literature, the sensitivity of transabdominal ultrasonography averaged 39 % (17—79 %) [9, 34].

Non-invasive imaging is primarily performed to assess the extent of the primary tumor or metastases. CT and MRI can detect tumors larger than 3 cm, but their results are questionable if the tumor is less than 3 cm [17]. According to D. V. Sahani [57] traditional imaging methods, which include computed tomography (CT) and magnetic resonance imaging (MRI), have low sensitivity that correlates with tumor size. Thus, the sensitivity does not exceed 20 % for gastrinomas less than 1 cm in size, 30—40 % for those between 1 and 3 cm, and exceeds 50 % for those more than 4 cm.

Computed tomography (CT) with contrast is informative in cases where the primary tumour is larger than 1 cm. When the tumour is located in the head of the pancreas and has metastases in the liver, the sensitivity is from 59 % to 78 %, and the specificity is from 95 % to 98 %, respectively. Conversely, the sensitivity decreases if the tumour is less than 1 cm, especially if it is located outside the pancreas [36].

MRI is considered one of the most sensitive imaging methods for liver and skeletal bone metastases in patients with NET and is recommended for monitoring the tumour's response to therapy. Contrast-enhanced MRI has shown a high specificity (namely, 100 %) in detecting small pancreatic gastrinomas and liver metastases, while its sensitivity varies from 25 % to 85 %. It should be noted that MRI showed a higher sensitivity for detecting liver metastases compared to CT [63].

Multidetector spiral computed tomography (MSCT) allows to detect a tumour in no more than 50 % of cases, and when the tumour size is less than 1 cm, the sensitivity decreases almost 2 times [34].

Endoscopic ultrasonography — endosonography (EUS), which allows detecting small tumours and determining their exact localization, has been widely used in the diagnosis of NET. The sensitivity of endoscopic ultrasonography in patients with NET pancreas is approximately 94 %, and in combination with computer tomography it reaches 100 % [9, 17].

Endoscopic ultrasound has become an important diagnostic test for the localization of gastrin, especially small (< 2 cm) pancreatic lesions. Its sensitivity and specificity are 75 %-100 % and 95 %, respectively, for pancreatic tumours. Unfortunately, its sensitivity sharply decreases in cases of duodenal localization, ranging from 38 % to 63 %. An additional advantage of this technique is the possibility of taking cytological/histological samples using a puncture/fine needle biopsy (FNA/B) to confirm the diagnosis of NET. False-negative results are possible mainly due to the low quality of the biopsy material. EUS-FNA/B is considered the primary technique for pancreatic tumour sampling, with a sensitivity of 80 % to 90 %, a specificity of 96 %, and a screening adequacy rate of 83—93 % [3, 73].

Endosonography is important in detecting multiple lesions of the pancreas in MEN 1 syndrome, as indicated by a number of authors, with a sensitivity of 55—88 %. However, despite the high efficiency of endoscopic ultrasonography (EUS), there are a number of limitations to its use. In particular, EUS has rather limited indications for tumor localization in the tail of the pancreas. This technique also has a low sensitivity for diagnosing duodenal gastrinoma. Tumour sizes less than 5 mm also significantly reduce the effectiveness of this method, especially in MEN 1 syndrome [62].

However, the results of using modern preoperative diagnostic methods to determine the prevalence of the tumour process make it possible to detect no more than 50 % of metastatic foci in the liver and less than 30 % of metastases up to 1.0 cm in size [14].

The informativeness of these diagnostic techniques in the recognition of extrahepatic metastases of NET (lymph nodes, peritoneum, bones, lungs) is even less [13].

Somatostatin receptor scintigraphy (SRS) is more sensitive than conventional imaging studies, including CT and MRI, and has a higher specificity for detecting extrahepatic gastrinoma. SRS involves the use of indium (In)-labeled octreotide, which has a strong affinity for somatostatin type 2 receptors found on gastrinoma cells and is called Octreoscan. This method showed quite good sensitivity (between 77 %-78 %) and good specificity (93 %-94 %) for detecting the primary tumour and

its metastases. However, sensitivity decreases for tumours smaller than 1 cm [61].

Visualization using PET-CT with 68 Ga-labelled somatostatin analogues has the highest sensitivity for the localization of P-NETs, as in general for other NETs, and also has a high specificity. In different studies of P-NETs, sensitivity ranged from 86 to 100 % (mean 93 %), and specificity ranged from 79 to 100 % (mean 96 %) for all P-NETs. This technique is particularly informative for localization of the primary tumour and determination of the stage of the disease, including metastases to other organs [40, 58, 68].

Non-invasive molecular imaging using positron emission tomography (PET) and somatostatin receptor (SSTR) indicators, combined with metabolic imaging using 2-[18F]Fluoro-2-deoxy-2-D-glucose (18 FDG), enables the evaluation of the tumour's structure and heterogeneity [58].

It is now well established that molecular PET/CT imaging using SSTR scanning in combination with FDG radioactive tracers plays a significant additional role in staging NET, changing its stage, and selecting patients for further treatment [45].

For localizing duodenal gastrinoma, the most informative method is transillumination [48].

Despite the availability of highly informative imaging methods, including radioisotope studies (scintigraphy with octreoscan, PET-CT with 68Ga), the localization of primary NET in 10—15 % of patients remains undetermined [71, 72].

Among the invasive examination methods aimed at establishing a diagnosis and determining the localization of the tumour, angiographic examination of the branches of the abdominal trunk and superior mesenteric artery, percutaneous transhepatic blood sampling with determination of the level of immunoreactive gastrin, as well as blood sampling from the hepatic veins after intra-arterial stimulation of various parts of the pancreas, are currently used. This is followed by the determination of the level of immunoreactive gastrin [7, 35].

However, even in patients with sporadic ZES and negative preoperative imaging studies, an experienced surgeon will detect gastrinoma in 98 % of patients, with 50 % achieving biological remission of the disease following surgery, which is comparable to the outcomes in patients with positive results [47].

Thus, in the vast majority of cases, modern methods of examination make it possible to diagnose ZES, determine the localization of gastrinoma, and develop a treatment strategy.

The main goals of drug therapy for ZES are to reduce the hypersecretion of hydrochloric acid as well as control the growth of the tumour and its metastases [4].

Currently, the «gold standard» of antisecretory therapy is the use of proton pump inhibitors (PPIs), the effectiveness of which has been proven in patients of this category [37, 39]. The main goal of using PPIs in patients with ZES is to achieve stable clinical and endoscopic remission. Various studies have shown that in patients with ZES, a reliable criterion demonstrating adequate control of the secretory function is BAO less than 10 mEq/h until the next dose of the drug [65].

In cases of ZES associated with MEN 1 syndrome, severe reflux esophagitis, or in patients after gastric surgery, the BAO levels should not exceed 5 mEq/h. To achieve the indicated goals of PPI therapy with an uncomplicated course of ZES, an initial dose equivalent to 60 mg/day of omeprazole is recommended. In other cases, the daily dose should be two times higher, divided into two doses (60 mg twice a day). If the level of BAO against the background of the indicated doses remains higher than 10 mEq/h, the PPI dose should be gradually increased and divided into 2 doses until the indicated goal is reached [4, 46].

Conservative treatment of PPIs with the correct dose selection ensures the absence of ulcer recurrence, which significantly affects the range of causes of mortality. Indeed, it contributed to a significant reduction in mortality from bleeding and perforations and an increase in the life expectancy of patients with ZES. In recent decades, the progression of the tumour process has caused more than half of the fatal consequences in patients with ZES [65].

The administration of synthetic analogues of somatostatin to patients with ZES not only suppresses the secretion of hydrochloric acid but also has an antitumour effect. The most common analogue of somatostatin on the market is octreotide. In addition, long-acting analogues of somatostatin (lanreotide, octreotide, somatulin, etc.) are now available. Their feasibility is determined by their comparable effectiveness at significantly lower cost. In a study involving 15 patients with ZES treated with somatostatin analogues, 53 % exhibited tumour advancement, 41 % experienced stabilisation, and just 6 % achieved tumour regression [59].

At one time, interferon-α (in a number of cases in combination with octreotide) was often used to stabilize the growth of pancreatic gastrin. According to the literature, interferon-α therapy led to the tumour's stabilization in 20—40 % of cases, and in 12 % of cases, its regression was observed [10].

The use of the technique of molecularly directed («targeted») therapy for the conservative treatment of NET has shown its effectiveness. In particular, this type of oncotherapy includes multitarget inhibitors of

receptors with tyrosine kinase activity (sunitinib) and mTOR inhibitors (everolimus, temsirolimus) [23].

The administration of sunitinib to 107 patients (66 with NET of the pancreas and 41 with carcinoid) resulted in tumour size reduction in 17 % of patients and stabilization in 68 %. In studies using mTOR inhibitors, the proportion of patients who responded to therapy was 7 % for temsirolimus and 15 % for everolimus [30].

Peptide-receptor radionuclide therapy (PRRT) is a promising direction in the treatment of NET. It is a highly targeted and effective form of radiopharmaceutical therapy (RFT) with minimal side effects for the treatment of NET with a large number of somatostatin receptors. In PRRT, the patient receives an intravenous injection of a drug such as octreotide (DOTATOC) and octreotate (DOTATATE) that is chemically bound to or radiolabelled with radioactive material, mainly lutetium-177. Somewhat less often, other radiopharmaceuticals, such as yttrium-90 or indium-111, are used. The radioactive drug binds octreotide to somatostatin receptors on tumour cells with subsequent irradiation and tumour regression [26].

Surgical treatment is indicated in patients with sporadic gastrinomas due to their high tendency to metastasize to the liver, lymph nodes, and distant organs. In cases where the process has progressed, preference should be given to nonsurgical treatment methods, including chemotherapy with everolimus, sunitinib, somatostatin analogues, interferon, chemoembolization, radioembolization, and radiofrequency ablation [51].

Currently, the primary treatment for sporadic gastrinoma, if technically feasible, involves either enucleation or local resection for damage to the pancreatic head or a distal pancreatectomy for distal pancreatic lesions. A Whipple resection is usually performed for large lesions of the pancreatic head or duodenum that cannot be adequately removed by enucleation [32, 37, 56].

Whipple's operation involves the removal of regional lymph nodes. This method allows for the detection of metastases in 30—70 % of patients when an isolated gastrinoma is located in the pancreatic head or in the case of duodenal gastrinomas. During the enucleation of gastrinomas, these metastases often remain unnoticed. Long-term results after Whipple's operation indicate an increase in the recurrence-free period with this surgical intervention [21].

However, after any type of surgical intervention, all patients with ZES should be monitored by a gastroenterologist to control the level of gastric acidity and blood gastrin, as well as, when necessary, adjust the PPI dose.

Thus, Zollinger-Ellison syndrome is a rare pathology that is quite difficult to diagnose. For a timely diagnosis, it is crucial to understand the characteristics of the clinical picture of this disease and have access to a comprehensive range of diagnostic methods that can identify effective therapeutic strategies. A multidisciplinary team must be involved in this process.

Declaration of interests

The authors declare no conflicts of interest.

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Authors contributions

Y. A. Dibrova: writing the manuscript; M. S. Kryvopustov: work concept and design, critical review.

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Еволюція вчення про синдром Золлінгера — Еллісона. Огляд літератури

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Сидром Золлінгера — Еллісона (СЗЕ) — рідкісна патологія, яка не має специфічних клінічних виявів та не завжди вчасно діагностується. Це зумовлено недостатньою обізнаністю лікарів щодо цієї патології та часто недоступністю необхідних методів обстеження. Проаналізовано зарубіжні літературні джерела з цієї проблеми. Наведено дані щодо відкриття цієї патології та походження назви синдрому. Висвітлено питання епідеміології захворювання. Детально описано найхарактерніші клінічні вияви та можливі ускладнення СЗЕ. Наведено зміни шлункової кислотопродукції, характерні для цієї патології, та їхнє діагностичне значення (чутливість і специфічність). При цьому значно підвищуються показники як базальної, так і максимальної стимульованої шлункової кислотопродукції. Найважливішим етапом обстеження пацієнтів із підозрою на СЗЕ є визначення рівня гастрину в крові, який значно підвищується за цієї патології. Однак за показником гастрину не завжди можна впевнено діагностувати СЗЕ. Абсолютним критерієм на користь СЗЕ є рівень гастрину натще ≥ 1000 пг/мл. Якщо цей показник < 1000 пг/мл, то значну діагностичну цінність мають тести із застосуванням секретину чи глюконату кальцію. Наведено дані про можливу локалізацію гастрином, частоту їх злоякісного переродження та шляхи метастазування. Детально описано методики визначення локалізації гастрином із зазначенням їхньої чутливості та специфічності. Висвітлено диференційовану тактику лікування хворих із СЗЕ на підставі результатів обстеження. Обґрунтовано необхідність постійного перебування цих пацієнтів під наглядом гастроентеролога та хірурга. Наведено диференційовану тактику лікування хворих із СЗЕ з урахуванням результатів обстеження, а також показання та протипоказання до хірургічного та медикаментозного лікування пацієнтів із СЗЕ. Висвітлено перспективи нового лікувального напрямку — застосування таргетної радіотерапії. Обґрунтовано необхідність для цих пацієнтів постійно перебувати під наглядом гастроентеролога та хірурга й періодично проходити необхідні обстеження.

Ключові слова: синдром Золлінгера — Еллісона, тактика лікування, гастрин, алгоритм обстеження.

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Difficult choledocholithiasis. Literature review

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The incidence of stones in the common bile duct in patients with symptomatic gallstone disease varies significantly and depends on age, ranging from 5 % to 33 %. In 85—90 % of cases, choledocholithiasis is effectively treated with endoscopic papillotomy (EPT) and lithoextraction, which is currently considered the standard method for managing this pathology. However, in 10—15 % of cases, choledocholithiasis is technically challenging for endoscopic treatment, requiring alternative methods and specialized equipment. This research examines the epidemiological aspects related to the increasing detection rate of choledocholithiasis, which is attributed to advancements in modern diagnostic techniques. Particular emphasis is placed on etiological factors such as genetics, obesity, and dietary habits that enhance bile lithogenicity. The pathogenesis section elucidates the mechanisms underlying primary and secondary stone formation in the bile ducts and their physiological impacts, including such complications as acute cholangitis, biliary sepsis, cholestatic hepatitis, and biliary cirrhosis of the liver. Distinct focus is placed on the criteria for difficult choledocholithiasis, encompassing stone characteristics, location, altered biliary anatomy, and the patient's general condition. Diagnostic techniques include laboratory and instrumental investigations, particularly ultrasound, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, and endoscopic ultrasound. The treatment section emphasizes the importance of timely stone removal to prevent complications. Modern treatment options are discussed, including both conservative and surgical methods such as endoscopic procedures and laparoscopic surgeries. The significance of an interdisciplinary approach to the diagnosis and treatment of choledocholithiasis and its many manifestations is emphasized.

Difficult choledocholithiasis remains a relevant issue in hepatobiliary surgery, and its effective treatment requires an individualized and multidisciplinary approach, involving endoscopic and laparoscopic technologies.

Keywords
difficult choledocholithiasis, choledochoscopy, choledocholithoextraction, mechanical jaundice, endoscopic retrograde cholangiopancreatography.

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Choledocholithiasis is a complication of gallstone disease, characterized by the formation of stones in the common bile duct (CBD) or their migration from the gallbladder. Most publications classify choledocholithiasis as difficult when it cannot be managed by primary endoscopic techniques due to specific criteria and signs (Table 1) [58, 67, 69, 79].

Some sources also consider the qualification and experience of the endoscopist as a criterion for difficult choledocholithiasis [78].

Etiology, epidemiology and pathogenesis of choledocholithiasis

In the early 1960s, choledocholithiasis was diagnosed in about 6—7 % of patients with gallstone disease. However, in the past two decades, the incidence has increased to 20—30 % [66, 70]. At present, choledocholithiasis develops in 5—33 % of patients with gallstone disease, and in 10—15 % of these cases, it presents challenges. This pertains to the advancement and accessibility of screening and non-invasive diagnostic techniques, in addition to nutritional influences [60].

Choledocholithiasis represents a significant issue in contemporary hepatobiliary surgery, as it accounts for 40 % of cases with obstructive jaundice [18, 45].

Common bile duct (CBD) stones may result in cholestasis and mechanical jaundice syndrome. If these conditions are not diagnosed promptly, they can progress to severe complications such as acute cholangitis and biliary sepsis [26, 33, 35].

Table 1. **Criteria for difficult choledocholithiasis** [12, 24, 35, 58, 79]

Category	Condition	Basis
Characteristics of bile duct stones	Large stone (> 15 mm) Multiple choledocholithiasis (> 3 stones, size > 10 mm) Atypical form of bile duct stones (barrel-shaped)	Indication for lithotripsy Impossibility of stone extraction with the Dormia basket
Location of bile duct stones	Intrahepatic ducts Bile duct stones above the stricture of the duct Mirizzi syndrome	Difficulty in reaching bile duct stones
Altered anatomy	Stenosis of the esophagus, stomach, or duodenum Condition after gastrectomy and Billroth II gastric resection Parapapillary diverticulum Vitreous edema of the duodenum Tubular stenosis of the distal common bile duct in chronic pancreatitis	Difficulty in reaching the major duodenal papilla
Patient condition	Various terminal states Significant coagulation disorders	High risk of fatal complications

Numerous publications identify genetics, excessive body weight, and poor nutrition as the primary etiological factors contributing to cholelithiasis, as they increase the risk of bile lithogenicity and stone formation [57, 70]. Gallstones and choledocholithiasis are associated with the patient's age, hypothyroidism, chronic cholangitis, and parasite infestation of the bile ducts [61].

The primary pathogenetic cause of choledocholithiasis is the presence of stones in the common bile duct, leading to obstructed bile flow and the subsequent onset of cholestasis and mechanical jaundice of varying severity [24, 33].

Based on the formation process of bile duct stones, primary stones are identified as those formed directly inside the bile ducts, whereas secondary stones originate from the gallbladder or cystically dilated intrahepatic bile ducts [68, 70]. Primary formation of stones in the bile duct occurs in about 1.0—5.7 % of patients with gallstone disease. This is typically linked to disrupted pigment metabolism, alterations in bile composition, inflammation of the bile ducts, and bile stasis [24, 33].

Primary bile duct stones, which are not associated with the gallbladder, are more common in Southeast Asian countries. The incidence of intrahepatic lithiasis varies significantly, ranging from 0.38 to 18 % (up to 50 % in Taiwan) [14, 60, 70]. Secondary bile duct stones are prevalent in most Western countries [70].

The passage of stones from the gallbladder to the bile duct is facilitated by its dilation or the formation of a cholecystocholedochal fistula (Mirizzi syndrome). The incidence of residual choledocholithiasis ranges from 2 to 10 %, whereas the recurrence rate varies from 1 to 7 % [4, 30, 37].

Solitary CBD stones are observed in 30 % of patients, whereas numerous stones are seen in 70 % of patients. Stones are detected in the common bile duct in 60—70 % of patients, in the intrahepatic bile ducts in 5—10 %, and in the major duodenal papilla (ampulla of Vater) in 15—25 %. Approximately one-third of choledocholithiasis patients, particularly those with stones in the distal segment of the CBD, are asymptomatic, whereas stones located in the terminal segment of the CBD are often impacted and result in significant clinical manifestations of mechanical jaundice [40, 78].

Diagnosis of difficult choledocholithiasis

The primary objective in managing both uncomplicated and complicated choledocholithiasis is prompt diagnosis, which minimizes the incidence of unnecessary invasive diagnostic interventions. ESGE (European Society of Gastrointestinal Endoscopy, 2019) and ASGE (American Society for Gastrointestinal Endoscopy, 2019) guidelines advocate for choledocholith extraction in all patients with either symptomatic or asymptomatic choledocholithiasis [29, 33, 70].

Due to the complexity of hepatopancreatobiliary surgery, a series of procedures are necessary to establish an accurate diagnosis and select the appropriate treatment technique. The process begins with the collection of anamnestic data and laboratory assessments, which include a total blood count (leukocytosis, left shift in the leukocyte formula, elevated erythrocyte sedimentation rate), a biochemistry blood test (total and direct bilirubin, total protein, glucose, potassium, sodium, calcium, creatinine, urea, amylase, liver transaminases, -glutamyl transpeptidase,

alkaline phosphatase), a coagulogram, procalcitonin, and other inflammatory markers, along with a general urinalysis. These procedures facilitate the assessment of primary liver functions and the identification of pathological syndromes requiring correction. Literature indicates that normal liver test readings suggest the absence of hepatic stones. Biochemical markers, namely total and direct bilirubin levels, γ-glutamyl transpeptidase, and alkaline phosphatase, serve as significant indications of mechanical jaundice, cytolysis, and choledocholithiasis [23, 67, 69].

Clinically, choledocholithiasis may present as pain in the right subcostal region (a symptom of acute cholecystitis), symptoms of mechanical jaundice (dark urine and acholic stool), often without pruritus, and occasionally as Charcot's triad (fever, jaundice, and biliary colic) [38].

Instrumental examination methods, particularly routine ultrasonography (US), are employed to diagnose choledocholithiasis due to their availability, non-invasiveness, cost-effectiveness, and relevance in assessing liver diseases [11, 54, 60]. A high sensitivity of ultrasound for detecting gallstones has been established (about 96 %), which is explained by the proximity of the gallbladder to the abdominal wall and the absence of gases between the sensor and the wall of the organ [22, 77]. The effectiveness of ultrasound in detecting CBD stones is about 50 %. The presence of stones predominantly in the distal and terminal segments of the common bile duct, which are inadequately visible by ultrasound, accounts for this, along with the physician's proficiency in transabdominal ultrasound diagnostics [11, 60]. Choledocholithiasis can be inferred from indirect ultrasound indicators: dilation of the bile ducts, indicative of biliary hypertension, and the presence of numerous small gallstones that frequently migrate into the common bile duct. Clinical and laboratory data, together with ultrasound diagnostic results, serve as primary diagnostic criteria for identifying signs of choledocholithiasis, as confirmed by the ESGE guidelines [9, 39, 67, 79]. Three risk groups for choledocholithiasis were established based on these findings (Table 2) [9, 66].

Computed tomography (CT) is widely used in abdominal surgery and serves as a secondary diagnostic method for choledocholithiasis. However, its effectiveness without contrast is only marginally superior to ultrasound and considerably less effective than magnetic resonance imaging [55]. Consequently, CT diagnostics for suspected choledocholithiasis is conducted using contrast, markedly enhancing its effectiveness and specificity. Literature indicates that CT with contrast is helpful in 69—96 % of choledocholithiasis cases. However, its sensitivity diminishes with small biliary stones (< 5 mm) in patients of older age groups and with a low calcium concentration in the stones [41, 47, 57].

A few decades ago, endoscopic retrograde cholangiopancreatography (ERCP) was extensively employed for diagnostic purposes and was regarded as the gold standard in diagnosing biliary tract pathologies [25, 54]. ERCP, when combined with endoscopic papillosphincterotomy, is an exceptionally successful diagnostic and treatment method for biliary tract disease [1, 73, 75]. The technique is used to detect gallstones, CBD stones, and CBD strictures. This procedure enables the examination of the gastric and duodenal mucosa, the bile duct, and the collection of a pure bile or pancreatic juice sample for microbiological (culture), cytological, and biochemical study [66]. An increasing number of studies emphasize the necessity for clear indications for such a procedure [54, 57]. A clear indication for ERCP is the presence of jaundice and bile duct stones detected during ultrasound. Some authors consider acute pancreatitis, acute cholecystitis, and purulent cholangitis with septic complications as contraindications to ERCP.

ERCP is generally regarded as an effective and safe diagnostic and therapeutic procedure. However, such complications as pancreatitis, bleeding from a papillotomy site, duodenal perforation, and cholangitis may arise, occurring at a frequency of 8—12 %, even when conducted by a highly skilled endoscopist. Under the ESGE and ASGE guidelines, ERCP should be performed only in cases of morphological confirmation of choledocholithiasis and in patients exhibiting clinical signs of cholangitis [21, 25, 79].

Currently, magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound diagnostics (endo-US) are the most accurate methods for detecting bile duct stones and are recommended for patients at «high» and «moderate» risk of

Table 2. **Predictors of choledocholithiasis**
(American Society of Gastrointestinal Endoscopy, 2019)

Predictors	Description
Very strong	Common bile duct stone on ultrasound Clinical manifestations of cholangitis Elevated total bilirubin level > 4 mg/dL
Strong	Dilated common bile duct on ultrasound (> 6мм) Elevated total bilirubin level (1.8—4.0 mg/dL)
Moderate	Elevated LFTs (ALT, AST Age > 55 years Clinical manifestations of biliary pancreatitis

choledocholithiasis [57]. MRCP is regarded as the most accurate non-invasive (non-endoscopic) method to detect bile duct stones, with high sensitivity (85—92 %) and specificity (93—97 %) [41, 60].

The research indicates that both methods are highly specific and informative but have a number of disadvantages. MRCP is contraindicated in patients with pacemakers, other metallic implants, obesity, and claustrophobia. Endo-ultrasound is marked by limited prevalence, high equipment costs, minimal invasiveness, and considerable challenges associated with altered gastrointestinal structure [70].

Invasive diagnostic techniques include intraoperative cholangiography and percutaneous transhepatic cholangiography, whose specificity is comparable to that of ERCP and MRCP. Nonetheless, they have some disadvantages. Research indicates that the incidence of bile duct stone detection during routine intraoperative cholangiography in patients with gallstone disease is 10—12 %. However, this technique has not gained popularity due to the greater availability of non-invasive diagnostic methods, which are continually improving in accuracy [21, 23].

Consequently, in diagnosing choledocholithiasis and difficult choledocholithiasis, it is essential to employ all available diagnostic methods and their combinations, contingent upon the particular clinical case and cost viability.

Treatment of difficult choledocholithiasis

Endoscopic methods of treatment are more often used in patients with choledocholithiasis. According to the literature, ERCP is one of the most complex endoscopic procedures. It was first performed in 1968 as an invasive diagnostic manipulation [39]. It is important that ERCP can easily transform from a diagnostic procedure into a therapeutic one. Such invasions include endoscopic papillosphincterotomy (EPST), endoscopic mechanical lithoextraction, and endoprosthesis of the bile ducts (bouginage and stenting), which are most often performed together and used in complex treatment [79]. Endoscopic papillosphincterotomy was first independently described in 1974 in Germany and Japan. Initially, it was used to remove residual or recurrent CBD stones after cholecystectomy with or without choledochotomy. Choledocholithiasis is the most common indication for conducting EPST. In patients with acute purulent cholangitis, usually caused by a stone, the method of choice is urgent endoscopic retrograde cholangiography with EPST [35]. When ERCP and EPST are introduced into clinical practice for the diagnosis and treatment of patients with the appropriate profile, it significantly improves the results of treating this pathology, particularly in patients with severe concomitant pathology [51, 66, 79]. According to various sources, the efficiency of papillosphincterotomy reaches 90 % depending on the experience of the endoscopist, the clinical case, and the presence of signs of difficult choledocholithiasis [66, 79]. Complex cannulations, such as parapapillary diverticula and altered anatomy of the upper parts of the digestive tract, typically lead to difficulties in performing EPST. Although this operation is considered quite safe, the complication rate is 5.0—9.8 % [7, 75]. According to the classification of complications after endoscopic transpapillary interventions (P. B. Cotton, C. B. Williams, 1996), the following complications are most common: bleeding (0.3—2 %), perforation of the duodenum (0.1—1.1 %), post-papillotomy pancreatitis (1.3—6.7 %), and mortality, which is 16—18 % [10]. In cases of difficult choledocholithiasis, ERCP and EPST are usually not enough; mechanical, balloon lithoextraction, electrohydraulic and laser lithotripsy, and extracorporeal shock wave therapy (EUHL) are used instead [12, 50].

Endoscopic papillary balloon dilation (EPBD), also known as papillosphincteroclasy, is a procedure for the extraction of CBD stones, introduced in the 1980s as a substitute or adjunct to EPST, particularly for difficult choledocholithiasis. Staritz et al. [63] reported that during EPBD, the sphincter of Oddi was dilated to 15 mm, facilitating the extraction of biliary stones. Nonetheless, about 40 % of patients required either EPST or mechanical lithoextraction. In 2003, Ersoz et al. [19] began to use larger-diameter balloons to dilate the sphincter of Oddi to 20 mm, which markedly enhanced the outcomes of lithoextraction in difficult choledocholithiasis, particularly with large stones, without employing lithotripsy techniques. The primary benefit of this technique is that it maintains the integrity of the sphincter of the major duodenal papilla. Furthermore, EPBD can be used in patients with considerable coagulopathy and abnormal anatomy of the upper digestive tract. Nevertheless, its implementation has been limited due to a substantial incidence of postoperative acute pancreatitis [17].

To enhance the outcomes of choledocholithoextraction, the majority of researchers use a combination of EPBD and minimal EPST, thereby mitigating the risks of perforation, severe hemorrhage, and cholangitis. ESGE and ASGE guidelines indicate that the principal technique for lithoextraction in difficult choledocholithiasis is partial EPST alongside EPBD [37].

Mechanical lithotripsy is the predominant technique for the fragmentation and choledocholithoextraction of stones. Riemann et al. first described it in 1982 [52]. In cases of difficult choledocholithiasis, where lithoextraction using Dormia baskets or balloons has proven ineffective, this procedure typically takes place after EPST. The research indicates that choledocholithoextraction is successful in 90 % of patients, particularly for large stones (> 20 mm) and is associated with a low complication rate [72]. The indications for this treatment method include solitary stones > 10—15 mm in diameter, < 10 mm stones in the presence of a constricted terminal segment of the common bile duct, numerous stones that occlude the hepatic choledochus and are in close proximity to one another, and the preservation of the sphincter apparatus of the major duodenal papilla in young patients with choledocholithiasis [78]. Mechanical lithotripsy is contraindicated in cases with dense, immovable stones that are firmly attached to the duct walls, particularly when accompanied by jaundice, purulent cholangitis, intrahepatic lithiasis, or considerable dilation of the intrahepatic ducts. Mechanical lithotripsy can be performed in a single session or several phases, contingent upon the size and number of stones and the technical specifications of the procedure [74]. Mechanical lithotripsy is employed alongside balloon dilation of the sphincter of Oddi in patients with large stones [48]. The dimensions of the stones designated for destruction vary significantly, ranging from 6 to 40 mm. The effectiveness of mechanical lithotripsy for stones measuring < 20 mm in diameter is 85—100 %, but for stones > 20 mm, it is 55—68 % [39, 48]. A retrospective study conducted by Lee et al. revealed that stones lodged in the ampulla of Vater, stones > 30 mm in diameter, and variations in the diameters of the common bile duct and the stone are risk factors for unsuccessful mechanical choledocholithoextraction, thereby requiring supplementary lithoextraction techniques [32]. 209 patients with CBD stones underwent mechanical lithotripsy [6, 57]. Numerous stones were discovered in 50 % of the patients. The stones varied in size from 4 to 8 mm, with the majority being between 10 and 19 mm in diameter. About one-third of patients presented with stone diameters of ≥ 20 mm. The success rate of lithotripsy was 87.6 %. Stones with a diameter of ≥ 20 mm were fragmented in 79.1 % of cases, whereas for stones with a diameter of ≥ 25 mm, mechanical lithotripsy achieved success in 67.6 % of cases. Despite the relative simplicity and availability of this procedure, there are a number of contraindications: 1) Acute myocardial infarction; 2) acute disruption of cerebral blood circulation; 3) diseases and conditions in which endoscopic manipulation is contraindicated; 4) presence of acute destructive pancreatitis of non-biliary etiology; 5) peritonitis; 6) inflammation of the bile ducts with septic complications; 7) significant coagulation disorders [57].

Technical issues during the procedure, such as damage to the lithotriptor basket or traction string or the entrapment of the lithotriptor basket with a stone in the distal segment of the CBD, typically cause complications following manipulation. This is because the lithotriptor's insufficient destructive power prevents the extraction of the stone. Numerous studies indicate that the overall complication rate ranges from 3 % to 34 % [27, 37, 57]. Currently, the preferred method for treating difficult choledocholithiasis is mechanical lithotripsy, especially when standard choledocholithoextraction proves inadequate and requires a specialized approach [32, 57].

Cholangioscopy-guided lithotripsy is conducted using two primary techniques: electrohydraulic and laser, originally introduced in 1977 and 1986, respectively, and subsequently employed without cholangioscopy [27, 32, 76]. Endoscopic cholangioscopy is an efficacious diagnostic technique and an integral part of surgical strategies for managing difficult choledocholithiasis [57].

There are three main types of peroral cholangioscopy (POC):

1) Two-operator peroral cholangioscopy («Mother-baby»), which requires a duodenoscope and a cholangioscope operated by two endoscopist surgeons. The cholangioscope is inserted into the working channel of the duodenoscope, and the bile ducts are examined. Nowadays, this technique is rarely used due to the high cost of the equipment, its poor durability, and the need for two experienced operators [41].

2) Single-operator peroral cholangioscopy (SpyGlass Direct Visualization System) was developed by Boston Scientific Corp. in 2005. Currently, the third generation of these systems is available. This cholangioscope provides a clear picture, a 30° angle of view in any direction, two irrigation channels, and a working channel with a diameter of 1.2 mm, which ensures lithotripsy and other manipulations. The main advantages are the ability to control the duodenoscope and cholangioscope at the same time, greater flexibility, and significantly greater functionality compared to the two-operator system [41].

3) Direct peroral. This system is an ultra-thin endoscope. Initially, it was used in pediatrics and during transnasal operations. The main advantages are maneuverability, multifunctionality, and the presence of one operator. Difficulties may arise in the

cannulation of the major duodenal papilla, which requires the use of conductors, balloon catheters, guide probes, etc. to stabilize the endoscope. Another drawback of this method is the 5—6 mm diameter of these endoscopes, which typically necessitates EPST or balloon dilation of the sphincter of Oddi. This, in turn, lengthens the intervention duration and increases the risk of complications [39].

Therefore, the development and availability of endoscopic cholangioscopy have led to the increased use of electrohydraulic and laser lithotripsy for difficult choledocholithiasis, since visualization is crucial for successful choledocholithoextraction [2, 5, 11]. The ESGE guideline recommends cholangioscopic lithotripsy (laser or electrohydraulic) as an effective and safe treatment for difficult choledocholithiasis [37].

Electrohydraulic lithotripsy (EHL) fundamentally involves the generation of high-frequency hydraulic pressure waves, which are absorbed by the stone, leading to its disintegration [17, 50]. Electrohydraulic lithotripsy was formerly conducted under fluoroscopic guidance. However, direct cholangioscopic visualization is now favoured, markedly decreasing the risk of biliary perforation [17, 47, 50].

Laser lithotripsy (LL) involves directing a laser beam of a certain wavelength onto the stone's surface, resulting in wave-like fragmentation comparable to laser ablation of tumours [20, 39]. Similar to electrohydraulic methods, laser lithotripsy can be conducted under fluoroscopic guidance. However, cholangioscopic visualization is preferred.

McCarty et al.'s meta-analysis [39] indicates that in patients with difficult choledocholithiasis, the success rate of intraductal stone fragmentation under cholangioscopic guidance was 91.6 %, the bile duct clearance rate in a single session was 76.9 %, and the complication rate was 8.9 % [39]. McCarty et al. [39] determined that there is no statistically significant difference in the incidence of successful intraductal fragmentation between EHL and LL (90.1 % vs. 92.9 %, $p = 0.360$). LL has a superior success rate in conducting lithotripsy in a single session compared to EHL (83 % vs. 70.9 %, $p = 0.021$) and a reduced treatment duration (75.7 min vs. 54.3 min, $p < 0.001$) [38].

Buxbaum et al. [9] state that in cases of difficult choledocholithiasis (large stones), cholangioscopic laser lithotripsy demonstrates significant advantages over mechanical lithotripsy or balloon papillary dilation, particularly regarding the efficacy of biliary stone clearance (93 % vs. 67 %, $p = 0.009$).

In another randomized study, Franzini et al. [21] compared cholangioscopic EHL and EPBD, revealing no significant differences in biliary stone clearance rates (77.1 % vs. 72 %, $p > 0.05$) or complication rates (4.2 % vs. 12 %, $p > 0.05$). However, in instances requiring an additional session, the biliary clearance rate was markedly superior for EHL compared to EPBD.

The primary drawback of cholangioscopic LL or EHL is the higher cost and prolonged duration of the surgical procedure; however, the considerate and competent application of these techniques in difficult cases of choledocholithiasis eliminates these disadvantages, aligning with the guidelines of ESGE and ASGE [37, 80]. Cholangioscopic lithotripsy techniques are used when mechanical lithoextraction or EPBD fails, serving as a viable alternative to open or laparoscopic choledochoscopy [17, 80].

Another method for treating gallstones is ESWL, which uses generated shock waves under the control of fluoroscopy to target the gallstone locations. In 1986, doctors first used it to manage choledocholithiasis, and they continued to use it for difficult cases or failures after ERCP [16]. The average rate of biliary tract stone removal is 84.4—90.2 %, necessitating a minimum of three sessions and the administration of either epidural or general anesthesia [3, 63, 66]. The incidence of complications after ESWL, as reported by many authors, varies between 9.1 % and 15.9 % [3, 66]. Most endoscopic associations recommend this treatment only in cases where traditional lithoextraction techniques fail or when cholangioscopic methods are unavailable [33].

Endoscopic sonography has led to an increasing use of choledochyloextraction methods under endo-US control, particularly in cases of unsuccessful or complicated ERCP [64]. There are two main methods of biliary interventions: endo-US rendezvous (EUR) technique and endo-US antegrade (EUA) technique. EUR is useful in cases of failed cannulation and difficulties with access to the major duodenal papilla. It is similar to conventional ERCP. Access to the extrahepatic bile ducts is provided through the stomach or small intestine. This technique's main drawback is its limited access to the left hepatic bile duct, making it technically challenging in cases of minor biliary hypertension [3, 66].

Surgical methods of treatment of choledocholithiasis include open and laparoscopic choledocholithoextraction. Open choledocholithoextraction has been used since the end of the 19th century and was the main method of CBD stone extraction until the 1970s. However, in some cases of difficult choledocholithiasis, it is still the method of choice [1, 34, 36]. However, open operations on the CBD in cases of perivesical infiltration or non-dilated ducts were technically challenging and frequently resulted

in serious postoperative complications, both in the short and long term [65—67]. Additionally, cases of recurrent choledocholithiasis, which could be caused by stenosis of the hepatic artery, foreign bodies in the hepatobiliary system, such as ligatures (ligature choledocholithiasis), or fragments of drain, were also observed after such interventions.

The introduction of minimally invasive technologies, in particular laparoscopic choledocholithoextraction, caused a review of approaches to the treatment of patients with choledocholithiasis. Now, minimally traumatic methods can be used to achieve optimal results during surgery [1, 34, 36].

Laparoscopic procedures are a viable alternative to endoscopic methods of lithoextraction for people with difficult choledocholithiasis and are often the best way to treat this condition [10, 71]. An important aspect of laparoscopic technology for the treatment of choledocholithiasis is the choice of access to the bile duct (through the cystic duct, choledochotomy), as well as the method of revision of the bile ducts (intraoperative cholangiography, ultrasound, choledochoscopy). Although intraoperative cholangiography and ultrasound have high specificity and sensitivity (63—99 %), in cases of difficult choledocholithiasis, laparoscopic choledochoscopy provides visualization of the bile ducts and complete lithoextraction [9, 69].

Laparoscopic choledochoscopy and choledocholithoextraction through the cystic duct are less traumatic, have fewer complications than choledochotomy, and hence result in a shorter stay in the hospital. Rhodes et al. [51] and DePaula et al. [15] found that choledocholithoextraction through the cystic duct was 96 % and 84 % efficient, respectively. However, this procedure has many limitations for use: the size of the stone is < 6 mm, the diameter of the stone must be the same or smaller than the diameter of the cystic duct, the number of stones is < 5, and there is a scar-infiltrative process in the area of the hepatoduodenal ligament. Furthermore, conditions such as proximal choledocholithiasis, common bile duct strictures, an acute angle between the cystic and common hepatic ducts, and difficult choledocholithiasis limit the use of choledochoscopy and cholelithoextraction through the cystic duct [77].

In the presence of preoperative contraindications (signs of difficult choledocholithiasis) or complications during peribladder lithoextraction, the majority of authors advocate for choledochoscopy and choledocholithoextraction using choledocholithotomy. This approach provides easy access to stones, allowing choledochoscopy in both distal and proximal directions and hence enhancing choledocholithoextraction. Choledocholithotomy facilitates the use of larger-diameter fibrocholedochoscopes, which have a larger instrument channel, thereby markedly improving visualization and choledocholithoextraction. The assessment of the bile ducts via choledocholithotomy is warranted under the following conditions during the initial choledochoscopy: 1) A large CBD stone (i 15 mm) is anticipated; 2) an intrahepatic bile duct stone is detected; 3) pre-existing bile duct strictures (regardless of etiology); 4) an impacted stone is present in the distal segment of the CBD; 5) multiple choledocholithiasis is observed > 3 stones, size > 10 mm) [65].

The main disadvantage of choledocholithotomy is possible complications related to the drainage of the bile duct, or remote complications such biliary tract strictures [65]. Rhodes et al. [51] indicate that bile inflow via the drain-catcher during choledochotomy is slightly more than through transcystic access (11.0 % vs 1.7 %, $p < 0.05$), which is consistent with the data of other authors (4.5—16.7 %) [65]. Regarding the efficacy of bile duct stone removal, there is no significant difference between the two methods [28, 51, 81]. The vast majority of authors recommend using laparoscopic choledocholithoextraction and choledochoscopy via the transcystic route, which offers benefits for reduced hospital stay and a lower rate of complications. However, in cases of difficult choledocholithiasis, it is necessary to perform choledocholitotomy with choledocholithoextraction and choledochoscopy [65]. The ESGE guidelines confirm that choledochoscopy is an effective and safe technique for choledocholithoextraction in patients undergoing transcystic or transductal cholecystectomy, particularly in cases with difficult choledocholithiasis. This management strategy should be chosen based on the availability of suitable resources and expertise in using this technology [37].

Notwithstanding the continuous advancements in laparoscopic and endoscopic technology and treatment techniques for patients with difficult choledocholithiasis, optimal management protocols using minimally invasive interventions on the bile ducts remain elusive.

Consequently, the chosen research direction is relevant and has substantial practical significance.

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Складний холедохолітіаз. Огляд літератури

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Частота утворення каменів у загальній жовчній протоці в пацієнтів із симптоматичною жовчнокам'яною хворобою значно варіює та залежно від віку становить від 5 до 33 %. У 85—90 % випадків холедохолітіаз ефективно лікують ендоскопічною папілосфінктеротомією та літоекстракцією. Нині це стандартний метод лікування зазначеної патології. Однак у 10—15 % випадків холедохолітіаз є технічно складним для ендоскопічного лікування, що потребує застосування інших методик та спеціалізованого обладнання. Розглянуто епідеміологічні аспекти, які вказують на зростання частоти виявлення холедохолітіазу завдяки використанню сучасних методів обстеження. Особливу увагу приділено етіологічним чинникам, зокрема спадковості, ожирінню та харчовим звичкам, що призводять до підвищення літогенності жовчі. Наведено механізм утворення первинних і вторинних каменів у жовчних шляхах, а також їхній вплив на організм, зокрема спричинені ними ускладнення, такі як гострий холангіт, біліарний сепсис, холестатичний гепатит і біліарний цироз печінки. Висвітлено критерії складного холедохолітіазу (характеристики каменів, їхня локалізація, змінена анатомія жовчних шляхів) і загальний стан пацієнта. Розглянуто діагностичні методи — як лабораторні, так і інструментальні (ультразвукове дослідження, ендоскопічна ретроградна холангіопанкреатографія, магнітно-резонансна холангіопанкреатографія, ендоскопічна ультрасонографія. Наголошено на важливості своєчасного видалення каменів для запобігання ускладненням. Наведено сучасні підходи до лікування (як консервативні, так і хірургічні методи, зокрема ендоскопічні процедури та лапароскопічні операції). Наголошено на важливості міждисциплінарного підходу до діагностики та лікування холедохолітіазу та його складних форм.

Складний холедохолітіаз залишається актуальною проблемою гепатобіліарної хірургії. Його ефективне лікування потребує індивідуального та міждисциплінарного підходу з використанням ендоскопічних і лапароскопічних технологій.

Ключові слова: складний холедохолітіаз, холедохоскопія, холедохолітоекстракція, механічна жовтяниця, ендоскопічна ретроградна холангіопанкреатографія.

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