LEKARZ WOJSKOWY
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- Differences related to the work of rescuers in the environment of a terrorist attack
- Potential of gene therapy in neurodegenerative diseases
- Assessment of the relationship between sensitization to specific allergens and the presence of micturition disorders in children
- Non-cardiac sequelae of Kawasaki disease. The survey of 90 cases and a literature review

WOJSKOWY
INSTYTUT MEDYCZNY
PAŃSTWOWY INSTYTUT BADAWCZY

Informacje dla autorów

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"Military Physician" has been published continuously since 1920, currently as a quarterly of the Military Institute of Medicine in Warsaw, Poland.

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   Calpin C, Macarthur C, Stephens D, et al. Effectiveness of prophylactic inhaled steroids in childhood asthma: a systemic review of the literature. J Allergy Clin Immunol, 1997; 100: 452–457
   Books:
   Rudzki E. Alergia na leki: z uwzględnieniem odczynów anafilaktycznych i idiosynkrazji. Lublin, Wydawnictwo Czelej, 2002: 338–340
   Chapter of a book:
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   6) ensure a professional publishing process;
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Letter from the Editor-in-Chief

Welcome!

Following the holiday season, we would like to present this new issue of “Military Physician”. As with the previous one, it is quite extensive and devoted to a number of different topics. I hope that you find here papers that will interest you, and there are some that I would especially like to recommend.

There are some very interesting papers that analyse the possibilities of gene therapy in neurodegenerative diseases and the differences in the work of rescuers in an environment following a terrorist attack. Another equally interesting paper published in the original article section examines the relationship between hypersensitivity to particular allergens and the presence of micturition disorders in children. Another section devoted to case reports includes works that can be used in practice and education: renal amyloidosis in ankylosing spondylitis and intracranial stenting after unsuccessful mechanical thrombectomy for a suspected atherosclerosis-related acute ischemic stroke.

I strongly encourage you to become acquainted with this issue, and I would like to invite you to send further works. Thanks to the quality of the published studies, as well as the meticulous work by the editorial team, “Military Physician”, as a scientific journal with a tradition dating back more than a century, has obtained higher scores on the list of scientific journals and peer-reviewed materials from international conferences. Currently, the authors receive 100 points for published articles. I would like to thank all of you for this hard work and assure you that I and my team will make every effort to maintain the high standard of the journal and continue to increase its recognition in the world of science.

Prof. Bolesław Kalicki MD, PhD

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Contents

CASE REPORT

REPORT

THE POTENTIAL FOR GENE THERAPY IN NEURODEGENERATIVE DISEASES

Potencjał terapii genowej w chorobach neurodegeneracyjnych

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Abstract: In recent years, there has been an increasing prevalence of neurodegenerative diseases worldwide. This is linked to the increasing age of the world population. Despite intensive research and clinical trials, in most cases no effective therapy has yet been developed. Typically, the management of neurological disorders only alleviates the severity of the symptoms without eliminating the causes of the diseases. The development of new treatments for neurodegenerative diseases is hampered by the limited permeability of the BBB ; as the penetration of drugs into the central nervous system is restricted. For these reasons, it is crucial to develop therapeutic strategies that can be applied directly at the pathologically altered site. In addition, a major challenge is to develop a treatment that inhibits disease progression. Numerous studies are being conducted to find alternative treatment methods, such as the use of nanoscale carriers, mesenchymal stem cells and gene therapy. In the case of gene therapy, a number of gene-targeted drugs are under investigation, including AADC, GDNF and HTT. Innovative treatments have the potential to bring therapeutic benefits to millions of people with neurodegenerative diseases.

Streszczenie: W ostatnich latach obserwujemy coraz większe rozpowszechnienie występowania chorób neurodegeneracyjnych na całym świecie. Jest to związane ze wzrostem wieku populacji światowej. Pomimo intensywnych badań naukowych oraz prób klinicznych, w większości przypadków nie opracowano do tej pory skutecznej terapii. Tradycyjne postępowanie w przypadku zaburzeń neurologicznych łagodzi jedynie nasilenie objawów bez likwidowania przyczyny choroby. Poszukiwanie nowych metod leczenia chorób neurodegeneracyjnych jest utrudnione przez przepuszczalność BBB, ponieważ istnieją ograniczenia związane z wnikaniem leków do ośrodkowego układu nerwowego. Z powyższych względów kluczowe jest opracowanie takiej strategii terapeutycznej, która umożliwiłaby zastosowanie terapii bezpośrednio w miejscu patologicznie zmienionym. Ponadto dużym wyzwaniem jest opracowanie leczenia, które hamowałoby rozwój choroby. Prowadzone są liczne badania w celu znalezienia alternatywnych sposobów leczenia, takich jak stosowanie nanoskalowych nośników, mezenchymalnych komórek macierzystych oraz terapii genowej. W przypadku terapii genowej w trakcie badań jest wiele leków celowanych w geny m. in. AADC, GDNF i HTT. Innowacyjne sposoby leczenia potencjalnie mogą przynieść korzyści terapeutyczne milionom osób z chorobami neurodegeneracyjnymi.

Keywords: neurodegenerative diseases, blood-brain barrier, gene therapy, AAV vectors.

Słowa kluczowe: choroby neurodegeneracyjne, bariera krew-mózg, terapia genowa, wektory AAV.

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Neurodegenerative diseases of the central nervous system (CNS) affect millions of people worldwide. They are associated with progressive and irreversible damage to the neurons. They can be congenital, such as in Huntington's disease, or acquired, such as in multiple sclerosis. Old age is a risk factor for developing acquired neurodegenerative diseases. In contrast, the incidence of congenital neurodegenerative diseases is primarily genetically determined. The most common neurodegenerative diseases include Alzheimer's disease, Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis and amyotrophic lateral sclerosis [1].

The causes of neuronal damage in neurodegenerative diseases are dependent on the type of disease. They are often associated with the accumulation of dysfunctional proteins in cells, a disorder related to neurotransmitter synthesis or the degeneration and atrophy of the CNS. The consequence of these lesions is brain cell death [2].

Symptoms developing in the individuals with a neurodegenerative disease depends on the CNS damage location. The most common symptoms are motor disorders (ataxia), memory impairment and dementia. Other symptoms include concentration problems, orientation and speech disorders, seizures, and mood swings [2].

Currently, the therapies for neurodegenerative diseases are based on using medication to alleviate the symptoms. The most common pharmacotherapy involves the administration of drugs that increase dopaminergic transmission and inhibit cholinergic transmission in the case of Parkinson's disease, cholinesterase inhibitors in Alzheimer's disease, and interferon β or glatiramer in multiple sclerosis [3]. As a neurodegenerative disease progresses, the effectiveness of the pharmacological treatment decreases. The side effects of the pharmacotherapy treatment worsen as the drug dose increases. The blood-brain barrier (BBB) restricts the passage of a significant amount of systemically administered drugs that should act on a target site. This is due to the lack of use of the local transport mechanisms and the high molecular weight and polarity of the medications [4]. It is estimated that 98% of drugs currently used in the treatment of neurodegenerative diseases (recombinant proteins, monoclonal antibodies, genes), are unable to effectively cross the blood-brain barrier [5].

Blood-brain barrier (BBB)

The blood-brain barrier (BBB) is a physical and metabolic barrier that regulates the transport of substances between the blood vessels and nerve tissue. It plays an important role in maintaining an optimal environment for brain tissues, preventing harmful substances and certain microorganisms in the blood from entering the brain, which protects the basic functions of the central nervous system [6].

Through its complex structure, BBB is one of the tightest barriers in the human body and the main mechanism for protecting the–CNS. The microcapillaries surrounding the CNS, just like other tissues, are composed of tightly adherent endothelial cells, forming the wall, and lining the vessels, as well as muscle cells and pericytes surrounding the endothelium from the outside [7]. The properties of the BBB are strongly influenced by the unique characteristics of the endothelial cells that build the brain's vasculature: these cells are connected by tight junctions (TJs, *zonula occludens*), which largely restrict the transport of substances.

At the TJs there are three important transmembrane proteins to be found: claudins, occludins and JAMs (Junctional Adhesion Molecules). They form complexes that seal the connections between the cells. Moreover, in the endothelial cell lining there are no gap junctions, and a reduced number of pinocytic vesicles are observed in the cells, further limiting transport across the BBB [6].

Endothelial cells are surrounded by an astrocyte network, which is a glial boundary and provides structural and functional support for the neurons. Depending on the immune microenvironment, these cells can undergo structural and functional changes, which causes a switch between an active and a resting phenotype. This phenomenon is known as astrocyte polarization. Pericytes, which are located on the surface of the brain's capillaries, control water transport. Along with the endothelium, these cells are surrounded by a basal lamina. Its main role is to regulate transport, provide structural support for the BBB and contribute to the astrocyte polarization [7].

The BBB permeability of substances depends on a number of physicochemical and physiological factors. Physicochemical factors include molecular weight, charge, lipid solubility, surface activity and relative molecular size. Physiological factors, on the other hand, include efflux transporters (e.g., P-glycoprotein (P-gp)), enzymatic activity, plasma protein binding and cerebral blood flow [8].

Transport across a BBB can occur via two pathways: paracellular (between neighbouring cells) or transcellular (through the cell). The paracellular pathway is a passive transport of molecules dependent on the concentration gradient. The transcellular pathway, on the other hand, is the receptor-mediated transport and transcytosis in addition to passive diffusion. Due to the reduced permeability of the CNS vasculature, the transport of most substances is controlled and occurs through transporters present in the endothelial cells, mainly efflux transporters and nutrient transporters. Efflux transporters, such as the Mdr-1 protein, use energy to move molecules and recognize many substrates. These molecules influence the transport of essential substances, such as electrolytes, nucleosides, amino acids, and glucose, and protect the CNS from harmful agents, providing an important barrier to pharmacotherapy [8].

Modern therapies in the treatment of neurodegenerative diseases

An alternative to traditional pharmacotherapy is direct intracerebral drug administration. The key task for modern science is to develop a treatment strategy that would allow crossing of the BBB and using site-specific pharmacotherapy. Nanoscale carriers enhancing drug passage across the BBB appears to be a promising solution. It is worth paying attention to lipid carriers, which can mimic the natural environment constituting biomembranes, protect the drug from degradation during transport, reduce toxicity and increase drug biocompatibility compared to systemic administration [5]. However, they have some limitations related to their stability and drug loading efficiency.

Another alternative to the traditional treatment of neurodegenerative diseases is Mesenchymal Stem Cell (MSC) therapy. For many years it was believed that the CNS cells could not regenerate. This approach has been challenged thanks to the studies demonstrating the new migratory stem cells in a rodent brain injury model and by the discovery of new neurons in the hippocampus of the human brain. The MSC therapy would involve administration of the cells by intracerebral injection, intradural injection, or infusion via the intranasal route [10]. MSCs transplanted into the brain would reduce apoptosis, regulate inflammation with the help of secreted factors, and may affect endogenous growth, regeneration, and the protection of neurons [11]. Such procedures will be based on the autologous (from the patient) or allogeneic (from a person related or unrelated to the patient) MSCs. The use of allogeneic MSCs carries the risk of abnormal cytogenetic development in cell cultures and the ectopic differentiation of cells into other tissues [11]. In addition, there is much controversy over the potential impact of MSCs on tumour progression and metastasis [12]. Therefore, a very important eligibility criterion for MSC therapy is the absence of previous brain tumours or other neoplasms within the past 5 years.

Gene therapy in the treatment of neurodegenerative diseases

Crossing the BBB is not the only problem in the treatment of neurodegenerative diseases. Although thanks to genetics, microbiology, and virology developments, we can understand the genesis of these diseases, unfortunately, there are still no therapies that would permanently eradicate the cause of the ailment. That is why gene therapy appears to be an alternative to the current methods of treatment. This is an innovative treatment that involves introducing a correct gene variant, turning on or off a function of a particular gene, or introducing an additional therapeutic gene. Gene therapy can be used to treat both hereditary and acquired diseases [13].

The first gene therapy drug approved by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) is Glybera, for the treatment of lipoprotein lipase (LPL) deficiency in patients with severe or multiple attacks of pancreatitis despite dietary restrictions [14]. Another example of a successful gene therapy is the conditional marketing authorisation for Carvykti, valid throughout the European Union (EU). Treatment with Carvykti involves genetic modification of a patient's T cells to produce a protein called chimeric antigen receptor (CAR). The CAR-modified T cells attach to a protein called a B-cell maturation antigen, resulting in the death of myeloma cells. In a multi-centre clinical trial, this drug was shown to be effective in patients with relapsed and refractory multiple myeloma [15]. In addition, gene therapy may be potentially used in treating such diseases as haemophilia, malignancies, diabetes, and neurological diseases.

The main limitation of designing gene therapies is finding efficient and safe carriers of genetic material (vectors). A virus is a natural particle that infects cells and then inserts its genetic material into them. Although this remarkable ability is undesirable in healthy individuals, it has led to the creation of a number of gene therapy tools based specifically on viruses, including adenoviruses, retroviruses and AAVs. Viral vectors effectively transfer their genome into host cells, but their use has some limitations. A human body does not distinguish between a drug and the pathogen, so such vectors can cause an immune response and thus, along with the transduced cells, can be quickly removed from the body [16].

In the case of neurodegenerative diseases, AAV-based vectors are the most commonly used in gene therapy. The latest vector-related success of medicine is granting a marketing authorisation to a drug called Upstaza. This is the first drug used to treat a rare genetic disorder of the nervous system: Aromatic Acid L-Decarboxylase (AADC) deficiency. It consists of the viral AAV-2 vector, which contains a functional version of the AADC gene. It introduces this gene into nerve cells, enabling them to produce the missing enzyme [17]. A similar strategy is used for Parkinson's disease, which is currently in phase II clinical trials [18]. Currently, treatment for this disease involves the administration of L-Dopa, which is converted to dopamine in a reaction catalysed by aromatic L-amino acid decarboxylase. It results in reducing the symptoms but does not eliminate the cause. Neuronal degradation still takes place, and the activity of the AADC enzyme and dopamine declines along with them [19]. Results from the first phase of the AAV2-hAADC clinical trials indicate improved quality of life, motor function, and less need for PD medications [20].

The AADC gene is not the only one being studied in the context of Parkinson's therapy. A vector with a recombinant glial cell line-derived neurotrophic factor (GDNF) gene seems equally interesting. GDNF plays a role

in the maintenance of neuromuscular junctions (NMJ). In addition, it is a neuroprotector and it helps to form new synapses between motor neurons and target tissues. With a lack of GDNF, nerve cells die, which in turn impairs the NMJ structure and function. A study in rats showed increased GDNF expression after AAV-GDNF injection into the striatum, which protected neuronal cells from death [21]. In contrast, studies in mice showed that increased GDNF expression significantly protected against dopamine loss and prevented the blocking of long-term synaptic potentiation (LTP) [22]. The GDNF gene therapy may in the future be used in the treatment of Parkinson's disease, and a phase I clinical trial is currently underway [23].

Huntington's disease is another disorder for which alternative treatments are being sought. This is a fatal neurodegenerative disease caused by an expansion of CAG trinucleotide repeats in the Huntington (HTT) gene. Scientists are conducting research on the AAV serotype 5 vector with a transgene encoding modified miRNA against HTT mRNA. During a single intracranial administration of AAV5-miHTT in a transgenic HD guinea pig model, both the mRNA and protein of human mutant Huntington were significantly reduced in all brain areas [24]. Equally promising results were obtained in studies of this vector in mice [25], rats and *Macaca fascicularis* [26]. AAV5-miHTT has been approved for phase I clinical trials [27].

Viruses are not the only way to deliver genes into cells. There are many physical and chemical methods of transfection. Physical methods include electroporation, gene gun, hydrodynamic injection, sonoporation and magnetofection. The chemical carriers include cationic lipids, cationic polymers, dendrimers, inorganic nanoparticles, and peptide-based vectors [28]. Scientists are constantly working on new gene therapy tools with improved bioavailability and reduced recognition by the immune system.

Summary

Developing drugs acting on the central nervous system take much longer than drugs that affect other systems. This is due to the complex structure of the brain, the lack of efficient drug delivery technologies, the frequent occurrence of side effects and the selectivity of the blood-brain barrier. Mainly micro and macromolecules are being studied as effective therapeutic agents for treating brain diseases. However, only small, and lipophilic molecules can successfully cross the blood-brain barrier.

The search for new therapies to treat neurodegenerative diseases is a challenge for modern science. To date, no suitable therapy has been developed to eliminate the cause of the ailments. Therapies using nanoscale carriers and mesenchymal stem cells appear to be promising alternatives to traditional ones. However, the greatest hopes lie in gene therapy, as through altering or inducing the expression of specific proteins it will be possible to correct the underlying pathogenic mechanism of the disease. Recent successes in the form of granting marketing authorisations show how valuable this field of medicine is. A great deal of research is currently underway both for potential treatments and for improving gene delivery tools. Rapid development of gene therapy in the future may not only eliminate the symptoms of neurodegenerative diseases but offer hope for their successful treatment.

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REVIEW ARTICLE

DIFFERENCES IN THE WORK OF RESCUERS IN THE ENVIRONMENT OF A TERRORIST ATTACK

Odrębności w pracy ratowników w środowisku zamachu terrorystycznego

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Abstract: Terrorism is a problem that has affected many countries and areas of human activity in the past few decades. Acts of terrorism can take many forms, with attacks being organized by groups or individuals. The means that have been used to inflict damage on the casualties of the attacks have also varied. Rescuers sent to provide help at the site of a terrorist attack must prepare themselves for work far from the generally accepted standards, with a large number of casualties and mechanisms for injuries different from those with which they deal in everyday practice. The key element of providing assistance in this type of incident is having an appropriate mental attitude and an understanding of the methods and procedures of treating the injuries resulting from the impact of firearms and the consequences of an explosion. The purpose of this article is to indicate the most important factors that should be taken into account when planning or starting rescue operations in the environment of a terrorist attack.

Streszczenie: Terroryzm jest problemem, który w ostatniej dekadzie dotknął wiele krajów i obszarów ludzkiej działalności. Akty terroru przybierały różne postaci: atak zorganizowanych grup bądź jednostek. Różne były też środki, które zostały wykorzystane do zadania obrażeń ofiarom ataków. Ratownicy skierowani do udzielania pomocy w miejscu zamachu terrorystycznego muszą się w takich przypadkach przygotować na pracę daleką od standardów ogólnie przyjętych, znaczną liczbę ofiar, mechanizmy urazów odmienne od tych, z którymi mają do czynienia w codziennej praktyce. Kluczowym elementem udzielania pomocy w tego typu zdarzeniach będzie przede wszystkim odpowiednie nastawienie psychiczne oraz znajomość procedur i sposobów zaopatrywania urazów powstałych w wyniku oddziaływania broni palnej i następstw wybuchu. Celem niniejszego artykułu jest wskazanie najważniejszych czynników, które należy brać pod uwagę, gdy planujemy bądź rozpoczynamy działania ratownicze w środowisku zamachu terrorystycznego.

Keywords: police, terrorism, blast injuries, gun shoot wounds, Emergency Medical Services.

Słowa kluczowe: policja, terroryzm, obrażenia spowodowane wybuchem, rany postrzałowe, Zespoły Ratownictwa Medycznego.

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Introduction

Dealing with casualties in the context of a Mass Casualty Incident (MCI) is always a major challenge for both the rescuers at the incidence scene and the hospitals to which the injured are sent. Since the threat of terrorism is increasing, special attention must be paid to this phenomenon not only by security authorities, but also by emergency services. The difference between a mass casualty incident and a mass casualty incident caused by a terrorist attack lies in the mechanism of injury (blunt trauma as opposed to penetrating trauma), types of event (a static situation as opposed to the dynamic, variable nature of mass casualty incidents caused by terrorism). This article aims at introducing the phenomenon of terrorism itself, its types, possible mechanisms of injury and priorities in dealing with them, psychological reactions behind such an event, and the need to develop appropriate tactics for rescuers based on an analysis of all the above factors. An essential prerequisite for taking proper action in the situation of such mass casualty incidents is a change in the mindset of the rescuers participating in the rescue operation. The basic change in mindset should involve a widely understood ability to adapt to the situation.

High Threat Incidents

Both types of incidents, i.e., a terrorist attack and an active shooter attack, can be covered by one common term: High Threat Incident (HTI), those in which rescuers face an increased risk of loss of life and health. Such a threat results from the nature of these incidents, whether it is an attack by a single attacker or a group of them aimed at inflicting the greatest possible damage to both bystanders and responding services, which may be a secondary target of the attacker(s). The following elements can be distinguished in this kind of events:

- multiple attackers, often well-prepared and trained to carry out a specific operation, accepting the risk of their own death,
- a single assailant aiming to inflict as much damage as possible using a whole spectrum of means from firearms to various types of vehicles,
- careful preparation of an assassination plan using military tactics, effective communication, and coordination,
- use of toxic or radioactive materials during the attack,
- fire, structural collapse making it difficult or impossible to reach casualties,
- intentionally delayed attacks on emergency services,
- operational difficulties for emergency services caused intentionally by the attackers, further complicated by the number and limited capacity of the emergency services [1].

In addition to definitions including terrorist attack and active shooter attack, the literature further distinguishes: an Active Armed Offender (AAO) and a Hybrid Targeted Violence Incident. Unlike an active shooter, an AAO may not use firearms during an attack. An AAO is more likely to resort to more conventional tools in the form of, for example, a kitchen knife or a home-made white weapon, as well as explosives. This kind of attack tactic often involves vehicles. A Hybrid Targeted Violence Incident includes operations with the use of conventional attack tactics against a specific person or group. These operations may have both a criminal and terrorist nature [1].

In addition, we must pay attention to the situation in which several attacks are carried out simultaneously, which gives terrorists the advantage of amplifying the effects of attacks due to the dispersion of security the forces and resources, and insufficient emergency services [2].

In a life-threatening situation, the mindset of those involved in the incident is disrupted. The behaviour of those exposed to direct terrorist attacks and those who arrive to provide help to determine the effectiveness of the rescue operation and the number of casualties who can be saved. Those who have not been seriously injured so far are not yet completely safe. Their condition may get worse both due to the danger that still exists and the lack of properly provided help. It should be noted that real danger exists in the area of the rescue operation as long as they are carried out, and the people involved should be aware of the existing danger. The behaviour of the injured is largely determined by stress. One should also remember the possibility of any other potential danger, which can be triggered at any time. The lack of reliable information and the inability to realistically assess the situation can distort perception of the danger, often triggering inappropriate and threatening reactions. Another type of difficult situation occurring in the event of an act of terror is an overload, which intensify psychophysical tensions, emotional states, and the awareness of imminent danger. Overloads also affect the rescuers themselves, as the situation forces them to operate at the limits of their physiological and psychological capacities [3].

The rescue efforts, both those aimed at auto-rescuing and helping others, are significantly interrupted by such elements as collapsing debris, fire zones, fences, shortage of rescue forces and resources, lack of information and impediments to its transmission, and errors in interactions [4].

Rescue during HTIs

The surprise of a terrorist attack or the sight of bloodied casualties may disrupt correct thinking. The loss of a small amount of blood, which does not constitute a condition threatening a casualty's life, may sufficiently distort the initial assessment of the casualty's condition. Overcoming the fear barrier and the proper assessment of the extent of the injury depends mostly on the rescuer's level of training. If they are unable to think logically, they may try to follow learned patterns: when they start to react, to provide assistance, and regain mental agility. Additionally, an accident or disaster scene attracts a crowd of onlookers surrounding the casualties and rescuers. In order to use them effectively, Someone in a uniform or the most active one should be picked and asked to move the onlookers away. If necessary, someone else should be designated to assist. The rescuer should give commands loudly and confidently, engage additional people to help and alert the professional emergency services, and tell disturbing individuals to hold an object (such as a bandage) or an uninjured limb of the casualty. The disturbing individual's activity will then be significantly calmed or turned in the right direction. The rescuer's example should set the example to others and help engage them in the rescue process. It is also important to prevent panic attacks. If these break out, the number of casualties may increase many times. Overly agitated people in the crowd should be assigned a caregiver or ordered to perform an action they are capable of. It may be necessary to use direct coercion against them [4].

To survive a life-threatening situation, one must have:

- the ability to concentrate mentally,
- the ability to improvise,
- self-confidence,

- the ability to adapt to the situation,
- the ability to remain calm,
- the ability to remain optimistic [4].

Rescuers are used to working in teams or pairs. In high-risk incidents, we often face a situation in which the number of casualties significantly exceeds the number of rescuers. This means rescuers will then have to work alone.

No matter what the situation is, the rescuer's safety should always come first. In a life-threatening situation, the most desirable behaviour should be to escape. While escaping, any objects that may impede escape from the danger area should be abandoned. We should assist others in escaping by encouraging them to find a safe shelter, while any individuals who impede escape should be left in the danger area. Other people should be warned against entering the danger zone. While in hiding, we should call the emergency services, and describe the attacker(s) as accurately as possible. If escape is not possible, it is a good idea to find a hiding place by getting out of the attackers' line of sight and keeping quiet. The hiding place should provide maximum protection against the attackers' influence. While in hiding, we should switch off the vibration of our cell phone, close and lock any door and turn off the lights. We should not hide in groups but disperse. The best form of communication is through social media or by placing a visible sign in the window of the room where the hiding place is. We should remain in hiding until the security forces give a clear command to leave the hiding place/building. As a last resort, a fight with an attacker(s) should be initiated. In this particular case, the actions taken must be aggressive (attempting to prepare an ambush on the attacker, attacking with books, fire extinguishers, scissors, etc., throwing objects at the attacker to incapacitate or distract them). By engaging in a fight, we must be prepared to inflict fatal or serious injuries on the attacker as a last resort. When the security forces arrive, any objects should be discarded, and hands should be put up so that your palms are visible. The task of the security forces is to resolve the emergency, and they may leave behind those in need of help. Officers will give loud commands to those found at the scene of the attack, including ordering them to lie down on the ground in order to ensure maximum security for the forces themselves. All commands should be followed and everyone should follow in the direction indicated by the officers or other soldiers. Everyone should take care of themselves first and take care of other injured people only when security forces arrive [5-8].

Characteristics of injuries during a terrorist attack.

The lack of an adequate set of data and guidelines on how to respond appropriately to a terrorist threat in Poland prompts us to look for a pattern of treatment in the ready-made solutions that have been adopted by the countries recently affected by terrorist acts, or in the national registries of countries where a large percentage of injuries or deaths are caused by the use of firearms [9]. Working with a trauma patient, especially when it comes to mass casualty incidents, is primarily focused on the organisation and procedures aimed at dressing wounds as quickly as possible and transporting the injured to appropriate hospital, where the treatment process can begin. Transferring the patient from the scene as quickly as possible plays a key role in the whole system of mass casualty incident management. A mass casualty incident (MCI) is a term used to define an event in which the number of casualties at any given time exceeds the ability of the local emergency system to provide help, using standard procedures. An event of this type primarily requires non-standard operations and external help to support the local rescue system. MCI can also be referred to as an event in which the number of casualties leads to a temporary disruption of the local rescue system [10].

Due to the capacity of the local rescue system, mass casualty incidents can be divided into four levels:

- MCIs requiring the involvement of the local rescue system and cooperating institutions to effectively minimise the effects of a mass casualty incident,
- MCIs requiring the involvement of the regional rescue system and basic assistance from surrounding regional aid systems to effectively minimise the effects of a mass casualty incident,
- The scale of the MCI requiring activation of the national emergency management system to effectively minimise the effects of a mass casualty incident,
- The scale of the MCI is so large that international assistance is needed to effectively minimise the effects of a mass casualty incident [11].

The unpredictability of the place and time as well as the type of the incident make each mass casualty incident a unique phenomenon, especially in terms of the number of casualties. For this reason, it is impossible for emergency services to plan and practice possible scenarios. The key to a successful response to an MCI is to maintain a consistent level of preparedness for all elements of the emergency system. At the core of maintaining an adequate level of preparedness is, first and foremost, the awareness of the occurrence of a mass casualty incident caused by terrorism. Unfortunately, despite the experience of many countries, maintaining preparedness for a mass casualty incident is not systematised and institutionalised through action plans, procedures, and the level of training of emergency services personnel. The action plan and procedures used during a mass casualty incident should include:

- the possibility of mitigating the effects of a mass casualty incident, with the possibility of some effects of the MCIs may be reduced even before the event itself, such as the preparation of an evacuation plan in the case of a flood,
- proper planning based on training and practice, as closely as possible, and revised (if any elements of the plans prove inadequate or erroneous) after the emergency services have completed their work at the site of the mass casualty incident. In the case of high-

risk incidents, it must be assumed that rescue operations will be initiated by survivors and witnesses to the incident, resulting in an influx of casualties to local hospitals without emergency services, prior segregation, or possible decontamination. Moreover, it is impossible to prepare plans for the occurrence of all types of mass casualty incidents and for all emergency services. Nevertheless, such a plan should be based on certain common elements and to some extent it should be adaptable to different situations. The basic level of providing assistance to the injured should be the same in all mass casualty incident management plans of all emergency services responsible for minimising the consequences of such an incident.

Mass casualty incident response phase: this is perhaps the most important phase of the emergency services' response to a mass casualty incident. The effectiveness of the response to a mass casualty incident depends on:

- activation, announcement of the mass casualty incident and the response of emergency services to the mass casualty incident according to the developed response plans,
- organisation of the command for the rescue operations at the scene of a mass casualty incident, one of the most important stages of the work of emergency services at the scene of a mass casualty incident. The commander of the operations at the scene must be selected as early as possible, as well as the necessary communication channels must be established, which is necessary for the proper management of forces and resources heading to the scene,
- search and rescue: depending on the type of incident or the system solutions adopted by the country, the search and rescue operation will be carried out by units of the rescue system, fire department, police and/or military. In some types of mass casualty incidents, the above-mentioned elements will have to work simultaneously, which requires their proper coordination and a clear action plan for all of them,
- extraction, triage, stabilisation, and evacuation of casualties, while in most rescue systems the injured are extracted by fire-fighting forces. Triage is aimed at providing the best possible assistance to as many casualties as possible, indicating the priority of transport to treatment facilities and identifying interventions to be taken to improve the condition of the casualty at the scene. As a result of the triage, we should determine the type of incident and the number of casualties, check the amount of resources available and the possible need for them, the ability of nearby hospitals to admit the casualties, and the scale of the incident. Transportation should be organised and planned in such a way that takes full advantage of the capabilities of nearby hospitals. It should be remembered that the first patients will be brought to hospitals when the first wave of less injured people, who will evacuate on their own from the scene, have already begun to arrive. We must also not forget that the injured may require decontamination before transportation to the hospital,
- recovery is a phase primarily involving restoring the scene to its pre-MCI condition. This phase also includes debriefing the emergency services responding to the incident and working with a psychologist to minimise the negative effects of the incident affecting rescuers [12].

When a wound (gunshot, caused by shrapnel, sharp instrument, as a result of using a car as a weapon, etc.) involves a single casualty, rescue operations may be carried out in a comfortable environment and according to current guidelines. When there are more casualties, the organisation and provision of assistance to the injured, in the case of gunshot and blast injuries, consumes considerable material and human resources and involves many complications, and the assistance at the scene should be limited to interventions that interrupt, as soon as possible, the life-threatening condition [13].

In a situation where there are more casualties, we need to segregate them. Triage can be defined as categorising patients during a mass casualty incident according to their medical needs and the available forces and resources [14]. Triage is the primary action of rescuers during a mass casualty incident. There are several levels of segregation during a mass casualty incident. The first segregation is performed by rescuers on the scene (paramedics or firefighter rescuers). The first rescuer, who categorises the patients, should quickly make decisions about further rescuers' actions consistent with the condition of the casualties. Making these decisions is facilitated by the mass triage algorithms. The most widely used algorithm for the segregation of the injured is START *(Simple Triage and Rapid Treatment)*. Using START, the rescuer should quickly assess: the casualty's ability to move, mental status, circulatory system efficiency, and respiration. Assessment of the described parameters should take no more than a minute and end with the assignment of one of four colour-coded categories of casualties: red (immediate assistance), yellow (urgent assistance), green (delayed assistance) and black (patient in whom spontaneous breathing has not returned despite opening the airway) [11]. The duration of the rescuers' work at the scene is determined by the available forces and resources. The extent of medical steps towards the injured at the scene, as well as the time of evacuation, will be determined by the number of ambulances available, the availability of air evacuation of the injured and the distance from the nearest hospital. The minimum level of medical services provided to casualties at the scene should include stopping massive haemorrhages, securing the airway, decompression of the pneumothorax and administration of specific antidotes. These life-saving interventions (LSIs) are listed and named under the SALT (Sort, Assess, Lifesaving Interventions, Treatment/Transport) casualty segregation system. In addition, SALT introduces an additional category of casualties marked in orange. These individuals have been

injured as a result of hazardous materials (HAZMAT) or paralysed as a result of combat poisonous agents (CBRN) [15].

Table. Classification of blast injuries.

	Mechanism	Possible bodily injuries
Primary injuries	Pressure injury caused by a sudden increase in pressure or a shock wave	Traumatic amputations, damage to air-filled organs by a sudden pressure increase, ear injury, air embolism
Secondary injuries	Shrapnel fragmentation	Injuries resulting in an increase in the number of casualties and the highest mortality rate: shrapnel wounds of various sizes and course
Tertiary injuries	Being buried by building elements, body collisions due to shock wave throwing of the body, falls	Blunt injuries to multiple areas of the body, crush syndrome, fractures, amputations damage to internal organs
Quaternary injuries	Exposure to high heat/flame resulting from explosions	Thermal burns of various degrees
Quaternary injuries	Additional elements to compound the consequences of injuries/explosions, i.e.: faeces, dead animals/corpses, elements causing biological, chemical or radiation contamination	Infections and tissue contamination

Source: **own compilation** *based on sources [17–18].*

Gunshot wounds and those sustained by casualties in explosions vary, depending on their location, the need for advanced medical procedures necessary for management, the severity of the injury and the subsequent prognosis for the casualty. This has a huge impact on the adopted method of management of the injured and preparation of the medical facilities to receive a patient injured by firearms or explosives. The adopted algorithm of action should be different for a gunshot and an explosion, which is due to the different mechanisms of injury (in order to understand how to deal with a casualty of a terrorist attack, it is necessary to know the mechanism of any injury caused by both explosives and firearms).

In a nutshell, we can divide various explosives according to how much energy we are able to release from each type of explosive and the speed of reaction that occurs in them. However, the explosion will be the same for each type. The differences in injuries and their consequences will result from the amount of material used, the use of mixtures, the finished product, additional components of the explosive device, the use of the explosive in rooms, open spaces, etc. The explosion itself, causing combustion of the used material in its entire volume, will cause sudden large temperature and pressure fluctuations, leading to the creation of a shock wave that will injure people within a certain range [Table].

From the perspective of the rescuer, a direct impact of the explosive on a person (e.g., the need to manage limb amputation) will be important, as well as the fragmentation of the device body and the ancillary components contained therein (screws, nails, metal balls, etc.) or parts of the infrastructure moved by the force of the explosion, which causes injuries very similar to those resulting from the use of firearms [16]. Exposure to the high temperature created by the explosion can cause thermal burns to the body or respiratory tract. Collapse of the structure can result in crush syndrome with secondary complications, such as cramping syndrome [19].

A gunshot wound is usually treated as a wound resulting from the impact of a bullet fired from small arms. In the course of a gunshot wound, we can distinguish the entry and exit of the bullet, the wound channel, and the instantaneous channel, which is formed during the penetration of particular tissues. However, the concept of a gunshot wound should be extended to include wounds inflicted by other types of projectiles, such as arrows or shrapnel. Shrapnel wounds are usually inflicted by multi-shaped shrapnel created by the bursting combat assets designed to inflict these types of wounds (e.g., a grenade) or pieces of infrastructure moved by the shock wave. Shrapnel of sufficient mass, size and velocity can have enough energy to knock down a person [17].

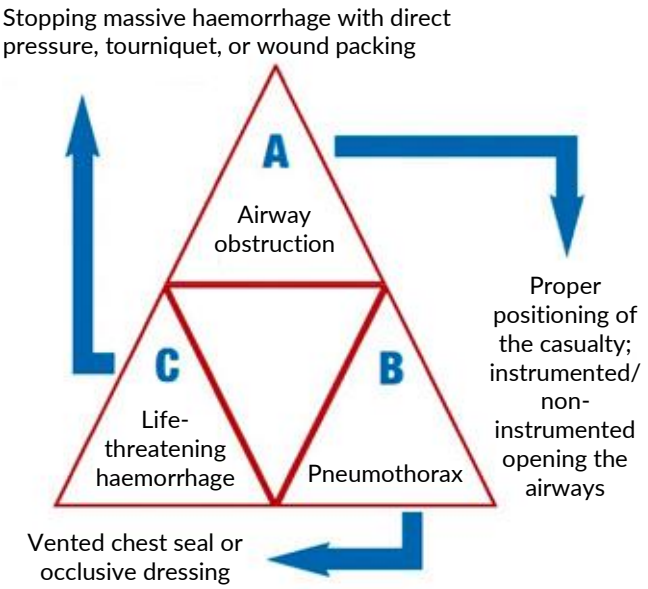
Factors affecting the severity of injuries include:

- type of firearm used (e.g., rifle, machine guns, handguns), which determines such parameters as the initial energy of the projectile, mass, loudness, rate of fire,
- type of bullet: its calibre, mass, design (profile, type of jacket), influencing the depth of penetration, trajectory within the tissues and body cavities, as well as the extent of tissue damage and the size of the instantaneous channel,
- nature of the shot: direct hit or ricochet,
- place of the hit and the direction determining the nature of internal injuries,
- possible use of personal protection elements in the form of vests, helmets, etc. [17].

All these elements affect the exact characteristics of the injury. There are static gunshots, penetrating injuries with the bullet left within the body or not. It should be noted that trajectory of the projectile may change after coming into contact with bone fragments, especially those of significant weight and thickness, resulting in the displacement of secondary fragments, causing additional injuries [17]. It should be emphasized that weapons of identical calibre and type can cause different injuries due to the amount of kinetic energy transferred and how this energy is absorbed and transferred through the tissues.

Wounds or injuries to the casualty can affect any area of the body. In the first 10 minutes after the onset of the injury-causing agent (the "platinum ten minutes"), death is caused by typical, preventable causes: chest and abdominal injuries and bleeding from the extremities [19].

Figure Triad of life-threatening consequences of firearm/explosion.



Source: own compilation based on sources [20].

Studies show that most of the causes of preventable death can be effectively treated by knowing the algorithms for trauma patient management, correctly assessing the casualty according to the scheme proposed by, for example, PH-TLS, ITLS or ATLS [18].

When assisting the injured in high-risk situations, attention should be paid to the following elements:

1. Injuries are different from those that medical personnel encounter on a daily basis. In the daily work of paramedics, the segregation of injuries by the mechanism that led to their occurrence is as follows: 70% blunt injuries, 20% penetrating injuries and 10% burns. In a situation involving firearms or explosives, in most cases we will be dealing with penetrating injuries, traumatic amputations, often combined with burns.
2. The constant danger present at the place of providing help to casualties threatens the rescuers' safety. It is important to remember that the rescuers' safety is a priority during a rescue operation.
3. Those who work with a trauma patient on a daily basis begin the initial assessment of the casualty with the examination of vital functions according to the ABC (Airway, Breathing, Circulation) approach. In the situations mentioned above, most preventable deaths are caused by massive haemorrhages, hence the scheme is changed to CABC (Circulation – stop massive haemorrhage, Airway, Breathing, Circulation).
4. It should be remembered that in a situation where we provide assistance to more than one casualty, we are limited by the equipment we have and, above all, its limited amount. The fact that the vast majority of the necessary devices is loaded on rescue vehicles must be taken into account.

The last element we need to pay attention to is the varying evacuation times of the injured and the methods of evacuation, which means that working with the injured at the scene will be significantly prolonged [20].

Given these distinctions, the rescuers who are the first to arrive at the scene of a high-risk incident should:

- retreat to a safe location and establish communication with the coordinator from there to determine the type of incident and the forces/resources needed at the scene to help as many casualties as possible,
- call the necessary police forces and wait for their arrival,
- if possible, prevent access to the scene by outsiders,
- provide assistance in accordance with current guidelines of internationally recognised organizations [21].

Before starting to work with an injured person in any situation it is necessary to assess their condition. The condition and need for help can be assessed remotely using the Rapid and Remote Assessment Methodology (RAM). The goal of this algorithm is to maximise the assessment of the potential to salvage and treat casualties that can be rescued. The RAM procedure takes into account all the

circumstances. The first step is to determine whether the area is safe. Standard care of the casualty is possible only when the rescuer is sure that the casualty cannot harm them. Otherwise, assistance should be waived until safety can be assured. Assessing the injured person's condition from a distance involves trying to discern the nature of the injury and the person's stability. If the patient seems stable, they should be given instructions on how to salvage themselves, and any medical procedures should be postponed until the tactical situation is resolved by the relevant services. RAM assumes the use of various means of observation (e.g., binoculars) or drones to assess the condition of casualties [22].

In such a situation, the Tactical Emergency Casualty Care Committee (TECC) proposes, first and foremost, to minimize all possible threats. It recommends assessing the danger on a continuous basis. A casualty in an emergency situation should be shown a safe place to hide. If a patient is unconscious, we must consider the balance of possible gains and losses of a possible rescue operation. As in the RAM strategy, in TECC a rescuers should initially identify those who have little chance of survival. Then they should consider stopping potentially life-threatening haemorrhages of casualties according to their intensity, using appropriate techniques and prioritising evacuation [23].

In the case of rescue operations according to the algorithms defined by ATLS, ITLS or PHTLS, all interventions with the casualty should result from the priorities established during the initial examination. They should follow the order of the examination, i.e.: A – airway, B – respiration, C – circulation. In the case of massive, unstopped external haemorrhage, this scheme changes the order to CABC [18]. Casualties with massive haemorrhage from the extremities, neck, groin, or axillary fossa area should be rescued first. In the first stage of casualty rescue, the instrument of choice for managing haemorrhages from the extremities should be a tourniquet (CABC). Haemorrhages from the neck, groin or axillary fossa should be managed by packing or tamponade (using an improvised or haemostatic agent) and compression at the bleeding site. Active bleeding into body cavities is not controllable at the scene and is an indication for transport and surgical supply as soon as possible [9]. A similar opinion is found in the PHTLS guidelines, which recommend modifying the initial examination from ABCDE to X-ABCDE. "X" stands for life-threatening exsanguinations. Thus, PHTLS emphasized the importance of stopping external haemorrhages [24]. A distinction in the ABC scheme for examining a casualty is also proposed by the instructors Magen David Adom. Their modification is an expansion of the acronym ABC1/2C, which refers to opening the airways, checking breathing, and applying a tourniquet in the case of extremity haemorrhage.

In the case of chest wounds, the first step is to ensure airway patency. The wound of the thoracic region should initially be sealed with the rescuer's own hand in a rubber glove, then with a vented chest seal, which should be made of an impermeable material and sealed on three sides to act as a one-way valve, or with a dedicated dressing for sealing chest wounds [18, 20].

In the case of abdominal wounds, the injured area should be exposed. Then, if possible, eviscerated bowel loops should be washed and assessed in terms of bleeding and continuity. The next step in securing the evisceration is to cover the intestinal loops with sterile gauze (from below and above) moistened with saline. The intestinal loops managed in this way should be secured with a film or occlusive dressing and then stabilised with a covering dressing [18, 20].

The injury in the pelvic region can be stabilised with a sheet or blanket. They should be spread over the stretcher with which we will evacuate the injured person, or under the injured person if we leave them at the scene. The ends of the sheet lying diagonally should be tied so that the knot is in the hip area. The action is repeated with opposite ends of the textile. The fixation tension should then be gently increased to achieve full stabilisation of the fractured pelvis.
When immobilising the pelvis, a commercial pelvic stabilization belt is recommended [18, 20].

A head injury should be secured with a pretzel-shaped dressing. It closes the lumen of the blood vessels in the area of bleeding without direct pressure at the site of injury. The bandage should be tightly attached to the casualty's head.

Examination and dressing of a burn casualty is often hampered by the dramatic nature of the injury. It is important to remember that a burn casualty with extensive burns rarely dies from the burn immediately after the accident. Immediate death usually results from the accompanying injuries, respiratory tract injuries or smoke or vapour inhalation. Careful examination and identification of injuries and their proper management improve the prognosis of the casualty. Immediately after the injured person is removed from the heat source, the skin is still hot, and the injuries increase. This damage can be reduced with proper cooling of the wound. Prolonged cooling of a burn wound can result in hypothermia. The use of lukewarm water is recommended to cool the wound. The use of cold water or ice is not recommended. After cooling the burnt area, it should be covered with a sterile dressing or film. The injured person needs to be covered when preparing for transport, even if the air temperature is not low, because burnt skin loses its thermoregulatory functions [18].

To prevent hypothermia, thermal insulation should be provided based on the following:

- materials used for thermal insulation should be dry and tightly laid,

- slight clearance should be left between layers,
- preferably, at least one layer should be formed by a thick, lightweight, pneumatic material, such as fleece,
- the materials used should be hydrophobic,
- the outer layer is especially important in an open environment to protect against wind and moisture,
- system solutions, such as sleeping bags, work best. They are designed for the lying position, made of suitable materials, and allow quick access to the casualty [26].

Under the conditions of a terrorist attack or AAO scenario, CPR plays a minor role, mainly due to the safety of the rescuer. In such a case, the rescuers' efforts should be directed toward evacuating the casualty from the danger zone as quickly as possible, only after which resuscitation should be undertaken according to the current procedures [25].

Summary

The environment of a terrorist attack where the rescuers happen to work is quite different from the environment in which they perform their daily duties. The differences result to the dynamics of such an event, the number of casualties, the mechanisms of injury, available forces, and resources, etc. The basis for undertaking rescue operations in such an environment is first and foremost safety, which must be assessed on a continuous basis. Thanks to the knowledge of the material used in the attack, the type of injuries may be predicted, and rescuers may be directed to take the right actions to provide proper assistance to as many casualties as possible. For this purpose, some knowledge of terrorist mass casualty incident plans and procedures (including medical segregation procedures) is needed. Despite the significant distinctiveness in the mechanisms of injury that may occur in a terrorist attack, most rescuers are familiar with the medical actions to be performed in such cases. It must also be taken into account that if there are insufficient resources necessary to secure these injuries, it may be necessary to secure them with improvised means, which must be trained for beforehand.

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LASER THERAPY IN THE TREATMENT OF IATROGENIC LESIONS OF THE ORAL MUCUS MEMBRANE – LITERATURE REVIEW AND CASE STUDY

Laseroterapia w leczeniu jatrogennych urazów błony śluzowej jamy ustnej – przegląd piśmiennictwa i opis przypadku

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Abstract: Iatrogenic lesions (chemical or mechanical) constitute a specific cause of oral mucositis (OM). In the treatment of OM, a low-level laser therapy (LLLT) is used because of its analgesic, anti-inflammatory and biostimulating effect. The article presents a literature review concerning LLLT application in dental physiotherapy (including oncological patients) and a case study of a female patient (42-years-old) suffering from an extensive iatrogenic OM being the consequence of endodontic treatment. The following LLLT parameters were used: wavelength 830 nm, power output 400 mW, IIIB, dosage 20 J/cm2, continuous fluency, 200 J; 8:20 min; 5 applications. Prior to each LLLT and one week after the first application (6 times in total), an evaluation was carried out using an original Oral Cavity Pain Scale and Laitinen Scale, as well as a photographic record. Already after the first, and especially after the second LLLT application, a decrease in pain level both using the Oral Cavity Pain Scale (respectively by 20 pts/% and 68 pts/%) as well as the Laitinen Pain Scale (respectively by 5 pts and 10 pts) was demonstrated in comparison with the primary condition. After 7 days from the first LLLT application, the patient felt only slight discomfort during eating (1 pt/% in the Oral Cavity Pain Scale). The results of the treatment and the data obtained from literature encourage the usage of LLLT in OM.

Streszczenie: Szczególną przyczyną zapalenia błony śluzowej jamy ustnej (*oral mucositis*, *OM*) są uszkodzenia jatrogenne (chemiczne lub mechaniczne). W leczeniu OM wykorzystuje się laseroterapię biostymulacyjną/niskoenergetyczną (*low level laser therapy*, LLLT) ze względu na działanie przeciwbólowe, przeciwzapalne i biostymulacyjne. W pracy przedstawiono przegląd literatury dotyczący wykorzystania LLLT w fizjoterapii stomatologicznej (także u pacjentów onkologicznych) oraz opis przypadku pacjentki (l. 42) z rozległym jatrogennym OM powstałym podczas leczenia endodontycznego. Zastosowano LLLT (830 nm, 400 mW, III B, 20 J/cm$_2$, emisja ciągła, 200 J; 8:20 min; 5 zabiegów). Przed każdym LLLT oraz po tygodniu od 1. zabiegu (w sumie 6 razy) dokonano oceny z wykorzystaniem autorskiej Skali Bólu Jamy Ustnej, Skali Laitinena oraz dokumentacji fotograficznej. Już po pierwszej, choć szczególnie widocznej, po drugiej aplikacji LLLT w porównaniu ze stanem pierwotnym.nastąpiło zmniejszenie poziomu bólu zarówno w Skali Bólu Jamy Ustnej (odpowiednio o 20 pkt/% i 68 pkt/%), jak i w Skali Laitinena (odpowiednio o 5 pkt i 10 pkt.). Po 7 dniach od 1. LLLT pacjentka odczuwała jedynie lekki dyskomfort podczas jedzenia (1 pkt/% w Skali Bólu Jamy Ustnej). Wyniki przedstawionego leczenia oraz dane literaturowe zachęcają do wykorzystania LLLT w OM.

Keywords: mucous membrane, mechanic injury, physiotherapy, lasertherapy, LLLT, case study, literature review.

Słowa kluczowe: błona śluzowa, urazy mechaniczne, fizjoterapia stomatologiczna, laseroterapia niskoenergetyczna, LLLT, opis przypadku, przegląd literatury.

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Introduction

Lesions of the mucous membrane (MM) of the oral cavity are a common complication after dental or orthodontic procedures. It should also be emphasized that they may occur in the course of neoplastic diseases and deep immune system disorders. In the course of treatment of MM lesions of the oral cavity, biostimulation by low level laser therapy

(LLLT) can be successfully used. In this paper, we present a literature review and a case report of treatment of iatrogenic oral MM lesions using LLLT.

Oral mucosa: structure and function

The MM of the oral cavity is composed of four layers:

- non-keratinised or keratinised epithelium,
- basement membrane made up of a monolayer dividing columnal epithelium,
- lamina propria made of collagen fibres and connective tissue cells, submucosa (bordering the muscle layer or periosteum) made of areolar tissue and containing glands: serous, mucous, or sero-mucous [1-3].

The primary functions of the MM include:

- shielding: dependent on the continuity and tightness of the epithelium separating the non-sterile interior of the oral cavity from the intraorganic environment [4],
- renewing: due to the proliferation of epithelial cells and their keratinization [2],
- defence: thanks to the components of saliva and the role of the reticular and reticulolymphatic system [4, 5],
- absorption: due to the presence of a thin epithelium and a dense network of capillaries [6],
- sensory: due to the presence of taste receptors, thermoreceptors, sensory receptors (corpuscles of Ruffini and Paccini) [7].

Inflammatory lesions and oral mucosal diseases

Oral mucositis (OM) manifests itself as: unpleasant mouth odour, redness, swelling, acute pain and burning of the MM, which greatly impede food intake and hygiene procedures [8, 9].

OM can be caused by infections (bacterial, fungal, viral), allergies, reactive changes, and systemic diseases [9, 10].

A particular cause of OM is oral trauma, including iatrogenic lesions resulting from dental (endodontic, surgical, implant, orthodontic or prosthetic) procedures. They may have a chemical nature, associated, for example, with accidental ingress of sodium hypochlorite (NaClO2) used to sterilise dental canals outside the hard tissues of the tooth. In such a case, a degree of damage to the MM of the oral cavity will depend on: concentration of NaClO2, time of preparation reaction and its temperature, and may be manifested by severe pain (despite the anaesthesia used), swelling and subsequent haematoma at a site sometimes distant from the application, burning of the MM of the oral cavity and maxillary sinuses, necrosis of the mucosa, skin and subcutaneous tissue, and others [11].

Iatrogenic dental lesions to oral MM may also have a mechanical nature. They occur, for example, during tooth extraction, alveolar preparation, endodontic treatment (e.g., improper technique of using a dental suction device) or the use of orthodontic appliances [12]. Sometimes, mechanical, and chemical factors may be combined.

Dental physiotherapy: application of LLLT

Physiotherapy is used in dental, orthognathic or maxillofacial surgery [13, 14]. Dental physiotherapy is used in the treatment of temporomandibular joint disorders, bruxism typeocclusal parafunctions, musculo-fascial pains in the face, atypical facial pains, headaches, non-systemic dizziness, limited mouth opening or blocked mouth opening or closing [15].

Attention should be paid to the physiotherapy procedures used in dentistry, especially LLLT understood as a low-power or "soft" (1-6 mW) and medium-power "mid" (7-500 mW) lasers.

LLLT is used as a complementary treatment (to pharmacology, surgery, manual therapy, and osteopathy) and sometimes as the main form of treatment [13, 14, 16]. Due to its analgesic, anti-inflammatory and biostimulatory effects, LLLT has been successfully used in the regeneration of soft tissue lesions (including OM and MM injuries), hard tissue lesions and the temporomandibular joint [17, 18]. According to the needs, LLLT can be applied both internally and externally to the oral cavity.

Dental physiotherapy specialists mainly use:

- gas lasers (e.g., helium-neodymium, HeNe), which accelerate wound and ulcer (also MM) healing due to the properties of the emitted red light,
- semiconductor devices (e.g., gallium-aluminium-arsenide, GaAlAs) to combat pain and treat inflammation, since the emitted infrared radiation (IR) penetrates deeper into the tissues than the HeNe laser.

LLLT in the treatment of mechanical lesions of the mucous membrane: case report

A 42-year-old woman of normal body build (BMI = 23.2 kg/m^2), non-smoker, came for a physiotherapy consultation (26 June 2022) with extensive mechanical and chemical iatrogenic lesions of the mucous membrane of the lower compartment of the tongue, the floor of the mouth and gums, formed 9 days earlier (18 June 2022) during the primary endodontic treatment of tooth number 46. It should be emphasized that very popular kofardam (latex or vinyl membrane covering the oral cavity) had not been used during the endodontic treatment. During the treatment, a dentist had permanently used a saliva ejector and, for most of the procedure, a dental suction device, which was incorrectly placed on the lower compartment of the tongue and then on the floor of the mouth (mechanical lesion of the MM). Despite the anaesthesia used, the patient reported constant pain in the tongue and gums during the activation of the suction device, which was sometimes so severe (7-8/10 VAS) that the patient moved in the chair. As a result, the NaClO2 used for disinfecting root canals penetrated beyond the hard tissues of the tooth into the interior of the oral cavity (chemical lesion of MM). Since the severe oral pain persisted after returning home and the

next day, the patient contacted her dentist. He recommended protecting the mucous membrane and antibacterial rinses. Despite following the above recommendations and avoiding irritation of MM (gentle eating, careful hygiene, avoiding talking), the wound did not heal, and the patient felt very severe pain both at rest and during talking, while eating was almost completely impossible (cf. Tables 1 and 2).

LLLT was applied using the point-by-point and contact method inside the oral cavity (infrared light; wavelength: 830 nm; power: 400mW; laser class: IIIB; energy density: 20J/cm^2; emission: continuous, fill factor 100%; total energy dose during the entire procedure: 200 J; treatment time: 8:20 min.) – once a day for the next 5 days, in the evening. According to the patient, the pain was the strongest in the evening, probably due to irritation of the mucous membrane throughout the day during normal activities (speaking, eating, swallowing saliva). LLLT was performed with a regular point probe tip, which was disinfected each time. When irradiating the oral cavity, we routinely use a disposable fibre optic tip, but this time we deviated from this method: the fibre optic tips have slightly sharper edges, which caused pain. No side effects were noted during LLLT apart from burning of the tongue during the 4th procedure, probably related to the accumulation of laser energy, which was immediately resolved by slightly moving the laser tip away from the irradiated surface.

Before each LLLT and one week after the first LLLT (6 times in total), the patient was subjectively assessed using:

- Oral Cavity Pain Scale self-authorship created for this purpose, containing 10 areas, each of which is rated from 0 to 10 points. (where: 0 is no pain/discomfort and 10 is the greatest pain/discomfort imaginable; the total sum is 0–100 points, and the number of points scored allows for direct estimation of the patient's discomfort as a percentage: 100% – maximum possible pain and discomfort, 0% – no pain or discomfort) (Table 1),
- Laitinen Scale (rated from 0–4, where: 0 is no pain/discomfort/limitation, and 4 is the greatest pain/discomfort/limitation imaginable) (Table 2),
- using photographic documentation (due to extensive lesion of the mucous membrane and the associated pain when trying to expose it, we only made photographic documentation of changes on the right lower compartment of the tongue).

Table 1. Oral Cavity Pain Scale (self-authored scale).

Oral Cavity Pain Scale (0–10 pts)	Examination date					
	Before the first LLLT 26-05-2022	Before the second LLLT 27-05-2022	Before the third LLLT 28-05-2022	Before the fourth LLLT 29-05-2022	Before the fifth LLLT 30-05-2022	After 7 days from the first LLLT 02-06-2022
Discomfort/pain when speaking	10	7	2	1	1	0
Discomfort/pain when eating	10	8	4	2	1	1
Discomfort/pain when drinking	10	8	4	0	0	0
Avoiding certain foods (e.g., fruit, hard foods, foods with sharp edges, spicy)	10	10	6	1	0	0
Avoiding certain drinks (e.g., fruit juices, fizzy drinks)	10	8	3	0	0	0
Avoiding speaking	10	7	2	1	1	0
Discomfort/pain at rest	9	6	1	0	1	0
The necessity to limit professional work due to discomfort/pain in the oral cavity	8	7	2	1	0	0
The necessity to limit social contacts due to discomfort	8	8	2	0	0	0
Feeling of irritation due to oral discomfort/pain	10	4	1	0	0	0
TOTAL (pt/% severity of lesions)	95 (pt/%)	75 (pt/%)	27 (pt/%)	6 (pt/%)	4 (pt/%)	1 (pt/%)

Table 2. Laitinen Scale

Laitinen Scale (0–4 pts)	Examination date					
	Before the first LLLT 26-05-2022	Before the second LLLT 27-05-2022	Before the third LLLT 28-05-2022	Before the fourth LLLT 29-05-2022	Before the fifth LLLT 30-05-2022	After 7 days from the first LLLT 02-06-2022
Pain severity	4	3	2	1	1	1
Pain frequency	4	3	2	1	1	1
Function restriction due to pain	4	2	1	0	0	0
Taking painkillers	4	3	1	0	0	0
TOTAL (pt)	16 pt	11 pt	6 pt	2 pt	2 pt	2 pt

Within 7 days, the treatment almost completely reduced the pain and other unpleasant sensations in the oral cavity (cf. Table 1 and 2) and initiated its rapid healing. It was noticeable already after the first, and especially after the second LLLT, both on the Oral Cavity Pain Scale (respectively: pain decrease by 20 points/% and 68 points/% compared to the initial state, cf. Table 1), as well as the Laitinen Scale (respectively: pain reduction by 5 points and 10 points compared to the initial state, cf. Table 2), which was a positive surprise. Seven days after the first LLLT, the patient experienced only slight discomfort when eating (1 point/% on the Oral Cavity Pain Scale). One month after the injury, no further discomfort was noted, and only a deeper scar remained on the lower compartment of the tongue.

Discussion

Modern medicine requires a holistic approach to the treatment of patients and, consequently, cooperation in interdisciplinary teams. Increasingly often, attempts are made to support or replace pharmacological methods, such as by physical therapy. One example is LLLT, which is used in physiotherapy, dermatology, surgery, and dentistry [19, 20].

Impact of LLLT on pain reduction

One of the most important goals and effects of using LLLT in dentistry is pain relief. In their study [18] regarding the assessment of the level of pain during infiltration anaesthesia in the jawbone, Sharifi et al. showed that LLLT can be successfully used to reduce pain during injection. In a triple-blind clinical study, a group of 84 patients (43 men and 41 women) received a total of 168 anaesthetic injections containing 1.8 ml of a 2% solution of lidocaine and 1:100,000 epinephrine. Each subject received two injections into the mucous membrane of the right cheek and in the area of the upper incisors, 14 days apart. The first injection was administered after LLLT (12 W, continuous signal, wavelength 810–980 nm, 4 J/cm^2), the second injection was not preceded by LLLT. The pain level was measured immediately after the injection using an analogue scale (VAS). In the group of women, there was a significant difference in the level of pain experienced during and without LLLT ($p < 0.05$), while in men this difference was not statistically significant ($p > 0.05$).

Another important aspect is the demonstration of the analgesic effect of LLLT in endodontic treatment, which has been confirmed in studies conducted by Assnahaari et al. [21]. Researchers confirmed pain reduction in patients after endodontic treatment of the molars after using LLLT. The group consisted of 80 patients who were randomly assigned to the study group (n = 40; LLLT) or control group (n = 40; placebo). In the study group, 5 LLLTs were performed, 4, 8, 12, 24 and 48 hours after dental treatment (70 J/cm^2, time: 80 secs, application directly to the tooth). Pain intensity after treatment was checked 5 times using the McGill Pain Questionnaire and the VAS numerical rating scale (at 4, 8, 12, 24 and 48 hours after dental treatment). The study group showed a significant ($p < 0.05$) reduction in pain in the first hours compared to the control group.

Researchers from the Department of Oral Medicine and Radiology at the Pacific Dental College and Hospital Rajasthan in India [16] assessed the clinical effectiveness of LLLT in reducing the pain caused by MM aphthous ulcers. The study involved 30 patients (18 men and 12 women) who suffered from two separate MM ulcers. Each lesion was randomly assigned to a group treated with LLLT (0.5 W, continuous wave, wavelength 810 nm, total duration 3 mins, with breaks of 30–60 sec between applications, 4 treatments) or a control group (sham treatment, without activating the device). Each patient was assessed 4 times in terms of pain, lesion size, and complete healing at the following intervals: immediately after LLLT and then sequentially on days 1, 2, and 3 of follow-up. The researchers proved that complete resolution of ulcers in the LLLT group lasted 3.05 ± 1.10 days compared to 8.90 ± 2.45 days in the sham control group ($p < 0.05$). Moreover, the use of LLLT led to immediate pain relief in 28 of 30 patients in the study group. Also in the clinical case presented by us, a quick, almost immediate decrease in pain was noticed after the use of LLLT (already after the first and especially after the second treatment), which was a positive surprise for us.

Impact of LLLT on wound and oral ulcer healing

The use of LLLT in the treatment of mechanical lesions and acceleration of the wound healing process is one of the best-known features by researchers of this physiotherapy method .

The results presented by Lalabanova [22], who examined the effect of LLLT in the treatment of MM ulcers, are promising (irradiated in the study, the diseased area and the surrounding mucosa). A group of 30 patients was divided into 3 groups: group I (LLLT: red light, wavelength 658 nm, 30 mW, 2 J, 1.22 mins); group II (LLLT: infrared light, wavelength 904 nm, 2 J, 20 mW, 1 mins), group III (control, pharmacological treatment: granofurin and solcoseryl). Treatment procedures were repeated once daily until the symptoms disappeared. In groups I and II, patients reported a reduction in pain after the first application compared to group III. Additionally, faster reduction of ulcers was noticed with LLLT compared to pharmacology, which is why we are starting to think about an attempt to completely eliminate some pharmaceuticals in the treatment of MM ulcers.

Also, in the clinical case presented here, we noted that the introduction of LLLT led to rapid regeneration of the MM, which could not be achieved with the pharmacotherapy previously used by the patient, and complete healing occurred 7 days after the first treatment.

LLLT in oral lesion and ulcer treatments in oncological patients

The regenerating properties of LLLT are also used in oncological patients in the prevention and treatment of ulcers and the inflammation of MM, as complications after chemotherapy, or as an impairment of the immune system. As a painless form of non-invasive treatment, LLLT can effectively improve the quality of life of cancer patients.

There are promising studies on LLLT in oncological patients with oral cancer and lesions in the oral mucosa resulting from chemotherapy or an impaired immune system. In the compilation by Jadaud and Bensadoun [23], in 11 selected randomised studies involving a total of 415 patients with head and/or neck cancer treated with chemotherapy and/or radiotherapy, the relative risk of developing OM was significantly reduced after LLLT (for dose 1–6 unit(s)/spot). There was also a significant reduction in pain and the severity and duration of severe OM (>grade 2) and, more importantly, without any adverse effects (compared to the placebo).

It is worth paying attention to the triple-blind, randomised studies conducted by Gautan et al. [24]. In 221 oncological patients treated with conventional radiotherapy (66 Gy, 33 fractions, 5 fractions/week, 45 days) and cisplatin (every 3 weeks), who were randomly divided into two groups: study (n = 111; LLLT) and control (n = 110; placebo). As a result of the LLLT (He-Ne, wavelength: 632.8 nm, 24 mW, 3 units/spot, 36–40 units/treatment, spot size: 1 cm^2, 5 treatments/week) a significant reduction in the incidence of OM ($p < 0.0001$), associated pain ($p < 0.0001$), dysphagia ($p < 0.0001$) and the need to use opioids ($p < 0.0001$)) by patients, compared to the control group.

In a 2012 study involving 15 children who were patients of an oncology department in Glasgow, LLLT was used to treat inflammatory lesions within MM [25]. The recommendations of Bensadoun et al. were followed [26] regarding the method of treating OM (wavelength: 633–685 nm, 780–830 nm, 10–150 mW). The results of the study were so satisfactory in terms of pain relief and reduction in inflammation that it was decided to conduct another study on a larger group of 39 patients (average age 4–17 years). A total of 319 LLLT treatments were performed, the doses depended on the severity of OM according to the WHO scale (scale 0–4, where 0 meant no changes; 1 – moderate pain, redness, no ulceration; 2 – redness, ulceration, ability to swallow solid food; 3 – severe ulcers, redness, inability to swallow solid food; 4 – inability to eat any food). There was a statistically significant change in the WHO classification ($p < 0.0005$). However, there was no correlation between the number of neutrophils and the response to pain reduction after LLLT ($p = 0.263$), or even the level of pain and the type of tumour ($p = 0.121$) [25].

Similarly, in their pilot study, Cauwels and Martens [27] proved that the use of LLLT influences pain relief and the ability to heal aphthous ulcers, ulcers and the inflammation of MM caused by the chemotherapy. The study involved 16 children with chemotherapy-induced OM (mean age 9.4 years) from the University Hospital of Ghent (Belgium) – Department of Paediatric Oncology/Haematology. During the clinical trials, a degree of OM was assessed using the WHO classification. All children were treated with a GaAlAs diode laser with a wavelength of 830 nm and a power of 150 mW. The energy released was adjusted to the severity of the OM lesions (the worse they were, the more LLLT energy was applied). The same protocol was repeated every 48 hours until each lesion healed. Immediately after the LLLT procedure, pain relief was noted, while complete recovery of the OM took an average of 7 days. Additionally, the researchers came to the conclusion that there is a need to develop a new WHO classification for OM. We are of a similar opinion, since the mere fact of the presence of an MM ulcer (or its absence) and the possibility (or lack of possibility) to eat food (divided into solid and liquid) do not fully describe the deterioration of the quality of life of patients with OM. That is why we suggest using more complex scales, e.g., our Oral Cavity Pain Scale, which allows the assessment of pain in 10 areas, including: at rest and while speaking, avoiding certain foods, the necessity to limit professional and social activities and irritation due to pain (cf. Table 1).

Summary

LLLT appears to be one of the most common forms of physiotherapy, which is used in many fields of medicine.

Availability, non-invasiveness, low operating costs, and high treatment effectiveness encourage researchers to look for new applications of LLLT in modern medicine. Additionally, the use of this form of treatment in patients suffering from OM may successfully replace pharmacological treatment. Importantly, LLLT affects the MM of the oral cavity at the cellular level, having a regenerating and nourishing effect. According to numerous sources, the use of LLLT effectively reduces inflammation and swelling as well as alleviating/eliminating the accompanying pain and discomfort. The results of the presented treatment, although case-specific, seem promising and encourage us to further explore the possibility of using LLLT in MM lesions of the oral cavity.

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REVIEW ARTICLE

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN PATIENTS TREATED WITH INTRAVITREAL INJECTIONS - DAILY PRACTICE OR AD HOC ACTIVITIES?

Niesteroidowe leki przeciwzapalne u chorych leczonych iniekcjami doszklistkowymi – codzienna praktyka czy doraźne działania?

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Abstract:

Intravitreal drug injections are one of the most common ophthalmic surgical procedures in everyday clinical practice. Drugs that block vascular endothelial growth factors are administered intravitreally. Intravitreal injections are performed under local drip anaesthesia, but not all patients are provided with sufficient analgesia. Therefore, ophthalmologists select other analgesic drugs, such as non-steroidal anti-inflammatory drugs. In addition, inflammation is a common component in the pathogenesis of several macular diseases treated with intravitreal injections, such as exudative age-related macular degeneration.

The article presents the mechanism of action of non-steroidal anti-inflammatory drugs and ophthalmological indications for their use. The effect of this group of drugs on the reduction in pain associated with intravitreal injections has been described. The beneficial effect is presented of a combination therapy with topical non-steroidal anti-inflammatory drugs on the frequency of administration of drugs blocking vascular endothelial growth factors and retinal morphology in patients with exudative age-related macular degeneration.

Non-steroidal anti-inflammatory drugs should be considered as an adjunct therapy to intravitreal injections of growth factor blocking agents. In addition, the analgesic effect of non-steroidal anti-inflammatory drugs justifies their use in everyday clinical practice in the peri-injection period, especially in patients experiencing increased pain in connection with repetitive procedures.

Streszczenie:

Iniekcje leków do ciała szklistego są jednymi z najczęstszych zabiegowych procedur okulistycznych w codziennej praktyce klinicznej. Do ciała szklistego podaje się przede wszystkim leki blokujące czynniki wzrostu śródbłonka naczyń. Iniekcje doszklistkowe wykonuje się w znieczuleniu miejscowym kroplowym, ale nie wszystkim chorym zapewnia ono wystarczającą analgezję. Dlatego okuliści sięgają po inne leki o działaniu przeciwbólowym, takie jak niesteroidowe leki przeciwzapalne. Dodatkowo zapalenie stanowi wspólny element patogenezy szeregu chorób plamki leczonych iniekcjami doszklistkowymi, np. wysiękowe zwyrodnienie plamki związane z wiekiem.

W artykule przedstawiono mechanizm działania niesteroidowych leków przeciwzapalnych oraz wskazania okulistyczne do ich zastosowania. Opisano wpływ tej grupy leków na zmniejszenie dolegliwości bólowych, które towarzysząc iniekcjom doszklistkowym. Przedstawiono korzystny wpływ terapii złożonej z miejscowymi niesteroidowymi lekami przeciwzapalnymi na częstotliwość podań leków blokujących czynniki wzrostu śródbłonka naczyń i morfologię siatkówki u chorych na wysiękowe zwyrodnienie plamki związane z wiekiem.

Wnioski. Należy rozważyć niesteroidowe leki przeciwzapalne jako terapię uzupełniającą do doszklistkowych iniekcji preparatów o działaniu blokującym czynniki wzrostu. Ponadto działanie przeciwbólowe niesteroidowych leków przeciwzapalnych uzasadnia ich użycie w codziennej praktyce klinicznej w okresie okołoiniekcyjnym, zwłaszcza u osób odczuwających nasilone dolegliwości bólowe w związku z powtarzalnymi zabiegami.

Keywords: intravitreal injections, non-steroidal anti-inflammatory drugs, wet age-related macular degeneration, anti-VEGF drugs.

Słowa kluczowe: iniekcje doszklistkowe, niesteroidowe leki przeciwzapalne, wysiękowe zwyrodnienie plamki związane z wiekiem, leki anty-VEGF.

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Introduction

Intravitreal drug injections are currently one of the most common ophthalmological procedures in everyday outpatient clinical practice. First of all the drugs administered into the vitreous cavity are ones that block vascular endothelial growth factors (VEGF). Anti-VEGF injections are used in the long-term treatment of retinal diseases, such as wet age-related macular degeneration (wAMD), diabetic macular oedema (DME), and macular oedema complicating central retinal vein thrombosis [1].

Intravitreal injections (IVI) are invasive procedures associated with varying degrees of discomfort or pain [2, 3]. IVI is typically performed under local anaesthesia with drops containing proximetacaine, proparacaine or tetracaine, but it does not provide sufficient pain relief for all patients [4, 5]. Less frequently, other forms of anaesthesia are used before IVI, such as subconjunctival or periocular injections of xylocaine, anaesthetic lotions, or gels. They reduce pain, yet the extent of pain relief is different depending on the method used [6, 7]. Anaesthesia other than using anaesthetic eye drops, may be associated with side effects, such as conjunctival oedema, haemorrhage after administration of the drug underneath the conjunctiva or the corneal epithelial lesions after lidocaine gel. Therefore, ophthalmologists use other painkillers, such as non-steroidal anti-inflammatory drugs (NSAIDs). Inflammation is a common element in the pathogenesis of several macular diseases, such as wAMD. Therefore, additional potential benefits from the use of NSAIDs can be expected in patients treated with intravitreal injections.

The paper reviews the available and current literature on the multidirectional effects of topically administered NSAIDs in patients undergoing chronic IVI therapy, primarily due to wAMD. When selecting the analysed literature, we mainly took into account items providing data on the impact of NSAIDs on the course of IVI treatment and the accompanying pain sensations.

Mechanism of the action of NSAIDs and ophthalmological indications

The mechanism of action of NSAIDs is related to the inhibition of cyclooxygenase (COX) responsible for the production of prostaglandins and thromboxane etc. There are two types of cyclooxygenases: COX-1 and COX- 2. COX-1 is present constantly in tissues, and the proteins produced by it are responsible for the protection of the gastrointestinal mucosa and regulation of the function of the platelets. COX-2, in turn, occurs in inflamed tissues. It is responsible for the formation of prostaglandins, which are inflammatory mediators. Prostaglandins cause local tissue pain and swelling, and an increase in vascular permeability. They sensitize the nerve endings and stimulate bradykinin release, which causes pain in experimental animal models [8-12]. NSAIDs can inhibit both types of cyclooxygenases or selectively only one of them. NSAIDs stabilize cell membranes and inhibit the transformation of arachidonic acid into prostaglandins, stimulated by cyclooxygenases.

Animal studies have clearly demonstrated that NSAIDs repress the development of choroidal neovascularization (CNV) or limit its size and activity. Based on an experimental animal model, Kim et al. demonstrated that ketorolac solution administered topically or intravitreally reduces the CNV leakage visible on angiography and the concentration of prostaglandins and VEGF in the retina [13, 14]. In mice lacking COX-2, the activity of CNV resulting from laser exposure was clearly lower, which can be explained by the lower concentration of VEGF in the retina [15]. Other authors independently presented similar observational results after topical or oral use of NSAIDs [16, 17].

One of the best-known NSAIDs administered into the conjunctival sac in ophthalmic drops is diclofenac sodium, which is a strong inhibitor of prostaglandin synthesis [18]. It is a derivative of aminophenylacetic acid. Its mechanism of action involves inhibiting the activity of COX-1 and COX-2 as well as the activity of phospholipase A2, lipoxygenase, the thromboxane-promoted aggregative effect, the prostaglandin E2 (PGE2) and the interleukin-6 (IL-6) pro-inflammatory effect. It has strong anti-inflammatory and analgesic effects. According to the Summary of Product Characteristics, diclofenac sodium in the form of drops (1 mg/ml) is recommended for inhibiting pupil constriction during cataract surgery, preventing inflammation during cataract and anterior segment surgery, and for combating ocular pain after refractive surgery [19, 20]. In accordance with the Summary of Product Characteristics, other topically administered NSAIDs may also be recommended in the treatment of subacute, chronic, non-infectious inflammation of the eyelids and conjunctiva [21]. Oral NSAIDs (most often sustained-release tablets) can also be used in ophthalmological conditions accompanied by pain or inflammatory reaction [22]. Clinical studies indicate that diclofenac drops effectively reduce pain after refractive surgery [23, 24] or after retinal photocoagulation [25], just as they alleviate pain after surgery in the posterior segment of the eyeball [26]. Additionally, administration of one oral dose of diclofenac before panretinal retinal photocoagulation is

effective in alleviating the pain associated with the procedure [27].

Bioavailability of NSAIDs administered topically into the conjunctival sac.

Several studies have measured intraocular concentrations of NSAIDs after topical application in humans. After a single administration into the conjunctival sac, the highest concentration of the following drugs in the aqueous humour was as follows: 0.1% diclofenac solution (82 ng/ml, peak concentration after 2.4 hours), 0.03% flurbiprofen solution (60 ng/ml, peak concentration after 2.0 hours), 0.1% nepafenac solution (205.3 ng/ml, peak concentration after 30 mins), amfenac (70.1 ng/ml), 0.09% bromfenac solution (25.9 ng/ml), 0.4% ketorolac solution (57.5 ng / ml, peak concentration after 60 mins) [28, 29]. Ketorolac inhibited primarily COX-1, while amfenac inhibited COX-2. Researchers demonstrated significantly greater bioavailability of napafenac.

More frequent and continuous administration of the drug further increases its concentration in the aqueous humour. It was found that the use of 12 doses of an 0.4% ketorolac solution and an 0.1% nepafenac solution for two days caused a concentration of 1079 ng/ml in the aqueous humour for 0.4% ketorolac and 353.4 ng/ml for amfenac, which is a metabolite of 0.1% nepafenac [30]. It significantly exceeds the reported values of the inhibitory concentration 50 (IC50) of COX-1 and COX-2 isoenzymes for both NSAIDs: ketorolac (COX-1 5.3–7.5 ng/ml, COX-2 33.9–45.2 ng /ml) and amfenac (COX-1 35.6–63.6 ng/ml, COX-2 0.51–38.1 ng/ml).

Unlike information on drug concentrations in the aqueous humour, there are few reports on NSAID concentrations in the vitreous humour after topical administration to humans. One published study measures the concentrations in the vitreous humour of the following drugs used for 3 days before vitrectomy: 0.4% ketorolac (administered 4 times a day), 0.09% bromfenac (administered 2 times a day) or 0.1% nepafenac (administered 3 times a day) [31]. The vitreous concentrations of these drugs were 2.8, 0.96 and 2.0 ng/ml, respectively, but a significant reduction in vitreous PGE2 concentration was observed only after the administration of ketorolac.

It appears that the NSAID concentrations achieved in the aqueous humour and vitreous humour directly influence the production of prostaglandins in the anterior segment of the eye (ciliary body and iris) and the posterior segment of the eye (retina and choroid).

Analgesic effect of NSAIDs and intravitreal injections

Ophthalmic drops containing various NSAIDs are used to aid local anaesthesia during IVI. 0.1% ketorolac, 0.9% bromfenac administered in drops before IVI, as well as 0.1% napafenac administered after IVI, reduce the pain sensations accompanying the procedure [32-34].

Popovic et al. analysed the effect of various topically administered NSAIDs on pain after intravitreal injections [35]. For this purpose, they conducted a meta-analysis of randomised controlled trials (RCTs). The analysis of the literature from the medical MEDLINE, EMBASE and Cochrane databases included only RCTs in which patients were administered topical NSAIDs and assessed pain after IVI. The literature was divided according to the time of pain assessment: one hour or less after IVI, 6 hours after IVI, 24 hours after IVI or more. Pain was assessed on a 10-point scale. The analysis also took into account the time of NSAID administration- before or after the intravitreal injection. Finally, out of 241 observations, 9 RCTs were selected with a total group of 598 eyes. After topical administration of NSAIDs, a significantly lower average pain sensation was found compared to the control group in all time periods. A greater analgesic effect was observed in patients who received topical NSAIDs into the conjunctival sac before injection compared to those administered after IVI. The limitations of the study included differences in pain sensation depending on age, gender, the number of previous intravitreal injections, and the methodology of the injection procedure. Additionally, a meta-analysis showed that napafenac administered topically before IVI reduces pain significantly more than ketorolac and diclofenac. Research on the impact of topical NSAIDs on pain sensations associated with IVI must certainly be continued and expanded, with attention to the unification of research groups and methodologies.

In turn, Makri et al. assessed the analgesic effect of diclofenac in patients treated with IVI [36]. It was a single-centre, prospective, randomized study conducted at the Hospital of Patras. It involved 74 patients. They were divided into groups:

- group 1: 25 patients: 0.1% diclofenac sodium was administered topically 45 minutes before the injection,
- group 2: 25 patients: 4 hours before IVI, a 75 mg diclofenac tablet was administered orally + 45 minutes before IVI 0.1% diclofenac sodium was administered into the conjunctival sac,
- group 3: 24 patients: placebo, not receiving NSAIDs before IVI.

The short-form McGill Pain Questionnaire (SF-MPQ) was used to assess pain intensity. Pain was assessed immediately after the injection and 6 hours later. Immediately after the injection, patients in group 2 reported significantly lower pain sensations compared to the placebo group. There were no significant differences in pain sensation between the group that received topical diclofenac and the placebo. Six hours after IVI, patients in both diclofenac-treated groups reported significantly less pain compared to the placebo group. Researchers have proven that combining topical and oral administration of

diclofenac produces a better analgesic effect than only local drops, both immediately after IVI and a few hours later.

The pharmacokinetics of dicofenac sodium drops have not been extensively studied in human eyes. Based on the Summary of Product Characteristics of diclofenac sodium drops maximum drug concentrations in the rabbits' cornea and conjunctiva were achieved approximately 30 minutes after drug administration. Drug elimination is rapid and almost complete after 6 hours, with the already mentioned maximum concentration in the anterior chamber after approximately 2 hours [29]. In the above-mentioned study, a drop of diclofenac sodium solution was administered into the conjunctival sac 45 minutes before IVI, while a sustained-release tablet of diclofenac 75 mg was administered orally 4 hours before IVI. The peak concentration of diclofenac in serum occurs 4 hours after taking the drug in this oral form, and significant drug concentrations persist for approximately 16 hours. Thanks to such a complex procedure, the analgesic effect of diclofenac sodium can be achieved in the time of IVI, which complements the local analgesic effect of this NSAID.

Anti-inflammatory properties of NSAIDs and anti-VEGF therapy

Important elements of the pathogenesis of wAMD (inflammation and age-related activation of the complement system) justify the use of topical NSAIDs [37]. Li et al. performed a systematic review of clinical trials, comparing the effectiveness of combination therapy versus anti-VEGF monotherapy in wAMD [38]. Data from the selected studies were subjected to meta-analysis. In total, the research material consisted of 278 patients, including: 62% treated with ranibizumab, 19% treated with aflibercept, and 19% treated with bevacizumab; 63% receiving topical bromfenac, and the others received ketorolac. Various anti-VEGF therapy regimens with or without a saturation phase were adopted. The follow-up period was 6–12 months. Researchers have shown that NSAID combination therapy can reduce the number of necessary anti-VEGF injections and significantly reduce the thickness of the central retina, which results from the reduction of fluid spaces. Researchers did not demonstrate significant functional differences depending on the use of NSAIDs. Patients receiving bromfenac required significantly fewer anti-VEGF injections. The mechanisms of action of bromfenac and ketorolac are different. Bromfenac is potently selective for COX-2, ketorolac for COX-1, and these differences may result in therapeutic implications [39]. Further studies are certainly needed to confirm the effect of bromfenac on reducing the number of anti-VEGF injections and functional parameters. Wyględowska-Promieńska et al. found significantly better functional effects for combined therapy of wAMD: aflibercept injections and topically administered bromfenac compared to aflibercept monotherapy [40].

In turn, Someraro et al. checked how the ketorolac drops influence the effects of wAMD therapy [41]. Some researchers have conducted a prospective, randomised pilot study in a group of 75 new wAMD patients. Randomisation was 1:1:1: monotherapy with intravitreal injections of ranibizumab, injections of ranibizumab + ketorolac, ranibizumab injections + photodynamic therapy with verteporfin. In the combined therapy subgroups, significantly fewer injections were administered over a 12-month period than in the subgroup treated with ranibizumab monotherapy. In the subgroup treated with ranibizumab and 0.45% ketorolac (3 times daily), better functional and morphological effects were observed (significant reduction in central retinal thickness). Visual acuity changed accordingly at month 12: -0.14 ± 0.52 logMAR (20/73 ± 20/29) for ranibizumab, -0.25 ± 0.60 logMAR (20/46 ± 20/27) for ranibizumab and ketorolac, -0.10 ± 0.30 (20/97 ± 20/40) logMAR for ranibizumab and photodynamic therapy. The average thickness of the central retina was reduced accordingly by 125 ± 15 µm for ranibizumab, 141 ± 21 µm for ranibizumab and ketorolac, and by 130 ± 15 µm for ranibizumab and photodynamic therapy. The researchers conclude that combined therapy for wAMD, including the use of NSAIDs, provides better results in patients with active macular neovascularization.

Potential ocular surface problems in patients treated with intravitreal injections.

Li et al. described undesirable effects in patients treated with IVI [38]. The most common were foreign body sensation, stinging, itching, eye pain, headache, conjunctivitis, dry eye, floaters in the field of vision, and hypersensitivity to light. Of these, only foreign body sensation was significantly more common in patients receiving topical NSAIDs. Verrecchia et al. investigated the effect of repetitive IVI on ocular surface condition. It was a prospective study conducted at three centres [42]. Patients received IVI in one eye. An appropriate concentration of povidone-iodine solution was used to disinfect the conjunctival sac and the ocular adnexa during each IVI. The primary endpoint of the study was the demonstration of differences between ocular surface condition (using the Ocular Surface Disease Index) before injection and one day after IVI. The secondary endpoint was the evaluation of factors predictive of ocular surface disorders and pain on the day after IVI, as well as a comparative assessment of the tear film of the eye undergoing IVI with that of the companion eye. The study involved 219 patients, at an average age of 75.9 ± 10 years. There was a significantly shorter time of non-invasive tear film disruption in the treated eye compared to the other eye, which correlated with the pain and the number of glaucoma drops used (in patients treated for glaucoma). The researchers conclude that in patients treated with IVI, the initial tear film should be improved, the time of exposure to povidone should be shortened as much as possible, and local treatment of other diseases should be modified. It is also important to remember the influence of such preservatives as

benzalkonium chloride on the destabilization of the tear film, the viability of corneal epithelial cells, and the loss of goblet cells [43-44]. Considering ocular surface problems, NSAIDs in the form of preservative-free drops should be considered in the group of patients treated with IVI to avoid exacerbation of symptoms and worsening of the local condition.

Summary

Currently, there are no recommendations from ophthalmological societies for periinjection topical antibiotic therapy, administering steroids or NSAIDs. Similarly, there is no clear position of practising ophthalmologists on the use of NSAIDs in this group of patients. However, the wAMD pathogenesis gives grounds for treatment with topical NSAIDs. Additionally, the analgesic effect of NSAIDs justifies their use in everyday clinical practice in the periinjection period, especially for individuals who experience severe pain due to repeated procedures.

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REVIEW ARTICLE

GUIDELINES FOR PREVENTING COVID-19 IN THE SCHOOL ENVIRONMENT

Wytyczne dotyczące zapobiegania COVID-19 w środowisku szkolnym

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Abstract: The ongoing COVID-19 pandemic has hit the paediatric population in many ways. By disturbing or preventing in-person education in schools, students are often deprived of a supportive learning environment. In many cases, remote learning leads to a decreased level of education quality. The reduction of peer contacts negatively impacts the psychological and emotional development of young people, which has been confirmed by many researchers. In order to effectively limit the transmission of the SARS-CoV-2 virus as well as other common viral infections in the school environment, appropriate preventive measures should be implemented. Maintaining the principles of physical distance, correct wearing of masks, adequate ventilation of closed spaces and hand hygiene are simple but effective tools in our fight against the COVID-19 pandemic. Moreover, thanks to the recent decision of the European Medicines Agency (EMA), children over 6 months old are given the opportunity to receive the most effective protection against COVID-19 in the form of a vaccination using Comirnaty (Pfizer-BioNTech) or Spikevax (Moderna), both based on revolutionary mRNA technology. These recommendations are based on peer-reviewed scientific articles concerning COVID-19 in the paediatric population and the guidance from the Centres for Disease Control and Prevention (CDC). The presented guidelines should be widely implemented in schools so as to minimize the risk of COVID-19 outbreaks in the school environment, and thus safely maintain in-person education, which is the most appropriate and beneficial for school-age children.

Streszczenie: Pandemia COVID-19 (ang. *Coronavirus Disease 2019*) na wiele sposobów dotknęła populację pediatryczną. Poprzez utrudnienie lub uniemożliwienie nauki w placówkach edukacyjnych w trybie stacjonarnym uczniowie często byli pozbawieni wspierającego środowiska szkoły. Nauka zdalna w wielu przypadkach może skutkować spadkiem jakości edukacji, a ograniczenie kontaktów rówieśniczych niekorzystnie wpływa na rozwój psychologiczno-emocjonalny najmłodszych. Celem skutecznego ograniczenia transmisji wirusa SARS-CoV-2 w środowisku szkolnym należy wdrożyć odpowiednie strategie zabezpieczające. Zachowanie zasad dystansu fizycznego, noszenie maseczek, wietrzenie pomieszczeń oraz higiena rąk są prostymi, ale skutecznymi narzędziami w walce z pandemią, a także innymi infekcjami występującymi w okresie jesienno-zimowym. Zgodnie z ostatnimi decyzjami Europejskiej Agencji Medycznej (ang. *European Medicines Agency*, EMA) dzieci powyżej 6. miesiąca życia otrzymały możliwość uzyskania najskuteczniejszej dostępnej ochrony przed COVID-19 pod postacią szczepienia szczepionkami Comirnaty (Pfizer-BioNTech) i Spikevax (Moderna) opartymi na nowoczesnej technologii mRNA. Obecne wytyczne powstały w oparciu o zweryfikowane artykuły naukowe dotyczące COVID-19 w populacji pediatrycznej oraz zalecenia Amerykańskiego Centrum Kontroli i Zapobiegania Chorobom (ang. *Centers for Disease Control and Prevention*, CDC). Przedstawione zalecenia powinny być szeroko wdrożone w placówkach edukacyjnych celem minimalizacji ryzyka powstawania ognisk COVID-19 w szkołach i tym samym bezpiecznego utrzymania edukacji w formie stacjonarnej, która jest najbardziej wartościowa i korzystna dla dzieci w wieku szkolnym.

Keywords: COVID-19, children, school, Comirnaty, Spikevax.

Słowa kluczowe: COVID-19, dzieci, szkoła, Comirnaty, Spikevax.

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Introduction

Approximately 8% to 18% of all cases of severe acute respiratory syndrome connected with coronavirus 2 (SARS-CoV-2) infections are reported among children under the age of 18 years [1, 2]. Despite a relatively mild course of COVID-19 in this age group, there have also been severe cases and other cases requiring hospitalisation. Children may also be a source of infection for groups at increased risk of severe disease, i.e., elderly people and pregnant women. Therefore, emphasis should be placed on implementing preventive measures that can protect the paediatric population from infection and the spread of SARS-CoV-2.

COVID-19 prevention in children primarily involves preventive activities in their everyday environment. Schools are one of the basic elements ensuring the proper functioning of this group of society. Apart from creating a safe and supportive learning environment for children, they perform many other, equally important functions, such as providing access to basic psychological and pedagogical care or facilitating contacts in their peer groups. This is crucial for the optimal emotional growth of the developmental age population [3–5]. Educational institutions are also places of employment, and by providing care for children, they enable their parents to work [6]. Although there have been outbreaks of SARS-CoV-2 virus infections in schools, many studies indicate that the level of transmission in the school environment, in conditions involving appropriate protective measures, is lower or the same as in the general population [7–9]. In the face of constantly emerging coronavirus variants and their high infectivity, the implementation of adequate security strategies is crucial for maintaining the continuity of the stationary functioning of educational facilities. Schools should cooperate with local epidemiological institutions, the District Sanitary and Epidemiological Stations (PSSEs), in order to determine the appropriate level of implementation of preventive measures against the spread of the SARS-CoV-2 virus, depending on such factors as the level of local transmission or vaccination rate against Coronavirus Disease 2019 not only among students, but also among the employees of educational facilities. US Centers for Disease Control and Prevention (CDC) and European Centre for Disease Prevention and Control (ECDC) have recommended vaccinations against COVID-19 in the paediatric population and believe that special emphasis should be placed on the promotion of vaccinations among students, siblings, and their parents [10].

Methods

The article was prepared on the basis of a review of the literature contained in the PubMed database regarding SARS-CoV-2 virus infections in children, with particular emphasis on the updated CDC guidelines on the prevention of COVID-19 in the school environment [11]. Additionally, the authors analysed the Summary of Product Characteristics of the Comirnaty and Spikevax vaccines intended for children over 6 months old and the Nuvaxovid vaccine for children over 12 years old [12–14]. On their basis, guidelines for primary and secondary schools have been presented, illustrating solutions aimed at reducing the risk of SARS-CoV-2 infection among students, teachers, and other employees of the educational facilities.

Recommendations

There is no single, effective method that can guarantee full protection against the SARS-CoV-2 infection. The best effects can only be achieved by implementing multiple preventive strategies [11]. The presented solutions should be adapted to the intellectual capabilities of the children and the actual conditions of the educational institution. We recommend implementation of the presented guidelines to the maximum possible extent.

Promoting vaccination against COVID-19

A key strategy in preventing the spread of the SARS-CoV-2 virus in both school and general populations is vaccination against COVID-19. Students, teachers, other school staff and their family members are recommended to undergo the complete process of vaccination. Vaccines should be authorised in the European Union (EU), and their administration in specific age groups should be in accordance with the provisions of the Summary of Product Characteristics (Table 1). Currently, three vaccines for school children are available on the Polish market, including two based on the mRNA technology with modified nucleosides in the lipid nanoparticles: Comirnaty from Pfizer-BioNTech and Spikevax from Moderna, and one vaccine based on protein technology, Nuvaxovid from Novovax. After analysing the studies, the European Medicines Agency (EMA) concluded that the benefits of using vaccines clearly outweigh the risks, especially in the case of diseases that increase the risk of severe COVID-19 [10].

Table 1. Vaccines against COVID-19 intended for the paediatric population, authorised in the European Union.

Proper name	Manufacturer	Type of vaccine	Dose (strength)	Date of conditional authorisation in the EU
Children aged from 6 months to 4 years				
Comirnaty	Pfizer/BioNTech	mRNA	0.2 ml (3 µg)	19 October 2022
Spikevax	Moderna	mRNA	0.25 ml (25 µg)	19 October 2022
Children aged 5–11 years				
Comirnaty	Pfizer/BioNTech	mRNA	0.2 ml (10 µg)	30 November 2021
Spikevax	Moderna	mRNA	0.5ml (50µg)	24 February 2022
Children aged 12–18 years				
Comirnaty	Pfizer/BioNTech	mRNA	0.3 ml (30 µg)	21 December 2020
Spikevax	Moderna	mRNA	0.5 ml (100 µg)	06 January 2021
Nuvaxovid	Novovax	protein-based	0.5 ml (5 mcg)	20 December 2021

The analysis of the Comirnaty vaccine presented by the manufacturer indicates that the vaccine has been 90.7% (95% CI: 67.7–98.3%) effective in preventing symptomatic COVID-19 in children aged 5–11 years, where the dose (10 µg) is lower than that used in people aged 12 years and older (30 µg). Very similar data has been presented by Moderna. According to them, Spikevax protects against symptomatic COVID-19 by 88.0% (95% CI: 70.0–95.8%) cases, taking into account children between 6 and 11 years of age. [15] The effectiveness of the Nuvaxovid vaccine is 79.5% (95% CI: 46.8–92.1%) in the population between 12 and 17 years of age [14].

mRNA vaccines use modified genetic material of the virus to prompt human muscle cells to produce the spike protein (S protein), which stimulates the immune system to produce antibodies (humoral response) directed against the S protein present on the surface of the SARS-CoV-2 virus, which is crucial for binding and penetrating the cells of the human body. Additionally, this reaction stimulates the formation of immune cells involved in the cellular response (T lymphocytes). Thanks to the two mechanisms mentioned above, COVID-19 vaccines provide protection against the development of SARS-CoV-2 virus infection [16–19]. In the case of the Nuvaxovid vaccine, purified, recombinant S protein of the SARS-CoV-2 virus is injected. To increase immunogenicity, the vaccine additionally contains a saponin-based Matrix-M adjuvant, which facilitates activation of the immune system cells, which increases the extent of the immune response specific to protein S. The vaccine components stimulate immune mechanisms dependent on B and T lymphocytes against protein S, including the production of neutralising antibodies, which contributes to protection against COVID-19 [19].
Vaccines do not contain coronavirus particles; therefore they cannot cause COVID-19 disease, and hence cannot give positive results from antigen or molecular tests based on the polymerase chain reaction (PCR) in vaccinated individuals. A positive test for SARS-CoV-2 after vaccination indicates a current infection [16–19].

mRNA vaccines are well tolerated, and the most common side effects are mild, e.g., flu-like symptoms, pain at the injection site, or nausea and vomiting. Very rarely, myocarditis is observed after administration of mRNA vaccines [20]. This disease mainly afflicts teenage boys and young men aged 12 to 30. Therefore, during vaccination, the vaccinated patient and/or their parents should be informed about possible symptoms related to this disorder. The risk of myocarditis in the course of COVID-19 is up to 6 times higher than after administration of an mRNA vaccine [21, 22]. The only permanent contraindication to vaccination is an allergy to the active substance or another ingredient of the product (mainly polyethylene glycol) and a current acute infection with fever [16, 17]. Children aged 5 to 11 years, like older age groups, are recommended to receive a two-dose course of the COVID-19 vaccination. The second dose should be administered at least 3 (Comirnaty) or 4 (Spikevax) weeks after the first one. In the case of those individuals with impaired immunity, the third (booster) dose should be administered at least 28 days after the second dose. Post-vaccination immunity develops within 1 to 2 weeks. The most common side effects observed in children aged 5–11 years were similar to those observed in older adults, and include: fatigue, muscle pain, chills, redness and swelling at the injection site. These are transient ailments [16]. It should be remembered that even people fully vaccinated against COVID-19 may become infected with the SARS-CoV-2 virus (breakthrough infections), but in a huge percentage of cases they are asymptomatic or oligosymptomatic.

Schools should imperatively promote vaccinations among employees and students by providing reliable scientific knowledge regarding vaccinations against COVID-19. Vaccination should be promoted in an understandable way adapted to the intellectual capabilities of the recipients and should also include the students' parents, because they have a deciding voice [11]. It would be ideal if vaccinations at schools were administered by a nurse/physician. The schools are recommended to prepare surveys for parents informing them about COVID-19 in children, possible complications, currently available vaccines, and the benefits of vaccination. Each parent should receive information about the vaccination program carried out at school by a physician/nurse. The parent should inform in writing about the refusal to vaccinate their child or any contraindications. After collecting information on the number of vaccinated children, the appropriate number of vaccines should be ordered, and parents should be informed (e.g. by text message) about the vaccination date. Administration of the COVID-19 vaccine can be combined with other vaccines, which is especially important in the autumn and winter, when the flu vaccine can be administered at the same time.

Using protective masks

Correct and continuous use of protective masks reduces the risk of infection with the SARS-CoV-2 virus [23]. This is especially important in closed rooms where an appropriate physical distance cannot be maintained. Masks should be worn by children over 2 years of age (over 4 years of age in Poland) and adults on school premises, excluding open areas, regardless of vaccination status [11, 24]. People with disabilities which prevent proper mask use do not have to wear them. Surgical masks or FFP 2/3 filtering masks should be used. Covering the nose and mouth with cotton masks, face shields, scarves or other items of clothing covering is not recommended. If a student has forgotten a protective mask or when, for financial reasons, they cannot afford to buy one, the school should provide access to the masks. The correct technique of wearing the mask is also very important: it should fit tightly to the face and cover the nose and mouth (Fig. 1) [26]. A correct way of putting on and taking off the masks is also important; teachers and students should receive appropriate instruction under the

supervision of experienced specialists in the proper use of personal protective equipment [25].

Figure 2. Respiratory hygiene.

Maintaining physical distance

Learning in the stationary mode brings much more benefits compared to the remote mode, so everything should be done to ensure that education is provided in this way. CDC recommends maintaining a minimum distance of 1.8 meters between unvaccinated students and/or teachers in the classroom. If students and teachers also use other preventive strategies, such as wearing a mask, this distance can be limited to approximately 1 meter. This is probably very difficult or even impossible, so it is worth remembering that maintaining distance between vaccinated students and/or teachers is not necessary. Additionally, it is recommended to cohort students by limiting contacts between students from different classes (e.g., having breaks at different times). This is aimed at reducing the number of social contacts and thus limiting the possible transmission of SARS-CoV-2 infection. This strategy is particularly important in the population of younger children, where the practice of wearing masks may be difficult or practically impossible to implement [11, 27, 28]. Stigmatizing children and school staff by wearing badges saying "I am vaccinated against COVID-19" is debatable.

Airing of the rooms

Appropriate ventilation of the rooms where students and/or teachers stay can effectively reduce the number of SARS-CoV-2 virus particles circulating in the air. Combined with other protective methods, it reduces the risk of infection for students and school staff. It is recommended to tilt or open doors and windows during breaks and, if possible, also during lessons. Adequate air circulation can be further increased by using portable fans or air conditioning systems [11].

Respiratory hygiene and hand hygiene

Students and school employees should follow the general rules of hand and respiratory hygiene. Hands should be washed frequently with soap and running water for at least 20 seconds. Teachers should teach younger children the appropriate hand washing technique and supervise its progress. If this procedure is impossible, it is recommended to use disinfectants with a minimum of 60% ethyl alcohol content. In children under 6 years of age, concentrated ethanol substances should be used under strict supervision due to the possible risk of irritation of mucous membranes and eyes if these substances are used incorrectly. It is equally important to teach children proper respiratory hygiene: covering their mouths when sneezing, coughing, yawning and an appropriate nasal cleansing technique (Fig. 2) [11, 29].

Figure1 . Use of protective masks

Staying at home in the case of infection symptoms

SARS-CoV-2 virus infection usually does not cause characteristic symptoms. Students, teachers, and other employees of educational facilities are advised to stay at home if they experience any cold or other symptoms, even mild ones, which may suggest infection with the SARS-CoV-2 virus (loss of smell or taste, digestive system symptoms). This recommendation applies to everyone, regardless of their vaccination status. Staying at home prevents further, rapid spread of COVID-19, especially among populations with a low vaccination rate (children under 5 years of age). Individuals with the above-mentioned symptoms should see a GP for health assessment, treatment, and testing for SARS-CoV-2. Currently, in Poland, test cassettes are available free of charge in primary care centres to confirm infection with the SARS-CoV-2 virus, influenza A and B or RSV [30]. Educational programs for parents should be conducted, emphasizing how important it is for a child to stay at home if they have symptoms of infection. If a child shows signs of infection at school, they should be isolated from the rest of the students by being sent to a previously prepared

isolation room. Parents should be informed about the child's condition and asked to collect the child from the educational facility as soon as possible [11].

Epidemiological investigation

School employees should closely cooperate with the Sanitary and Epidemiological Station in conducting a reliable epidemiological investigation aimed at establishing a list of close contacts of a person with confirmed COVID-19 in order to correctly determine the group of people at risk of infection with the SARS-CoV-2 virus. Parents of exposed students should pay special attention to the development of possible symptoms of infection in their children, and if they appear, make the child stay at home. Currently, isolation in the event of COVID-19 detection is only a recommendation, but not an obligation. The Sanitary and Epidemiological Station is informed about a positive test result, but the patient is no longer subject to mandatory isolation or quarantine for other household members.

Screening tests

Widespread screening enables detection of SARS-CoV-2 virus infection at an early stage and also identifies asymptomatic or oligosymptomatic infections, which allows for the rapid implementation of measures to prevent further coronavirus transmission. According to the CDC guidelines, testing asymptomatic individuals who are fully vaccinated against COVID-19 is not necessary. Unvaccinated students should be tested when community transmission is moderate or high, while unvaccinated teachers should be tested regardless of the level of local transmission. Testing may be most useful in the areas with significant or high levels of community transmission, low vaccination rates, and in schools where other safety measures are difficult to implement. Antigen or PCR-based tests can be used for screening. Swabs should be taken by qualified medical workers, e.g., a nurse or school hygienist. Schools must obtain consent from parents and/or students themselves to conduct the tests. Screening tests for the SARS-CoV-2 virus should be financed from public funds [11, 31].

Cleaning and disinfection

The SARS-CoV-2 virus is very rarely transmitted to humans through contact with an infected surface. Nevertheless, surfaces with which students may come into contact should be regularly cleaned. Desk surfaces, door handles and handrails should be cleaned or disinfected at least once a day, using appropriate products which remove coronavirus particles [11, 32].

Eating meals and the school canteen

School kitchen staff should wear masks throughout the entire process of preparing and serving meals. Students should wear masks while waiting in line for meals. Masks can be removed only after taking a seat at the table, immediately before eating. If possible, physical distancing rules should also be followed within the canteen. Students should be reminded about the rules of hand hygiene and encouraged to wash them before and after meals [11, 29, 33].

Summary

Keeping schools functioning in the full-time mode should be one of the main goals in the fight against the pandemic. When properly implemented, the presented strategies allow for effective minimisation of the risk of SARS-CoV-2 virus infection in the school environment, both for students and teachers. Most of them do not require large financial outlays, but do require proper training of students, staff, and parents. Another important element is the parents' responsible attitude, which should be demonstrated by giving their consent for their child's vaccination against COVID-19 and making the child stay at home in case of symptoms of infection. Only through cooperation between parents, schools, and health care workers, can the negative effects of the COVID-19 pandemic be limited, as it directly or indirectly affects the student population.

The above recommendations are also useful in the event of an increase in the incidence of influenza in the autumn and winter.

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REVIEW ARTICLE

PENICILIN FOR THE WARSAW UPRISING
Penicylina dla powstania warszawskiego

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Abstract:
Introduction and aim
Penicillin was the first antibiotic introduced as a medicine. The process of its isolation, obtaining a stable form, implementation into production and introduction into treatments, which were carried out in Oxford by Howard Florey's team, coincided with the outbreak of World War II. In the first half of 1944, the drug was sent to the front hospitals in larger quantities, including to the 2nd Polish Corps fighting in Italy. In the existing literature, there were indications that after the outbreak of the Warsaw Uprising, penicillin was transferred to the fighting city. The main objective of the article was to answer the question whether the antibiotics were actually flown to the Polish capital on board Allied planes.

Material and methods
The author conducted a query in the London archives: The Polish Underground Movement (1939-1945) Study Trust and The Polish Institute and Sikorski Museum.

Results
A secret message sent from Italy to a commander of the Home Army, General Taduesz Komorowski, containing information that Penicillin was in a package onboard a Liberator aircraft of the Polish 1586th Special Duties Squadron would be flying to Warsaw on the night of 10/11 September 1944. In another document, containing a list of medical material sent to Warsaw between 1st August and 15th September 1944, 4.5 million units of sodium salt and 191,000 units of calcium salt of penicillin were listed. The document contains an annotation that the antibiotic was a gift of the 2nd Polish Corps, and the fact of its transfer to the insurgents should remain a secret from the British authorities.

Conclusions
The collected archival material allows the confirmation that penicillin was among the drugs and medical material transferred to Warsaw. However, it has not been found at this stage of research whether the penicillin reached Warsaw and whether it was used to treat wounded insurgents or civilians. In the face of the tragedy that befell the city's population, the amount of medicine sent was symbolic, and even if the entire declared supply arrived, it would only be enough for a handful of the wounded.

Streszczenie:

Wprowadzenie i cel
Penicylina była pierwszym antybiotykiem, który znalazł się w asortymencie medycyny. Prace nad jej wyizolowaniem, otrzymaniem w trwałej postaci, wdrożeniem do produkcji oraz wprowadzeniem do lecznictwa, które prowadzone były w Oksfordzie przez zespół kierowany przez Howarda Floreya, zbiegły się w czasie z wybuchem II wojny światowej. W większej ilości lek ten trafił na front w pierwszej połowie 1944 r. Otrzymał go również walczący we Włoszech II Korpus Polski. W dotychczasowej literaturze istniały przesłanki wskazujące, że po wybuchu powstania warszawskiego penicylina została przerzucona do walczącego miasta. Podstawowym celem pracy była odpowiedź na pytanie, czy antybiotyki rzeczywiście poleciały do stolicy Polski na pokładach alianckich samolotów. Materiał i metody

Autor przeprowadził kwerendy w londyńskich archiwach:
Studium Polski Podziemnej oraz Instytucie Polskim i Muzeum im. gen. Sikorskiego.

Wyniki
Depesza szyfrowana nadana z Włoch do dowódcy Armii Krajowej gen. Tadeusza Komorowskiego zawierała informację, że w paczce znajdującej się na pokładzie jednego z samolotów należących do polskiej 1586. Eskadry Specjalnego Przeznaczenia, lecącego do Warszawy w nocy z 10 na 11 września 1944 r., znajduje się penicylina dla najciężej rannych. W kolejnym z dokumentów zawierającym listę materiału sanitarnego wysłanego do Warszawy pomiędzy 1 sierpnia a 15 września 1944 r. wymieniono 4,5 mln jednostek oksfordzkich soli sodowej i 191 tys. jednostek oksfordzkich soli wapniowej penicyliny. Dokument zawiera adnotację, że antybiotyk był darem II Korpusu Polskiego, a fakt jego przekazania powstańcom powinien pozostać w tajemnicy przed Brytyjczykami.

Wnioski
Przeprowadzona kwerenda pozwoliła potwierdzić, że w zasobnikach lecących do Warszawy znalazła się penicylina. Niestety wciąż brakuje przekonujących dowodów na użycie antybiotyku podczas powstania. W obliczu tragedii, która spotkała ludność miasta, ilość wysłanego leku była symboliczna i nawet gdyby cały deklarowany zapas doleciał, starczyłby on jedynie dla garstki rannych.

Keywords: penicillin, antibiotics, Warsaw Uprising 1944, air drops, history of medicine.

Słowa kluczowe: penicylina, antybiotyki, powstanie warszawskie 1944, zrzuty, historia medycyny.

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Introduction

Since its discovery, isolation, implementation of mass production and introduction, the first antibiotic, penicillin, has been widely considered to be one of the most significant achievements of 20th century medicine.

Penicillin was included in the medical supplies during World War II. In the first half of 1944, the Western Allies fought heavy battles in Italy. At that time this "miracle" drug came into regular use in military hospitals[1] on the Apennine Peninsula. Initially strictly rationed, it was intended only for the most seriously injured. Very quickly, within a few months, the drug started to be produced so extensively that the indications for its use were significantly expanded, including non-surgical diseases like pneumonia, as well as selected venereal diseases. However, penicillin was still a valuable resource, and its use was controlled.

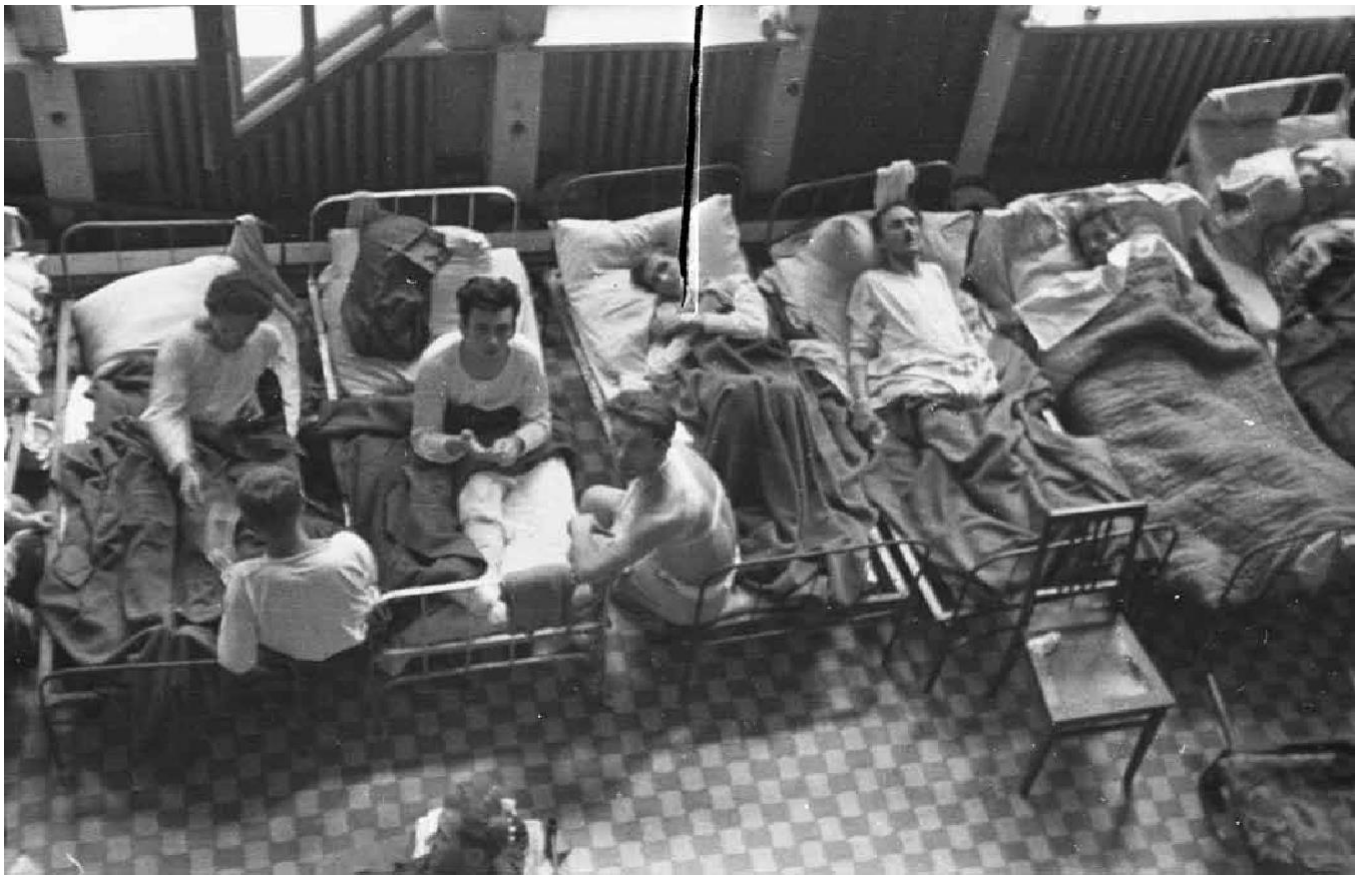
When the uprising broke out in Warsaw on 1 August 1944, the health care service was not prepared for long-term work in isolation. The supplies accumulated in the period preceding the outbreak of the uprising were quickly used up, and the possibilities of obtaining supplies from Warsaw pharmacies and warehouses did not in any way meet the enormous needs. Due to the rapidly growing number of casualties, the insurgent paramedics relied heavily on air supplies (Fig. 1).

The first Allied supply flights to fighting Warsaw were made on the night of 4-5 August. Planes of the Polish Air Force, Royal Air Force (RAF) and the South African Air Force (SAAF) flew to the Polish capital many times. In this way the insurgents received weapons, ammunition, food, as well as supplies of medications, dressings, and surgical instruments. In September, a large formation of American planes appeared over the city and tried to deliver supplies to the insurgents during the daily air drop.

Stanisław Bayer, the head of one of the insurgent hospitals, wrote in the study "Służba zdrowia Warszawy w walce z okupantem 1939-1945 [The medical service of Warsaw in the fight against the occupying forces: 1939-1945]" that the fighting city also received penicillin. "It is a historical fact that the health care staff of the uprising were the first in Poland to receive penicillin and dry plasma. These were minimal amounts, coming from the daily American air drop, and could not in any way really affect the treatment conditions," he wrote [1]. Although laconic and, as it turns out, imprecise, Stanisław Bayer's account was for years the only publicly available evidence indicating the transfer of penicillin to Warsaw. In later years, it was referred to by other participants of the uprising, as well as historians [2–4]. The issue of antibiotic use during the Warsaw Uprising also appeared in the memories of some insurgents, whose accounts are available in the Oral History Archive run by the Warsaw Uprising Museum. Krystyna Bernat, who was a civilian helping in the field hospital at 34 Chmielna Street organised at the Weber Maternity Clinic, recalls: "I joined in [help – author's note] and went [to the hospital – author's note]. I came home at night because during that time my mother collected water and cooked it with juices, because people already had juices in August. My milk cans were full of soup, and I carried it all to the hospital. When necessary, the field nurse, that's how she was called at that time, I think she's called the ward nurse now, directed me. I held the tray and washed the sick. Of course, no injuries, because you had to have some [training]. But it was hard. As long as Weber had penicillin injections and medications, it was not that bad, later it was very difficult. They performed the operations without anaesthesia because it was no longer possible. It was very difficult..." [5].

[1] The term "war hospital" was used with its popular meaning equivalent to the term "military hospital". It should be emphasized that the structure of the British military health service included General Hospitals, which in the Polish military terminology was translated as war hospitals.

Figure 1. Injured people in the corridor of an improvised hospital.

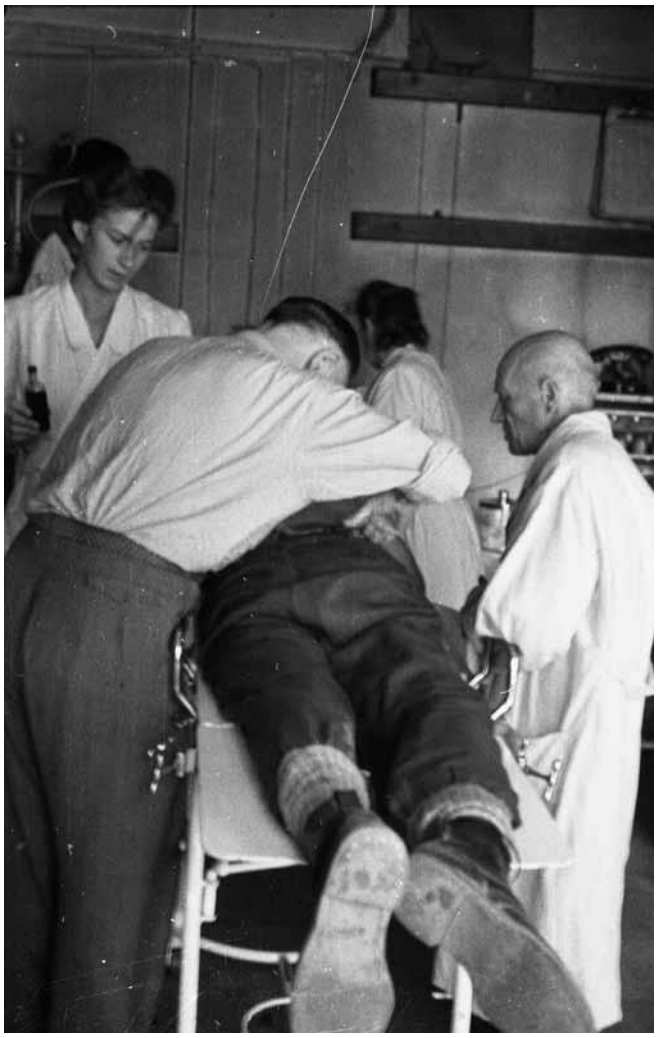


The huge number of casualties exceeded the capabilities of the insurgent health service. In the face of the sanitary crisis, medics counted heavily on the air drops. The photograph shows the injured lying in the corridor of an improvised hospital organised in the building of the Powszechny Bank Zwiazkowy at 11 Zgoda St. The photo was taken by Marian Grabski alias "Wyrwa". Source: Licensed by the Warsaw Uprising Museum, ref. MPW-IN/1769.

In turn, Tadeusz Ejmont, who was burnt during the fighting, recalls the help given to him at the dressing station as follows: "I managed to reach 11 Poznańska St. There was a dressing station on the ground floor of the dentist's apartment, and they brought those from the hospital from Marszałkowska Street, which was on fire... I ran there and sat down in the dentist's room... and two nurses sat down with me. One was older, sister Felicja, and the other was younger. And they started managing my hands I mean, washing my skin... my nails a bit... they started managing it, but they gave me a morphine injection, I think. I think I was given some antibiotics and morphine... They took the skin off my face, and everything was at once. They powdered it with some dermatol or something yellow" [6]. Another person treated in the insurgent hospital was Kazimierz Piechotka, who recalled years later: "I had a high temperature, but I had all my arms and legs, so I wasn't much of a surgical patient, so they put me in a dark corner and gave me one Cibazol pill or some antibiotic a day. Actually, nothing special happened" [7]. A question must be asked about the reliability of the above accounts. Stanisław Bayer, who was the only physician among the witnesses quoted above, did not specify how he learnt about the use of penicillin during the Warsaw Uprising, nor did he specify whether he personally had the opportunity to use the antibiotics during the fights. Other witnesses, lacking professional knowledge, could have confused the antibiotic penicillin with other antibacterial agents, i.e., sulfonamides. They were basic pharmacological bacterial infection treatment methods at that time. And it was a drug from the sulfonamide group that was most likely administered to Kazimierz Piechotka, who clearly indicated that he had received a tablet (penicillin was administered by injection or applied topically, while Cibazol, i.e., sulfatiazole, was intended for oral administration).

Anna Marek, a historian of medicine conducting studies on the uprising health care service, did not find evidence of the use of penicillin during the Warsaw Uprising in the form of more reliable accounts, medical reports, or other documents. She expressed her doubts in the monograph "Leczenie ran wojennych w powstaniu warszawskim 1 sierpnia – 2 października 1944" [Treatment of war wounds in the Warsaw Uprising 1 August – 2 October 1944 [4]. Anna Marek's research, although extensive, covered mainly national archives, while the references included in the above book includes only two archival groups from the London Underground Polish Study. In turn, Sławomir Łotysz, in his monograph devoted to the post-war penicillin production program in the "democratic" countries: Poland,

Photo 2. Foreign body removal procedure for an injured insurgent.



Wound infections, including those caused by anaerobic bacteria, constitute an important clinical problem in military surgery. During World War II, wounds were generally treated with surgical debridement. This principle is still valid. Sulfonamides were widely used in the prevention and treatment of wound infections in the 1940s. In the case of gas gangrene, serum was administered to patients as an adjunct treatment. Penicillin offered a new quality in the treatment of wound infections. Its use was associated with significantly fewer complications than in the case of sulfonamides, and above all, it was more effective in fighting infections. In 1944, penicillin was a drug widely available only in Allied war hospitals. During the Warsaw Uprising, there was a shortage of everything: access to surgical aid, sulfonamides, and serum. The photo shows the foreign body removal in an injured insurgent. The photo was taken in the building of the Powszechny Bank Zwiazkowy at 11 Zgoda St., to which the Hospital of the Sovereign Order of Malta was evacuated. Its author is Marian Grabski alias "Wyrwa". Source: Licensed by the Warsaw Uprising Museum, ref. MPW-IN/1537.

Czechoslovakia and Yugoslavia, only mentions the transfer of penicillin to the insurgent Warsaw, citing one of the documents from a foreign archive [3]. Both mentioned scientists, quoting Stanisław Bayer, did not decide to verify his words. The document indicating that penicillin was found on board one of the planes flying to Warsaw is quoted in the study entitled "Lotnicze wsparcie Armii Krajowej" [Air support of the Home Army] by Kajetan Bieniecki [8].

The author did not comment on the fact that antibiotics were used during the Warsaw Uprising, most likely not seeing anything extraordinary in it. Therefore, there is no publication in the literature that would analyse the issue of the transfer of penicillin to insurgent Warsaw in more detail and present it in a broader context.

The main aim of the work was to answer the question whether and under what circumstances penicillin was transported to the insurgent Warsaw. The answer to such a question must be sought in Polish archives in England: in the Polish Institute and the Sikorski Museum as well as in the Polish Underground Movement Study. They include lists of sanitary supplies that were sent to Poland during the Warsaw Uprising. The presented article is the result of research conducted in both indicated institutions.

The work did not analyse the complex political situation or the operational and technical details of the supply operations for Warsaw. However, a full understanding of the content of the discovered documents requires presenting a broader medical, political, and operational context. This is the purpose of the first two chapters of the article.

Penicillin in the 2nd Polish Corps

Although it is generally believed that penicillin was discovered by a Scottish researcher, Alexander Fleming, working in London's St. Mary's Hospital, the world owes the drug penicillin to an Oxford group of researchers led by Howard Florey[2]. The work of Florey's team coincided with the outbreak of World War II. Scientists from Oxford developed a method for purifying penicillin and keeping it in a stable saline form. Working initially on animal models and then on humans, they confirmed that the drug was not toxic and, above all, proved effective in clinical trials, when administered systemically rather than only topically. They also introduced a unit for measuring the amount of antibiotic (Oxford unit) and initially determined its chemical structure [3, 9–10].

Penicillin has turned out to be a drug that inhibits the growth of selected bacteria, including streptococci (very effective against *Streptococcus pyogenes* causing soft tissue

[2] While Fleming's observation in 1928 bears the hallmarks of a discovery, the introduction of penicillin into treatment was associated with structured and comprehensive research conducted by a team of scientists from the University of Oxford in the late 1930s and early 1940s. A commemorative plaque in Oxford, funded in 1953 by the *Albert and Mary Lasker Foundation* for the following scientists working on penicillin: E. P. Abraham, E. B. Chain, C. M. Fletcher, H. W. Florey, M. E. Florey, A. D. Gardner, N. G. Heathley, M. A. Jennings, J. Orr-Ewing, A. G. Sanders. In turn, in 1945, the Nobel Prize in Physiology or Medicine was awarded to A. Fleming, H. Florey and B. Chain.

infections etc.), staphylococci, anaerobic *Clostridium* responsible for the development of gas gangrene and tetanus, as well as some gram- negative, including *Neisseria meningitidis* bacteria causing meningitis and *Neisseria gonorrhoeae* causing gonorrhoea [11]. Importantly, it was also active against *Treponema pallidum*, the spirochete that causes syphilis. The drug was much more effective than antibacterial chemotherapeutic agents from the sulfonamide group and associated with a much lower risk of complications.

World War II was continuing, and the research results gave reason to hope that penicillin would actually bring a revolution in medicine and save countless lives. Realizing this, Howard Florey did not agree to patenting penicillin, which could limit its production in other countries [9]. The first major clinical trials on the treatment of complicated war wounds with the antibiotic were carried out in 1943 in North Africa, and later during fighting in Sicily [3, 10].

Before the next attempt to break the Gustav Line, which blocked access to Rome from the south, planned for May 1944, each corps of the British 8th Army was to receive a supply of the drug. The 2nd Polish Corps, which was incorporated into it and fought in the Monte Cassino-San Angelo massif, received a very modest amount at that time: only 2 million Oxford units [12]. The entire supply of penicillin was sent to the Bacteriological and Chemical Field Laboratory, from where it was to be distributed to various health care units. First it was intended for those units operating as logistics support to the front line, i.e., two corps evacuation hospitals and field surgical headquarters. The amount of the drug that the Allies had at their disposal at that time was still small, so the indications for its use had to be very restrictive. In a short letter, probably from mid-May 1944, Polish Corps doctors were informed that "the use of penicillin is permitted only in severe and more than moderate cases. The decision to use penicillin is made by the unit's chief surgeon" [12]. Therapeutic priorities were then established and the indications for antibiotic use were narrowed down to the following cases:

1. prevention and treatment of gas gangrene,
2. head wounds,
3. chest wounds with damage to internal organs,
4. compound fractures of the femur.

The author of the letter, most likely the head of the health service of the 2nd Polish Corps, Col. Marian Dietrich MD, emphasized that "penicillin allocations through normal routes are almost non-existent, it is currently issued for research purposes [and the Corps health service must – author's note] urgently cooperate with this research" [12]. Health care professionals could read more extensive information on penicillin in two newsletters of the Field Bacteriological and Chemical Laboratory prepared by its head, Lt. Col. Władysław Dybowski MD, dated 21 and 25 May 1944 [13–14].

The antibiotic production method developed by Oxford scientists was time-consuming and ineffective, and initially the quantity delivered to advanced health care units in Italy was limited. The drug was new, and its use was subject to reporting and analysis. As the amount of penicillin delivered to the front increased, the indications for its use were gradually expanded [10]. The rapid increase in production was related to the introduction of the American technology of deep fermentation in tanks specially constructed for this purpose and the commencement of production by several large pharmaceutical companies. By the time they landed in France in June 1944, the Allies had accumulated large supplies of penicillin [3]. It should be emphasized, however, that the antibiotic was still considered valuable [10].

On 1 August 1944, i.e., on the day of the outbreak of the Warsaw Uprising, official recommendations regarding the use of penicillin in war conditions were issued [15]. The directives signed by the surgical consultant of the Allied forces in Italy, Brigadier Harold C. Edwards, were sent to the medical services of the 2nd Polish Corps seven days later [16]. It is worth quoting the most important provisions of this document in the context of the possible transfer of antibiotics to Warsaw, which was involved in the uprising. Health care units received penicillin in the form of water-soluble salts: sodium salt, which was mainly intended for systemic use, and calcium salt, which was used for local treatment. The sodium penicillin available on the Italian front came from both British and American sources. British suppliers packaged it in tablets containing 7,500 Oxford units, while American manufacturers released the drug in ampoules, each containing 100,000 Oxford units of the antibiotic in a powder form. After dissolving in water, the antibiotic was administered by intramuscular injections or, less frequently, by intravenous infusions. In turn, penicillin calcium was most often available in the form of a mixture with sulfatiazole or sulfanilamide, as a powder for topical use or for liquid preparation to rinse body cavities and wounds. The document emphasized that factory-made penicillin should be stored in a cool place, preferably in a refrigerator. However, in a ready-to-administer form i.e., after dissolving in water, the drug required unconditional storage in the refrigerator. Otherwise, after a few hours, the antibiotic lost its properties [15]. The instructions clearly indicated that in health care units at the front, the indications for antibiotic therapy were narrow. They were limited to the cases of gas gangrene, massive wounds, penetrating joint wounds, and complex fractures. In hospitals that operated far from the front line, penicillin could have been and should have been used in a much wider range of cases [15]. For the sake of clarity, these recommendations are presented in a table. In the context of this work, one more point of the instructions is important. In fact, Brigadier Edwards obliged the health care units to report cases treated systemically with penicillin, and the lists of patients who received the drug were to be sent each month to *"A" Penicillin Control Team*, which operated with the British 2nd War Hospital [15].

Table. Indications for the use of penicillin in surgery: British recommendations from August 1944.

	Systemic treatment (sodium salt)	Topical treatment (calcium salt)	Topical treatment (sodium salt)
Front units	Gas gangrene. Extensive and multiple wounds if the patient cannot be quickly evacuated to the support area.	Penetrating chest wounds – intrapleural application. Open fractures, penetrating joint wounds, extensive muscle wounds, hand wounds: the drug were administered to the wound only after its debridement and haemostasis, and after immobilising the fracture (joint).	
Base hospitals	Gas gangrene. Extensive and multiple wounds treated with a strategy of delayed primary closure ("open" treatment). It also concerned cases of amputations performed in front units. Extensive hand wounds. Definitive amputation of limbs leaving a drain. Septicaemia caused by pyogenic bacteria. Antibiotics were administered if an infection was suspected without waiting for the culture results. Progressive infections with pyogenic bacteria, including abscesses and severe infections of hand tissues. Meningitis.	Wounds treated with a delayed primary closure, except for cases qualified for systemic antibiotic therapy. Penicillin was administered to the wound at the second stage of treatment, i.e., before wound closure. Penetrating chest wounds – intrapleural application. Joint wounds (in the case of a joint haematoma, penicillin was administered in a form of the intra-articular injection after prior puncture and evacuation of the haematoma); Head wounds: penicillin was administered to the wound before it was closed.	Meningitis: intrathecal administration as an adjunct to systemic treatment. Purulent and gonococcal infections of the eyeball: administration into the conjunctival sac.

Own work based on: IPMS, Służba zdrowia, II Korpus Polski, sygn. A.XV.3/10, Allied Force Headquarters directive on the surgical use of penicillin, document dated 1 August 1944.

Night flights

Until August 1944, several hundred special flights to Poland were made during three operational periods[3]. Initially, these types of mission were carried out mainly by Polish crews from the 138th RAF Squadron, which took off from airfields in England.

In November 1943, the fully Polish 1586 Special Duties Squadron was formed. Not only people, but also weapons, ammunition, explosives, radio stations, money, training materials, as well as medical equipment, dressing materials and medications were transported to Poland. The missions carried the highest risk. The length of the flight itself was a challenge, because the route totalled 3.5 thousand kilometres and passed over areas occupied by the Germans. The crews had to deal with anti-aircraft defence, navigation difficulties, wind, and icing. The flight time was not accidental. An attempt to break through the enemy territory during the day by a single, relatively slow, and poorly armed bomber would inevitably result in it being shot down. So, the night provided cover. However, the night had to be long enough, hence transport operations were planned mainly in the months from autumn to spring [17–20].

Flight routes over Germany or Denmark became increasingly dangerous over time. However, when the Allies captured Sicily and southern Italy, it became possible to fly from bases located in the south part of the Italian Peninsula. Due to the closure of the northern routes at the end of 1943, the Polish squadron was based at the Campo Casale airfield in the area of Brindisi, Italy. The new route to Poland now led over the Adriatic Sea, Yugoslavia, the area of Lake Balaton and the Tatra Mountains. Estimated flight time was 11–12 hours. The British 148th Special Duties Squadron also operated from the same airport. It also made flights across pre-war Poland [17–20].

The 6th (Special) Division of the Commander-in-Chief's Staff was responsible for communication with the country, recruitment and training of soldiers transferred to Poland, and preparation of supplies for the Home Army. This unit cooperated closely with Special Operations Aviation Units and the Polish section of the British Special Operations Executive (SOE). After transfer of the 1586th Special Duties Squadrons to Italy, the 6th Division organised the Main Transfer Base in Latiano, code-named "Jutrzenka", responsible for preparing the equipment being flown to Poland. The communication centre, code-named "Mewa" and located in Mesagne [18-20], was responsible for radio communication with the country.

[3] Trial period: from February 1941 to April 1942; "Intonacja" operational season: from August 1942 to April 1943; "Riposta" operational season: from August 1943 to July 1944

Figure 3. Loading containers and packages onto the Handley Page "Halifax" aircraft of the 148th RAF Special Duties Squadron at Campo Casale airfield.

The squadron's crews made supply flights for the underground armies of: Poland, Yugoslavia, and Italy; this included flights to Warsaw, which was affected by the uprising. The containers held weapons, ammunition, communications equipment, as well as surgical instruments, dressing materials and medications. Source: Licensed by *Imperial War Museum*, ref. CNA 3138.

The outbreak of the uprising in Warsaw was a surprise for the crews of the Polish squadron. However, a decision was made almost immediately to prepare supply flights to the capital. The British authorities opposed this idea, rightly claiming that the flights would not affect the course of the fighting and would be a source of huge losses among the air crews. It should be noted that the British had already made it clear that in the event of an uprising in Warsaw, the Poles could not count on effective air supplies [18–19].

Due to the explicit ban on flights to the capital of Poland issued by the British authorities, the first supply flight was made in secret. On the evening of 4 August 1944, 14 machines took off from Campo Cassale with the official task of making an air drop outside Warsaw. Half of the machines belonged to the Polish squadron; the rest were planes of the British 148th Special Duties Squadron. According to a previously developed plan and with the consent of the crews, three Polish planes changed the flight route and made an air drop in the area of Kercelego Square, Młynarska Street, the Jewish Cemetery, Powązki and Elbląska Street and Tatarska Street. In total, five machines were lost during the mission, including four shot down and one crashed during landing. Four RAF crews did not return to the base. And although these crews did not fly directly to Warsaw, such large losses clearly showed how dangerous the supply flights to Poland had become. The British authorities did not agree for further supply missions. Meanwhile, there were radiographs came from Warsaw requesting weapons, ammunition, and medicines. Ultimately, the British gave in and allowed their crews to officially participate in flights to Poland [18–20].

Allied planes appeared over Warsaw many times. These were not only from the two Special Duties Squadrons mentioned above, though, as the Polish squadron made an great and understandable effort here. The planes of the 31st and 34th South African Air Force Squadron as well as the 178th RAF Bomber Squadron also flew over the Polish capital. The expeditions were extremely difficult. Although several or a dozen machines were sent at a time, the crews did not fly in formation, and each of them had to find the target independently. Celestial navigation and pace counting navigation techniques were relied upon. The threats included technical failures, which occurred not so rarely, weather conditions, including icing, and violent August storms developing in the Carpathian region. On the way, anti-aircraft artillery batteries and night fighters were also waiting for the aircraft. The crews reported that after crossing the Tatra Mountains, the glow over the burning city could be seen on the horizon. Over Warsaw, the

aircraft were greeted by anti-aircraft guns and small arms fire. There were also attacks from the Soviet side. Air drops were made from various heights, often low or very low [18–20].

A departure from this air drop methodology was the American daytime expedition, codenamed "Frantic VII", which took place on 18 September 1944. At the time, over 100 Boeing B-17 "Flying Fortress" heavy strategic bombers from the 8th Air force Army took off from bases in south-eastern England. Air Army, which, flying in compact formations known as "combat boxes", headed for the Polish capital. They were escorted by a strong group of fighter aircraft [18–19]. Nearly 1,300 containers were dropped from an altitude of 5,000 meters. Despite the euphoric reception of the operation by the insurgents, the effectiveness of the drop was low, and only about 20% of the containers ended up in their hands [21]. The formation of American bombers did not return to their bases but landed at Soviet airfields in western Ukraine as planned.

Losses among the crews were enormous, and even the initial enthusiasm of the 1586th Special Duties Squadron, visibly waned, turning into a sense of helplessness and discouragement. The study prepared after the war, devoted to Polish aviation for special duties, contained the following extract: "Flights over Warsaw did not arouse enthusiasm among the crews because they caused a lot of losses and offered no prospect of providing real help. After several attempts, due to Russia's negative attitude, everyone realised that from the aviation point of view that the situation was hopeless. Generally, very little was said about it. Nobody wanted to be misunderstood. Flights were treated as an order, an obligation. Writing a last will after being assigned to fly was a common phenomenon" [22]. Despite such attitudes, the Allied crews showed great courage and professionalism in this unprecedented action. The flying staff were well aware of the risk, yet they conscientiously performed the tasks assigned to them. A total of 147 airmen died during the supply missions over Warsaw and its vicinity, including 59 serving in the Polish Air Force, 39 in the RAF, 37 in the SAAF and 12 in the United States Army Air Forces [19].

"Penicillin in a white package"

Many original coded messages that were sent between Warsaw and Mesagne during the uprising have survived. Nowadays, the documents collected in both of the London archives draw a specific picture of the tragedy of the Polish capital, enclosed in telegrams consisting of several sentences. From the telegram of 29 August 1944, sent by the commander of the Home Army, we can learn what the greatest needs were in terms of medicines and sanitary materials. The list included: anti-tetanus serum, morphine, pantopon, sulfonamides, hexobarbital, vitamin C, transfusion sets, catgut thread, personal dressings, and condensed milk for infants [23].

Between the coded messages we find the first trace of penicillin. On 10 September 1944, the "Mewa" radio station broadcast the following announcement: "Roch to Lawina. Today, 20 planes to the city from high altitude and 1 from normal altitude. Targets Śródmieście and Mokotów, reserve Żoliborz. In two of our Lila directed to Śródmieście in white RMK containers with phosphor strips, two hundred and fifty thousand each rmk. One from a low, the other from a high ceiling. In Lila from a low ceiling, penicillin in a white package for immediate use for the seriously injured. The content of the air drop according to your wishes. I rule out Kampinos" [24]. Indeed, on 10 September 1944, 20 machines left for Poland from bases in southern Italy. Five planes from the 1586th Special Duties Squadron took off from Campo Casale, including three Halifaxes and two Consolidated B-24 Liberators, as well as four Halifaxes from the British 148th Special Duties Squadron. Four Liberators from the British 178th RAF Squadron flew from the base in Amendola, and seven Liberators from the 31st and 34th SAAF Squadron flew from Celone [18, 20].

So, penicillin flew to Warsaw on board one of the Polish Liberators, because this is how the above message should be read. Unfortunately, five machines, including three Polish ones, did not return from this mission. Among the downed planes was a Liberator with the number EW278 and the code letter "U". On the way to Warsaw, it fell victim to a German night fighter over Yugoslavia. The second Polish Liberator also did not reach the capital. Its crew, not recognizing the signals on the ground, made an air drop into the Kampinos Forest [8, 25].

On the evening of 11 September, a telegram was sent from Italy: "Roch to Lawina. 20 took off yesterday. One was made to Śródmieście on the Henryk signal and two to Mokotów. They dropped on Śródmieście without seeing the signals, and two of them dropped on the city through the clouds. All of them were English. Contents – 6 containers in Mokotów, 12 in others. All of them report heavy cloud cover, relatively good visibility of the Mokotów signals, very poor visibility in Śródmieście. Two of them did not find signals in the city, so they dropped their loads on Kampinos – one English and one Polish – from a high altitude, while Lila went missing from a low altitude. The contents of both is 548. Moreover, two Polish and two English ones have not yet returned. Flights cancelled for today – bad met. Tell us what you have received and what you know about the lost people" [26].

There is nothing about antibiotics among the cryptograms confirming the receipt of the dropped supplies. If penicillin was really only on board of one of the Polish Liberators, it did not reach Warsaw that night.

The drop made on the night of 10–11 September 1944 was one of the last ones made by planes taking off from Italy. The last one was a single Liberator from the 1586th Special Duties Squadron, which appeared over Warsaw on the night of 13–14 September. Later, there was only a massive daily air drop made by the Americans on 18 September [20].

In secret

We have managed to find another document proving that penicillin was actually transported to Warsaw. This is a list

Figure 4. Polish pilots from the 1586th Special Duties Squadron photographed at the Campo Casale base with the Consolidated B-24 Liberator aircraft in the background.

On the night of 10–11 September 1944, penicillin was flown to Warsaw on board of one of the Polish Liberators. Source: private collection courtesy of Tomasz Hodyra.

of sanitary material that was sent to the capital between 1 August and 15 September 1944. The list is long. The following resources were transported to the planes: seven large wicker baskets with standardized medical kits (one Field Surgical Pannier No. 1 and Field Surgical Pannier No. 2 and five Regimental Medical Panniers), 11 surgical kits, 14,000. personal dressings, 11,458 bandages, a supply of gauze, cotton wool, plasters, and plaster cast, 9,196 ampoules of morphine, 7,784 ampoules of omnopon, 2,650 ampoules of thiopental, several dozen thousand sulfonamide tablets, 608 bottles of anti-tetanus serum, 2,004 bottles of anti-gas gangrene serum, over 100,000 vitamin tablets, 109 boxes of water disinfectant, 1,171 individual water disinfection packages and nine American-made sets of dried plasma. The last item on this list is penicillin. According to the document, 4.5 million Oxford units of penicillin sodium and a mixture of calcium salt of penicillin with sulfathiazole containing a total of 191,000 Oxford units were sent to Warsaw. There is an annotation at the end: "This last item is a gift from the 2nd Polish Corps and should not be disclosed to the British authorities" [27].

Taking into account the previously described realities, including the limited availability of penicillin at the front, as well as the need to report its use to the Penicillin Control Team, the decision to keep the fact of transferring the antibiotic from military stocks a secret from the British becomes completely understandable. After all, only recently, at the beginning of August 1944, Lt Col. Władysław Dybowski MD reprimanded the doctors of the 2nd Polish Corps: "The wastefulness in the use of drugs applies even to the valuable penicillin, the quantity of which is still very limited. After my appeal for savings, one of the health care units used 3,900,000 or 3,300,000 units from 3/7 to 10/7 [of July – author's note]. Penicillin was administered in the form of an intramuscular injection in single doses of up to 50,000 units [...] penicillin was used in cases unforeseen by orders, without seeking the advice of the head of the laboratory to investigate whether the case was actually infected with penicillin-sensitive microorganisms. (...) I recommend reducing the rate of penicillin consumption, especially sodium, by at least half. The penicillin possessed and received by Polish units is intended only for Poles, if it is necessary to use it for other wounded people temporarily undergoing treatment in Polish units, it must be indicated in the penicillin request from the penicillin issuing unit. (...) The currently released sodium penicillin (and also calcium penicillin, although it is slightly less sensitive to heat) in ampoules must be stored at a temperature no higher than +5 degrees Celsius. Target. (...) Reporting is seriously flawed (...) I would like to point out that the report is also a calculation of the penicillin received and should include the entire amount of penicillin used, not just part of it. Accurate reporting will be

important; further supply will depend on confirmation that this medicine is used appropriately and not wasted" [28]. The need for support of fighting compatriots, the uniqueness of the Warsaw uprising and the atmosphere prevailing among the units of the Polish Armed Forces in the West allow us to understand the motivation for breaking the applicable rules. However, it was not possible to determine whether the antibiotic was given to the Main Transfer Base with the consent of the head of the health care service of the 2nd Polish Corps. There were so many controversies and disputes surrounding supply flights to Warsaw that another one, this time concerning penicillin, was certainly inadvisable. Sending it far beyond the operating area of the 8th British Army, and the 2nd Polish Corps was part of it and was under its direct operational command, could be interpreted as a waste of valuable medicine.

Two questions arise in the context of sending penicillin to Poland. The first one is fundamental: did the medicine reach the insurgents? At the current stage of research, we have neither documents nor reliable reports that could confirm this, so the question remains open. The second question concerns how much penicillin was actually sent; the quantity being measured not by Oxford units but by the number of patients who could be treated with it. To answer such a question, we should again refer to the official recommendations from 1944. The instruction *The Use of Penicillin in Treating War Wounds* developed by the Penicillin Clinical Trials Committee and published in the "*Medical Research Council War Memorandum*" series indicated that in systemic treatment, penicillin sodium should be administered in the intramuscular injection at a dose of 15,000 Oxford units every three hours [11]. The daily dose was therefore 120,000 Oxford units. The minimum duration of therapy was three to five days. One patient therefore required 360,000 up to 600,000 units of antibiotic per course of therapy. Even assuming that all of the 4.5 million Oxford units of penicillin that were sent to Warsaw ended up in the hands of the insurgents, this amount would only be enough for a few, or a dozen wounded people.

"Frantic VII"

As mentioned in the introduction, Stanisław Bayer directs our attention to the Americans and the "Frantic VII" operation. According to the plan, the Flying Fortress aircraft were to take on board a total of 1,320 containers, of which only 12 contained sanitary material. It was not possible to determine what exactly was inside them: the documents show that the lists of medical supplies sent were placed inside each of the containers [29–30]. However, we know that the American expedition did not provide the insurgent health service with antibiotics.

Even before the Frantic VII operation, the organisation of the second daily expedition began. On 16 September, the 6th Division of the Commander-in-Chief's Staff organized a conference on this issue. It was then decided that the medicines and food sent in the next tranche would be intended for the civilian population [31]. On 23 September, the Head of the Special Division of the Commander-in-Chief's Staff, Lt Col. Marian Utnik, sent a letter to the Head of the Health Service of the Ministry of National Defence, in which he raised the issue of sanitary materials and medicines. From this document, we learn that penicillin was not flown to Warsaw on 18 September. Lt Col. Utnik wrote: "*To avoid major errors, I requested the delivery of exactly the same quantities and types of equipment as were sent in the first 60 containers, with the addition of penicillin and cholera and dysentery vaccines, which could not be delivered at that time*" [32]. So, penicillin was officially about to fly to Warsaw. However, the second expedition never took place.

Summary

The air operation of the insurgent Warsaw bore the hallmarks of improvisation, and the flights were extremely difficult and were associated with unacceptably high losses in relation to the effects they brought.

Machines taking off from southern Italy and England between 5 August and 18 September 1944, transferred weapons, ammunition, uniforms, medicines, and dressings to the Polish capital. The conducted query allowed us to confirm that penicillin was also found in the containers flying to Warsaw. However, it has not been found at this stage of research whether the penicillin reached Warsaw and whether it was used to treat wounded insurgents or civilians. In view of the tragedy that struck the city's population, the amount of medicine sent was symbolic at best, and even if the entire declared supply had arrived, it would have been enough for only a handful of the wounded.

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ASSESSMENT OF THE RELATIONSHIP BETWEEN SENSITIZATION TO SPECIFIC ALLERGENS AND THE PRESENCE OF MICTURITION DISORDERS IN CHILDREN

Ocena związku nadwrażliwości na poszczególne alergeny z występowaniem zaburzeń mikcji u dzieci

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Abstract:

The relationship between the exposure to allergens and the presence of voiding disorders in the paediatric population has been observed for many years. The first such observation was documented in the 1930s. It was found that the elimination of an allergen from the patient's environment reduces not only the allergic symptoms in the upper respiratory tract, but also reduces the lower urinary tract symptoms.

The study included 40 children with confirmed sensitization to the IgE-mediated mechanism. Subsequently, the patients were divided into 2 groups: with and without voiding disorders.

Total IgE, specific IgE in the inhalation and gastrointestinal panels were measured in all patients, and skin prick tests were performed.

There was no statistically significant correlation between the total IgE concentration in groups of patients with the allergy and micturition disorders and with the allergy without micturition disorders. There were no differences in the number of allergens for which the increased concentration of specific IgE was obtained between the groups and, both in the inhalation panel ($p = 0.5$) and the gastrointestinal panel ($p = 0.45$), the same result was obtained in the skin prick tests. No significant differences were noted in the number of patients with a positive result for specific IgE concerning particular allergens between the groups. A severe sensitization (class ≥ 3 or class ≥ 5) to any allergen has not been found to predispose children to micturition disorders. In summarizing, the results, there was no relationship between micturition disorders and allergy to individual allergens.

Based on the above data, it was found that the degree of polysensitization does not affect the occurrence of micturition disorders in children.

Streszczenie:

Niejednokrotnie w populacji pediatrycznej obserwowano związek ekspozycji na alergeny z nasileniem zaburzeń w oddawaniu moczu. Pierwsze takie obserwacje udokumentowano w latach 30. XX wieku. Stwierdzono, że wyeliminowanie alergenu ze środowiska pacjenta, ogranicza nie tylko objawy alergiczne ze strony górnych dróg oddechowych, ale także ze strony układu moczowego.

Do badania włączono 40 dzieci z potwierdzoną reakcją nadwrażliwości w mechanizmie IgE zależnym. Następnie dokonano przydziału pacjentów do dwóch grup z zaburzeniami w oddawaniu moczu oraz bez zaburzeń w oddawaniu moczu. U wszystkich pacjentów oznaczano stężenie IgE całkowitych, IgE swoistych w panelu wziewnym i pokarmowym oraz wykonano punktowe testy skórne. Nie stwierdzono istotnej statystycznie różnicy w stężeniu IgE całkowitych pomiędzy grupami pacjentów z atopią i zaburzeniami mikcji oraz bez zaburzeń mikcji.

Nie stwierdzono także różnicy w liczbie alergenów, w kierunku których uzyskano podwyższone stężenie IgE swoistych pomiędzy badanymi grupami pacjentów, zarówno w panelu wziewnym ($p = 0,5$), jak i w pokarmowym ($p = 0,45$), a także w punktowych testach skórnych. Nie zaobserwowano różnicy, porównując liczbę pacjentów, u których uzyskano wynik dodani IgE swoistych w kierunku poszczególnych alergenów w obu grupach. Nie zaobserwowano także istotnych różnic, porównując wyniki IgE w klasie ≥ 3 oraz w klasie ≥ 5 swoistych dla poszczególnych alergenów. Nie zaobserwowano także istotnych różnic, porównując wyniki IgE w klasie ≥ 3 oraz w klasie ≥ 5 swoistych dla poszczególnych alergenów.

Podsumowując wyniki, nie wykazano związku zaburzeń mikcji z alergią na poszczególne alergeny. Na podstawie powyższych danych stwierdzono, iż stopień nasilenia polisensytyzacji nie wpływa na występowanie zaburzeń mikcji u dzieci.

Keywords: micturition disorders, allergy, specific IgE, monosymptomatic nucturnal enuresis.

Słowa kluczowe: zaburzenia mikcji, alergia, IgE swoiste, monosymptomatyczne moczenie nocne.

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Introduction

Allergic diseases are one of the most common reasons why patients consult a paediatrician. Their clinical picture is diverse, as are the severity of the symptoms: from light, even cosmetic skin lesions to severe shortness of breath, which significantly impedes the functioning of the patient and their family. Allergic diseases affect many systems. The mechanisms related to allergic reactions in the lower and upper respiratory tract, skin, conjunctiva, and gastrointestinal tract have been well documented for many years.

Another common reason for paediatric consultations is micturition disorders, which affect children all over the world. For many years, this problem was often downplayed, both by parents and health care professionals, and was suggested that it had a psychological basis. It is now known that micturition disorders can lead to the development of emotional disorders and rarely the other way around. Children and adolescents struggling with this problem have low self-esteem and limited social contacts [1]. There are many different causes of micturition disorders in children. Most often, they are functional. However, it should be remembered that this is a diagnosis by exclusion. Functional micturition disorders can only be diagnosed when there are no alarm symptoms and, in accordance with individual indications, the diagnostics is extended to exclude organic causes of symptoms, such as urinary tract defects or chronic diseases [2].

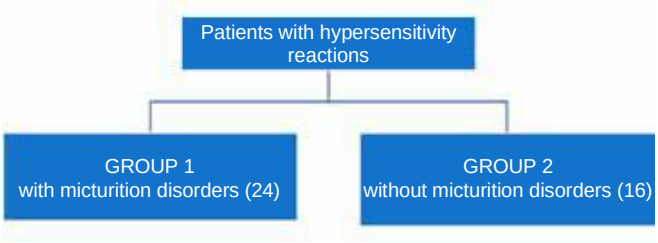
The relationship between exposure to allergens and the severity of micturition disorders has also been frequently observed in a paediatric population. The first such observation was documented in the 1930s. It has been found that eliminating the allergen from the patient's environment reduces not only the symptoms of the upper respiratory, but also the urinary tract [3].

This study aims to assess whether hypersensitivity to specific inhalant and food allergens may cause micturition disorders in children. It also assesses whether the severity of hypersensitivity reactions contributes to the occurrence of micturition disorders.

Material

The study involved 40 children with confirmed IgE-dependent hypersensitivity reactions, who were hospitalised in the Department of Paediatrics, Nephrology and Allergology of the Military Institute of Medicine in 2018–2021. During the eligibility screening for the study, the total and specific IgE concentrations in the serum were determined, and skin prick tests (SPTs) were performed. The study involved patients who had a tendency to atopic dermatitis, defined as an increased total IgE concentration (after excluding other causes of this condition) and/or an increased specific IgE class > I concentration to at least one allergen. The SPT results played a complementary role.

Figure 1. Division into groups of patients eligible for the trial (group sizes are given in brackets).



Groups of patients with hypersensitivity reactions were divided into those with and without micturition disorders (Figure 1). The children were assigned to the above groups on the basis of medical history and a thorough physical examination for the presence and type of micturition disorders. When symptoms of the lower urinary tract were reported, the diagnostics were extended to exclude patients with an organic origin for the symptoms from the study. Additionally, children with parasitic infections or taking antihistamines and glucocorticoids were excluded. The group of children with micturition disorders included patients with various symptoms of the lower urinary tract, such as: monosymptomatic nocturnal enuresis (MNE), daily enuresis, urgency, urinary frequency, and dysuria. The necessary criteria for inclusion in the study was a written consent of legal representatives and young people over 16 years of age.

Methods

The concentration of the total IgE antibodies and specific IgE was determined in the Biochemistry and Protein Laboratory of the Laboratory Diagnostics Department of the Military Institute of Medicine using an enzyme immunoassay. The concentration of specific IgE was determined in the ImmunoCAP 100 analyser, according to the user's manual, using the ImmunoCAP Specific Ig reagent kit. ImmunoCAP calculates all results automatically. Values <0.35 IU/ml were considered negative.

The SPT was each time performed by the same person at the Department of Paediatrics, Nephrology and Allergology of the Military Institute of Medicine. Selected skin prick test solutions from Allegropharma were used. Food allergen extracts (apple, cocoa, orange, banana, peanut, hazelnut, wheat flour, cow milk, egg white, egg yolk, cod, tomato) and airborne extracts (grasses, rye, birch, alder, hazel, artemisia, *Plantago lanceolata*, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, dogs, cats, *Alternaria alternata*, *Cladosporium*). The presence of a wheal response with a diameter of at least 3 mm surrounded by erythema was considered a positive result.

The research results were subjected to statistical analysis. Calculations were performed using the R program, version 3.6.2 with packages. Throughout the analysis, p values < 0.05 were considered as the significance threshold.

Results

Total IgE concentrations were compared in groups of allergic patients with micturition disorders and in allergic patients without co-occurring micturition disorders. There was no statistically significant difference between the total IgE levels in both groups of patients (p = 0.1261). The results are presented in Table 1 and Figure 2.

Figure 2. Total IgE concentration in both groups of allergic patients on a logarithmic scale.

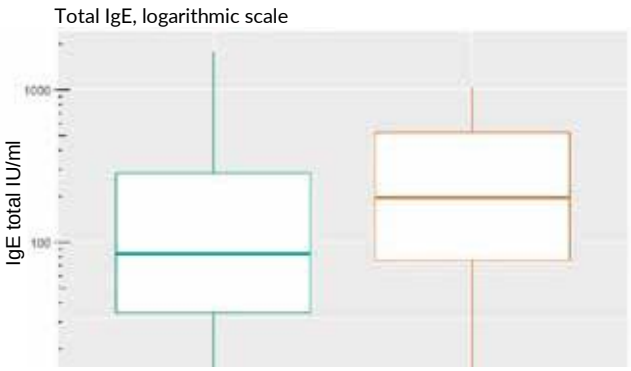


Table 1 Total IgE concentration in groups of patients with allergy and micturition disorders and without micturition disorders.

Parameter	Group 1	Group 2
IgE total median (q25–q75)	84.0 (34.5–284.0)	196.0 (77.5–528.0)

It was also analysed whether any of the allergens particularly often caused hypersensitivity reactions in both study groups. However, there was no statistically significant difference in the number of patients with a positive food and inhalant allergen specific IgE result between patients with and without micturition disorders. The results are presented in Table 2.

Table 2 Comparison of the number of positive results of IgE specific to individual allergens in groups 1 and 2.

INHALATION PANEL	Group 1		Group 2		Test of proportion – result – adjusted p-value
	Number of positive results	Group size	Number of positive results	Group size	
Anthoxanthum odoratum	12	24	8	16	1
Dactylis glomerata	10	24	9	16	1
Timothy (*Phleum pratense*)	12	24	8	16	1
Rye	12	24	7	16	1
Alder	6	24	7	16	1
Birch	7	24	7	16	1
Hazel	6	24	6	16	1
Oak	5	24	4	16	1
Ambrosia artemisiifolia	3	24	3	16	1
Artemisia	3	24	6	16	1
Plantago lanceolata	1	24	5	16	1
Dermatophagoides pteronyssinus	9	24	6	16	1
Dermatophagoides farinae	10	24	7	16	1
Cat	6	24	5	16	1
Dog	0	24	0	16	-
Horse	1	24	0	16	1
Peniclium notatum	0	24	1	16	1
Cladosporium herbarum	0	24	0	16	-
Aspergillus fumgitaus	0	24	1	16	1
Alternaria alternata	4	24	2	16	1

FOOD PANEL	Group 1		Group 2		Test of proportion – result – adjusted p-value
	Number of positive results	Group size	Number of positive results	Group size	
Egg white	1	24	1	16	1
Egg yolk	0	24	1	16	1
Cow milk	3	24	1	16	1
Baker's yeast	0	24	0	16	-
Wheat flour	0	24	2	16	1
Rye flour	1	24	2	16	1
Rice	1	24	3	16	1
Soy	2	24	2	16	1
Peanut	0	24	2	16	1
Hazelnut	3	24	4	16	1
Almond	2	24	4	16	1
Apple	2	24	4	16	1
Kiwi	0	24	0	16	-
Apricot	1	24	3	16	1
Tomato	1	24	3	16	1
Carrot	2	24	4	16	1
Potato	1	24	4	16	1
Celery	1	24	3	16	1
Cod	2	24	0	16	1
Crab	2	24	0	16	1

It was assumed that hypersensitivity to allergens in the upper classes of IGE may contribute to the occurrence of micturition disorders, because, as it is known, only upper class IgE correlate more often with symptoms in patients. However, there was no statistically significant difference in the number of patients with an allergen specific IgE class ≥3 between patients with disorders and without micturition disorders. The results are presented in Table 3.

Table 3 Comparison of the number of results specific in class ≥3 towards particular allergens in groups 1 and 2.

INHALATION PANEL	Group 1		Group 2		Test of proportion – result – adjusted p-value
	Number of positive results in class ≥3	Group size	Number of positive results in class ≥3	Group size	
Anthoxanthum odoratum	9	24	7	16	1
Dactylis glomerata	9	24	7	16	1
Timothy (*Phleum pratense*)	9	24	7	16	1
Rye	7	24	6	16	1
Alder	4	24	5	16	1
Birch	5	24	5	16	1
Hazel	2	24	4	16	1
Oak	3	24	3	16	1
Ambrosia artemisiifolia	1	24	1	16	1
Artemisia	2	24	2	16	1
Plantago lanceolata	0	24	1	16	1
Dermatophagoides pteronyssinus	4	24	3	16	1
Dermatophagoides farinae	6	24	3	16	1
Cat	3	24	3	16	1
Dog	0	24	0	16	-
Horse	0	24	0	16	-
Peniclium notatum	0	24	0	16	-
Cladosporium herbarum	0	24	0	16	-
Aspergillus fumgitaus	0	24	0	16	-
Alternaria alternata	1	24	0	16	1

FOOD PANEL	Group 1		Group 2		Test of proportion – result – adjusted p-value
	Number of positive results in class ≥3	Group size	Number of positive results in class ≥3	Group size	
Egg white	0	24	1	16	1
Egg yolk	0	24	0	16	-
Cow milk	1	24	0	16	1
Baker's yeast	0	24	0	16	-
Wheat flour	0	24	0	16	-
Rye flour	0	24	0	16	-
Rice	0	24	0	16	-
Soy	1	24	0	16	1
Peanut	0	24	0	16	-
Hazelnut	1	24	2	16	1
Almond	0	24	2	16	1
Apple	1	24	3	16	1
Kiwi	0	24	0	16	-
Apricot	0	24	0	16	-
Tomato	0	24	0	16	-
Carrot	0	24	0	16	-
Potato	0	24	2	16	1
Celery	1	24	0	16	1
Cod	0	24	0	16	-
Crab	1	24	0	16	1

A positive result in the allergen specific IgE class ≥ 5 almost always correlates with allergic symptoms in the respiratory tract, skin, or gastrointestinal tract. Therefore, it was assessed whether such an intensified hypersensitivity to any of the surveyed allergens could affect micturition disorders. However, there was no significant difference in the number of patients with an allergen specific IgE class ≥ 5 between patients with and without micturition disorders. The results are presented in table 4.

Table 4 Comparison of the number of results specific in class ≥5 towards particular allergens in groups 1 and 2.

INHALATION PANEL	Group 1		Group 2		Test of proportion – result – adjusted p-value
	Number of positive results in class ≥5	Group size	Number of positive results in class ≥5	Group size	
Anthoxanthum odoratum	0	24	3	16	1
Dactylis glomerata	1	24	3	16	1
Timothy (*Phleum pratense*)	2	24	4	16	1
Rye	0	24	2	16	1
Alder	1	24	1	16	1
Birch	4	24	4	16	1
Hazel	1	24	1	16	1
Oak	0	24	0	16	-
Ambrosia artemisiifolia	0	24	0	16	-
Artemisia	1	24	1	16	1
Plantago lanceolata	0	24	0	16	-
Dermatophagoides pteronyssinus	0	24	0	16	-
Dermatophagoides farinae	0	24	2	16	1
Cat	1	24	1	16	1
Dog	0	24	0	16	-
Horse	0	24	0	16	-
Peniclium notatum	0	24	0	16	-
Cladosporium herbarum	0	24	0	16	-
Aspergillus fumgitaus	0	24	0	16	-
Alternaria alternata	0	24	0	16	-

FOOD PANEL					
Egg white	0	24	0	16	-
Egg yolk	0	24	0	16	-
Cow milk	1	24	0	16	1
Baker's yeast	0	24	0	16	-
Wheat flour	0	24	0	16	-
Rye flour	0	24	0	16	-
Rice	0	24	0	16	-
Soy	0	24	0	16	-
Peanut	0	24	0	16	-
Hazelnut	0	24	0	16	-
Almond	0	24	0	16	-
Apple	0	24	0	16	-
Kiwi	0	24	0	16	-
Apricot	0	24	0	16	-
Tomato	0	24	0	16	-
Carrot	0	24	0	16	-
Potato	0	24	0	16	-
Celery	0	24	0	16	-
Cod	0	24	0	16	-
Crab	1	24	0	16	1

It was assumed that perhaps not the type of allergen, but the hypersensitivity severity (assessed on the basis of IGE classes) may affect the occurrence of urinary system symptoms.

However, there was no statistically significant difference in the number of patients with a positive result in class ≥ 3 to at least one food or inhaled allergen between patients with or without micturition disorders.

There was also no difference in the number of patients with a positive result in class ≥5 to at least 1 food or inhaled allergen in both groups of patients.

The results are presented in Table 5.

An assumption was made that perhaps it was not only the hypersensitivity reaction severity assessed by the IgE classes to a particular allergen that may affect bladder function, but rather polysensitization or a hypersensitivity to multiple allergens.

To evaluate this assumption, a comparison was made in the study groups between the number of allergens with a positive skin prick test, as well as elevated levels of specific IgE in groups of patients with micturition disorders (group 1) and without micturition disorders (group 2).

There was no statistically significant difference between the study groups in the number of food and inhalant SPT positive allergens (Figures 3 and 4) or in the number of IgE-positive allergens in both the inhalant (p = 0.5) and the food panel (p = 0.45). The results are shown in Figures 5 and 6.

Table 5 Comparison of the number of patients in class ≥3 and ≥5 to of at least 1 allergen in groups 1 and 2.

	Group 1	Group 2	Test of proportion – result – adjusted p-value
The number of patients with IgE class ≥3 to at least 1 allergen	14	9	1
The number of patients with IgE class ≥5 to at least 1 allergen	8	7	1
Size of the group	24	16	

Figure 3. The number of SPT positive inhalant allergens in groups of patients with and without micturition disorders.

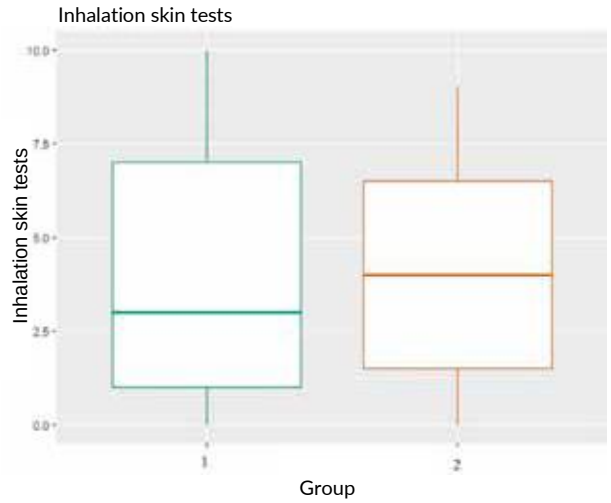


Figure 4. The number of SPT positive food allergens in groups of patients with and without micturition disorders.

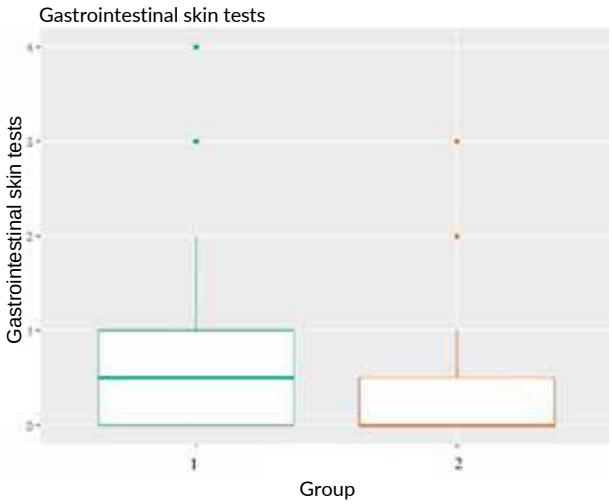


Figure 5. The number of allergens in the inhalation panel with elevated specific IgE levels in groups of patients with and without micturition disorders.

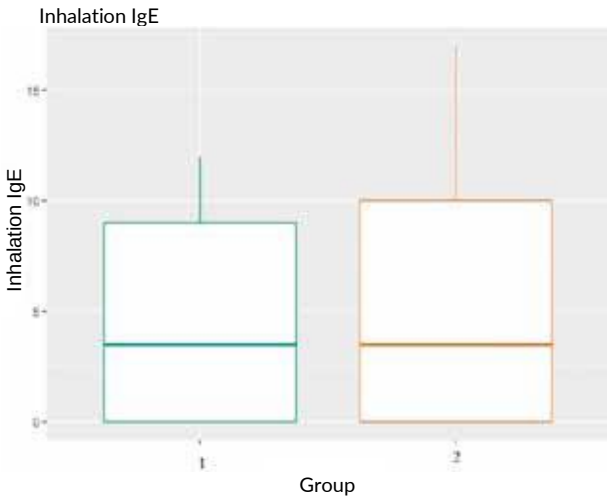
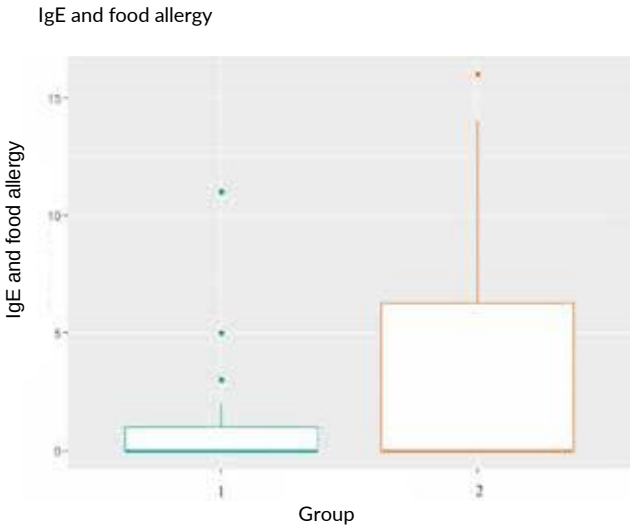


Figure 6. The number of allergens in the gastrointestinal panel with elevated specific IgE levels in groups of patients with and without micturition disorders.



In summarizing the above results, no association was demonstrated for micturition disorders with an allergy to particular allergens. The degree of polysensitization severity did not correlate with the frequency of micturition disorders.

Discussion

Over the past few decades, there has been a significant increase in the incidence of allergic diseases, both in the adult population and in children. In Poland, in the paediatric population, bronchial asthma is diagnosed in 8.5% of children, slightly less often in adults. Allergic rhinitis affects less than 11% of adults and 8.5% of children, atopic dermatitis, respectively, 0.9% of adults and 9.2% of children. The Epidemiology of Allergic Diseases in Poland (EADP-ECAP) provides the latest data. A 2014 analysis found an even higher prevalence of bronchial asthma and allergic rhinitis: 11% and 22%, respectively [4]. Interesting observations were made in Tokyo, Japan, where in a study conducted in 2021 the prevalence of atopic dermatitis, assessed by the presence of specific IgE in the serum of patients tested for inhalant allergens, was estimated at 78% [5].

Analysing the above statistical and epidemiological data, it can easily be observed that allergic diseases are an important problem, both from the patient's perspective and the health care system. One of the theories explaining the increasing number of patients with allergic diseases is the “hygiene hypothesis”. It is based on the decreasing exposure to microorganisms in early childhood in developed countries, which in turn induces some changes in the immune system leading to a tilt in the Th1/Th2 balance toward Th2 [6].

As was already mentioned in the introduction, paediatricians are increasingly often encountering micturition disorders in children. This is due to the fact that that parents and health care professionals start to

understand that at a certain point in a child's development this problem ceases to be physiology and requires in-depth diagnostics and therapy.

There are not many reports available in the literature describing the relationship between micturition disorders and allergic diseases. One of the mechanisms described so far to exacerbate bed-wetting in patients with bronchial asthma or obstructive sleep apnoea is the occurrence of apnoea during sleep [7]. This probably explains the observation that nocturnal micturition disorders more often affect patients with uncontrolled asthma [8].

However, it has been shown that allergic lesions found directly in the bladder mucosa may cause micturation disorders. It has been found that histamine and other mediators of the mast cells cause bladder inflammation and hypersensitivity [9]. An increased number of histamine receptors in the bladder wall has been described in patients with interstitial cystitis, a disease of unclear aetiology, in which one of the postulated pathomechanisms are allergic reactions occurring in the bladder [10]. Other works have shown that certain allergens can reduce the functional capacity of the bladder and cause instability of the detrusor muscle [11–12]. Some studies have found elevated levels of specific IgE in patients with monosymptomatic bed-wetting compared to the controls. Boys with bed-wetting had a higher incidence of allergic rhinitis, urticarial lesions, and food and drug allergies [13–14]. In contrast, paediatric patients diagnosed with bronchial asthma and allergic rhinitis (ANN) are more likely to report bed-wetting [7–8, 15]. Tsai et al. estimated that the frequency of bed-wetting increased with the number of diagnosed allergic diseases, e.g., as mentioned above in the case of co-occurrence of ANN and bronchial asthma [16]. However, the study by Tsai et al. showed no statistically significant difference in serum total IgE levels between the study and control groups. A positive skin prick test result was found in 67% of the patients with bronchial asthma and MNE, compared to 40% of the patients with bronchial asthma but no micturition disorders. This difference was particularly significant for grass, cereals, and tree allergens [8]. Mungan et al. evaluated serum IgE levels in children with bed-wetting and in a group of healthy children. No significant difference was observed in both total IgE and IgE specific to inhalant allergens. However, elevated IgE to soy and hazelnut allergens were found in patients with micturition disorders [17]. There are also publications in which completely different results were obtained. Kaplan et al. and also Siegel et al. showed no differences in the prevalence of food allergy and specific IgE levels in patients with bed-wetting compared to the controls in their study [18-19].

In our work, we also did not observe a significant difference in the concentration of total IgE in atopic dermatitis children with and without micturition disorders. However, it is known that the total IgE levels, within the normal range for a particular age, does not exclude an allergic disease. On the other hand, in a significant proportion of cases of elevated total IgE levels, no allergic symptoms are observed. Therefore, this test is a low-sensitivity and low-specificity parameter for assessing allergic reactions [20].

In the present study, we analysed the severity of hypersensitivity reactions to particular allergens based on the height of specific IgE classes: none of the allergens was shown to predispose to the development of micturition disorders in children.

An attempt was also made to assess polysensitization severity in groups of patients with and without micturition disorders. There was no difference in the number of allergens causing the elevation of specific IgE levels in both groups of patients, either in the inhalation or gastrointestinal panel. A similar result was obtained by analysing a number of positive results for specific allergens in the gastrointestinal and inhalation SPTs.

In conclusion, because of the significant frequency of the co-occurrence of allergic symptoms and micturition disorders, especially in children, we need further in-depth observation of the possible association of these conditions as well as studies on a wider group of patients.

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LEKARZ WOJSKOWY
MILITARY PHYSICIAN

NON-CARDIAC SEQUELAE OF KAWASAKI DISEASE. A SURVEY STUDY OF 90 CASES AND A LITERATURE REVIEW

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Abstract:
Introduction and objective

The best-known long-term complications of Kawasaki Disease (KD) are coronary artery aneurysms. However, there are numerous case reports concerning other unusual chronic complications. These data are only anecdotal, and more systematic observation is lacking. Our aim was to detect and describe the chronic non-cardiac complications of KD.
Material and methods

We surveyed the parents of children with KD diagnosed between 2014 and 2019 by telephone, using a standardized questionnaire. Clinical data about the acute phase of the disease, treatment, outcome, symptoms and signs observed within a three month period since KD diagnosis were recorded from the caregivers. We selected children from 3 children's hospitals in Warsaw, along with a support group on social media.
Results

Ninety children met the inclusion criteria. The parents of 30 children (33%) reported some neurologic sequelae, with persistent irritability being the most common, followed by sleep disturbances, aggression, and chronic fatigue. Seventeen children (19%) suffered either arthralgia or unspecific pain in the upper and lower extremities. In nine children (10%), either atopic or seborrheic dermatitis began shortly after KD. Five children (6%) presented ophthalmic complications.
Conclusions

Various unspecific complications may emerge after the acute phase of KD. Although correlation does not imply causation, and the possible explanations of the observed abnormalities are numerous, our data may enhance the clinicians' awareness of the frequent and poorly understood findings observed in children after KD. It also might help reassure parents that what they observe lies within a range of common and usually transient KD sequelae.

Keywords: immunomodulation, paediatrics, inflammatory disease, extracardiac manifestations.

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Introduction

Kawasaki disease (KD) is a relatively common, acute, febrile, self-limited, systemic vasculitis of unknown aetiology, occurring most commonly in children under 5 years of age [1]. The disease may involve any medium-sized arteries, while any organ or tissue may be affected during the acute, febrile phase. The best-known long-term complications for KD are coronary artery aneurysms (CAAs), which develop in around 4% of children treated with intravenous immunoglobulin (IVIG) [2]. However, there are numerous case reports about other unusual late complications, including arthritis, myositis, facial nerve palsy, and ptosis [3-5]. These data are only anecdotal, and more systematic observation is missing.

We aimed to identify and report any non-cardiac persistent complications of KD.

Material and Methods

Patient's recruitment

In this retrospective cohort study, we surveyed the parents of children diagnosed with KD between 2014 and 2019, using a standardized phone questionnaire. We recruited children from three children's hospitals in Warsaw and one social media support group. All phone calls were made between August and November 2019.

The inclusion criteria were:
1) Age <18 years old at the time of KD diagnosis,
2) Diagnosis of classic or incomplete KD according to the American Heart Association (AHA) guidelines [2],
3) At least three months since diagnosis.

The initial diagnosis was made by clinicians who treated the child in the acute phase of KD, but we verified it based on the clinical data reported by the caregivers and the patient's medical records.

After obtaining an informed consent, we surveyed the child's caregivers with the use of a standardized questionnaire that included multi-choice and open questions. We asked about the signs and symptoms in the acute phase of KD, and any abnormalities observed during the convalescence phase. In case of any sign or symptom, we asked about its characteristics and total duration. The Bioethical Committee of the Medical University of Warsaw approved the study (AKBE/162/2020).

We considered the signs or symptoms to be persistent if they lasted or appeared at a time when the fever had already subsided (convalescence phase). Periungual skin desquamation was not involved in the analysis, being a cardinal and well-known late sign of KD.

Statistical Analyses

We presented the results as counts and percentages for the categorical data, medians and interquartile ranges (IQRs) for continuous data. In addition, we split the children into groups regarding classic vs. incomplete KD and IVIG resistance. Statistical data analyses were performed with the use of Excel 2016. Results with a p-value < 0.05 were considered statistically significant.

Results

We have called the parents of 92 children with KD diagnosis, and 90 met the inclusion criteria. The vast majority, 79 children, were recruited from hospitals, and the rest from a social media group. We summarized the demographic and clinical characteristics of the analysed group in Table 1.

Most of the children were healthy except for the KD. Among patients with comorbidities (present before KD diagnosis), two had atopic dermatitis, one had a food allergy, one had allergic rhinitis, one had hypothyroidism, one had autism, and one had drug-resistant epilepsy with mental retardation. Children were admitted to the hospital after a median of three days (IQR 2-5 days) of fever. All but two patients were treated with IVIG. These two patients presented an anaphylactic reaction to IVIG: one was not treated with immunomodulatory agents afterwards, and the other received infliximab. Among 12 children with IVIG failure, 11 received a second IVIG dose, seven received glucocorticosteroids (GCS), and two received infliximab. Two children had recurrent KD (two episodes each).

The parents of 44 (49%) children recalled any symptoms and signs which were present after fever of the acute phase of KD had subsided. These are summarized in Table 2.

Among the neurologic complications, the most frequently reported was irritability. The parents of four children reported that irritability had never resolved, whereas, in the remaining group, irritability lasted for a median of four weeks (IQR 4-18 weeks). In case of sleep disturbances, the caregivers of five children reported it never resolved (one of them was surveyed four months after the disease onset).

Table 1. Demographic and clinical characteristics of children with Kawasaki disease.

Characteristic	All subjects N = 90	Typical KD N = 73	Atypical KD N = 17	IVIG-responsive N = 76	IVIG-resistant N = 12
Age [years]	2.8 (1.4; 4.3)	2.8 (1.4; 4.5)	2.8 (0.7; 4.2)	3 (1.4; 4.6)	2.2 (1.2; 2.9)
Male gender	49 (54%)	40 (55%)	9 (53%)	40 (53%)	9 (75%)
Comorbidities	7 (8%)	6 (8%)	1 (6%)	5 (7%)	2 (17%)
IVIG timing	6 (3; 8)	6 (5; 7.3)	8.5 (6; 10)	6 (3; 8)	6.5 (5; 7.5)
IVIG resistance	12 (13%)	9 (12%)	3 (18%)	0	12 (100%)
GCS treatment	21 (23%)	16 (22%)	5 (29%)	12 (16%)	7 (58%)
Infliximab	3 (3%)	1 (1%)	2 (12%)	0	2 (17%)
Coronary arteries abnormalities in the acute phase	20 (22%)	15 (21%)	5 (29%)	15 (20%)	5 (42%)
Persistent coronary arteries abnormalities	7 (8%)	3 (4%)	4 (24%)	4 (5%)	3 (25%)

KD = Kawasaki disease, IVIG = intravenous immunoglobulin, GCS = glucocorticosteroids; results are presented as counts and percentages for categorical data and medians and interquartile ranges (IQRs) for continuous data.

Table 2. Symptoms and signs observed in children after Kawasaki disease.

Symptoms and signs	All N=90	Typical KD N = 73	Atypical KD N=17	IVIG-responsive N = 76	IVIG-resistant N = 12
Any neurologic issue	30 (33%)	25 (34%)	5 (29%)	25 (33%)	4 (33%)
Irritability	16 (18%)	13 (18%)	3 (18%)	14 (18%)	1 (8%)
Sleep disturbances	12 (13%)	9 (12%)	3 (18%)	10 (13%)	1 (8%)
Aggression	10 (11%)	10 (14%)	0	8 (11%)	1 (8%)
Chronic fatigue	10 (11%)	8 (11%)	2 (12%)	9 (12%)	1 (8%)
Anxiety	8 (9%)	7 (10%)	1 (6%)	7 (9%)	1 (8%)
Concentration deficit	7 (8%)	7 (10%)	0	6 (8%)	0
Learning difficulties	3 (3%)	3 (4%)	0	3 (4%)	0
Headaches	2 (2%)	2 (3%)	0	2 (3%)	0
Finger numbness	1 (1%)	1 (1%)	0	1 (1%)	0
Hearing impairment	1 (1%)	0	1 (6%)	1 (1%)	0
Psycho-motor delay	2 (2%)	2 (3%)	0	2 (3%)	0
Any limb pain	17 (19%)	13 (18%)	3 (18%)	12 (16%)	4 (33%)
Arthralgia	9 (10%)	9 (12%)	0	6 (8%)	2 (17%)
Joint swelling	4 (4%)	4 (5%)	0	3 (4%)	0
Limping	4 (4%)	3 (4%)	1 (6%)	3 (4%)	1 (8%)
Muscle pain	4 (4%)	3 (4%)	1 (6%)	4 (5%)	0
Any cutaneous	13 (14%)	11 (15%)	2 (12%)	12 (16%)	1 (8%)
Atopic/seborrheic dermatitis	9 (10%)	8 (11%)	1 (6%)	9 (12%)	0
Albinism	1 (1%)	1 (1%)	0	0	1 (8%)
Insect bite allergy	1 (1%)	0	1 (6%)	1 (1%)	0
Any gastrointestinal	9 (10%)	7 (10%)	2 (12%)	8 (11%)	0
Loss of appetite	5 (6%)	4 (5%)	1 (6%)	5 (7%)	0
Abdominal pain	5 (6%)	4 (5%)	1 (6%)	5 (7%)	0
Diarrhoea	4 (4%)	3 (4%)	1 (6%)	4 (5%)	0
Constipation	2 (2%)	1	1 (6%)	1 (1%)	0
Celiac disease	1 (1%)	1 (1%)	0	0	0
Any ophthalmic issue	5 (6%)	5 (7%)	0	4 (5%)	0
Photophobia	4 (4%)	4 (5%)	0	4 (5%)	0
Ptosis	1 (1%)	0	1 (6%)	0	0
Other					
Chest pain	2 (2%)	2 (3%)	0	2 (3%)	0
Growth retardation	2 (2%)	2 (3%)	0	2 (3%)	0
Thyroid gland involvement	2 (2%)	2 (3%)	0	2 (3%)	0
IgA vasculitis	1 (1%)	1 (1%)	0	1 (1%)	0

KD = Kawasaki disease, IVIG = intravenous immunoglobulin; results are presented as counts and percentages.

The remaining children's median duration of sleep disturbances was 16 weeks (IQR 8-22 weeks). The parents of four children acknowledged that they persisted in being more aggressive since the KD diagnosis – in all those cases, over one year had passed since then. In the remaining group, aggression lasted for a median of four weeks (IQR 4-12 weeks). Chronic fatigue had never resolved in two children, and in the remaining group lasted for a median of 24 weeks (IQR 20-24 weeks). In one boy with recurrent KD, autism symptoms and epilepsy developed after the first episode, worsening after the second episode. Family history was positive for epilepsy in this case. Moreover, two infant boys diagnosed with KD, at the age of five and seven months regressed in neurologic development (loss of head control in one and loss of sitting and crawling in the other), but both recovered within 2-3 months. In one 1.5-year-old girl, parents reported poor motor coordination for eight weeks after KD. Altogether parents of six children (7%) reported that some neurologic complications persisted.

About 19% of all children suffered from limb pain. Among children whose parents reported arthralgia, in one case it referred to the wrist, in one the hip, while the rest had painful knees or ankles. Knee and ankle involvement was symmetrical in all cases. The parents noticed a limited range of motion in two children with swollen and painful joints. Since the KD diagnosis, two girls had had recurrent arthralgia, concomitant with infections. In the remaining children, limb pain lasted for a median of eight weeks (IQR 4-24 weeks).

Complications affecting the skin developed in 14% of the patients. In the majority, atopic dermatitis had been diagnosed. The parents usually reported symptoms of the itchy, dry, rough skin in the remaining group. The parents

observed exacerbation following KD diagnosis in two boys formerly diagnosed with atopic dermatitis. Among patients with new-onset atopic dermatitis, in two cases it persisted, while in the remaining group it lasted for a median of 24 weeks (IQR 24-24 weeks). In two children, the caregivers recalled hair problems – loss of hair in one and weak, breakable hair in the other.

The parents of nine children after KD diagnosis recalled gastrointestinal complications. Among five children with abdominal pain, four continued to have recurrent stomach-ache episodes, and in one, it resolved after about 12 weeks. Poor appetite never resolved in one patient, and in the remaining children, it lasted for four to 24 weeks. In two children, the parents declared that diarrhoea never resolved. In two others, it had been recurring for six months and three years, respectively. In two children, constipation lasted for four and 12 weeks, respectively. One girl was diagnosed with celiac disease at the time of KD diagnosis, with no symptoms or signs suggestive of celiac disease in her personal or family history. Among all children with any gastrointestinal signs and symptoms, one had transient growth retardation, and the rest had no complications in terms of somatic development.

Five children (6%) presented with ophthalmic complications. Two children had photophobia and eye fatigue for 16 weeks and one year, respectively. In one girl, ptosis developed after KD treatment and resolved spontaneously after eight weeks.

The parents of two children reported that they had had chest pain and fatigue, presenting an effort ever since KD diagnosis. Neither of them had any cardiovascular complications. The parents of two girls (1.6 and 5.1 years old) recalled that they had had growth retardation since KD diagnosis, one for approx. 6 months and the other for approx. 12 months. The first one was treated with pulsed methylprednisolone for three days in the acute phase of KD. The other one did not receive GCS but presented chronic episodes of diarrhoea and abdominal pain.

Two children developed thyroid-related complications. One developed symptomatic hypothyroidism with significant weight gain and high thyroid-stimulating hormone levels. The other one developed anti-thyroid peroxidase antibodies, which were negative before KD. One girl developed typical purpura of IgA vasculitis on the 10th day of KD (after IVIG administration and fever resolution), with concomitant arthralgia and positive occult blood in stool sample – the girl received GCS, and symptoms resolved within one week.

Discussion

We present systematic and comprehensive observations concerning late symptoms and signs following KD in children observed by their caregivers. Half of the parents reported some late sequelae in their children, with neurologic disturbances and limb pain being the most prevalent.

Neurologic symptoms and signs

Neurologic sequelae were the most frequently reported in our group. There are several papers concerning neurologic complications of KD in the literature, although the conclusions are inconsistent. Children after KD presented a number of neurodevelopmental disorders more frequently than found in the general population, including epilepsy, intellectual disability, autism spectrum disorders, Tourette syndrome, and attention deficit hyperactivity disorder [6]. In addition, some degree of hearing loss was observed in up to 36% of patients after KD [7]. Facial nerve palsy, not noted in our cohort, is another neurologic complication reported in the case series [5,8].

On the other hand, some symptoms and signs within this category (e.g., behavioural abnormalities, sleep disturbances) could be explained by stress due to prolonged hospitalization and invasive medical procedures. However, Carlton-Conway et al. found that KD patients had more common behavioural complications than children hospitalized for other diseases [9]. Interestingly, Baker et al. analysed children's physical and psychosocial well-being after KD using the Child Health Questionnaire. They found that children with prior KD and without giant CAA did not differ in general health from other children in the population. However, their parents expressed lower general health perceptions than parents in the United States population sample [10]. This observation may reflect the influence of acute severe disease in a child on long-term parental perceptions. Thus it is difficult to determine which of the neurologic sequelae reported by parents are objective complications of the disease and medical procedures, and which are subjective parental concerns.

Limb and chest pain

Limb pain was the second most common symptom observed by parents in their children after KD. Limb pain can be due to both arthritis and myositis, which are difficult to differentiate, as most children in our group were too young to describe their complaints precisely. Arthritis is a well-known complication of KD, reduced from 30% to 2-7.5% after the introduction of IVIG into treatment [3]. The case series have also reported myositis complicating KD [4]. The self-limiting character of limb pain in both our cohort and the literature data is reassuring.

Skin problems

Most children with skin issues after KD presented with atopic dermatitis. This observation is consistent with a paper by Brosius et al., who found atopic dermatitis to be more prevalent in children with KD than in healthy controls [11]. Psoriasiform eruptions have also been reported to flare after the acute phase of KD [12]. We have not found any literature about hair problems, albinism, or insect-bite allergy in patients after KD.

Gastrointestinal complications

Gastrointestinal complications reported by parents of children with KD are challenging to interpret. Multiple medications administered to those patients, including antibiotics, typically induce some gastrointestinal sequelae. Moreover, diarrhoea, constipation, and abdominal pain are frequent and unspecific symptoms in young children. Thus, chronic symptoms in this category should be interpreted with caution. The lack of persistent influence of abdominal issues on children's somatic development in our cohort is reassuring. On the other hand, Italian authors revealed a higher prevalence of celiac disease (5.5%) in children after KD [13]. Thus, monitoring for celiac disease in children after KD, mainly when gastrointestinal symptoms persist, should be considered.

Ophthalmic complications

There are a few case reports of ophthalmic complications of KD, including retinitis, uveitis, and keratitis [8,14,15]. In one case report, photophobia and blurred vision developed three weeks after KD and was diagnosed as crystalline-like keratopathy and interpreted as a complication of IVIG administration [16]. Ptosis after KD may be a part of facial nerve palsy presentation. However, ptosis cases unrelated to oculomotor nerve injury as a complication of KD were also reported [17]. Ophthalmic complications were likewise self-limiting in our cohort.

Other

A few case reports of IgA vasculitis concomitant with KD have been reported [18]. We have not found any publications regarding growth retardation or hypothyroidism as KD complications.

Limitations

Our study has some potential limitations:
1. Its retrospective nature could have resulted in biased information from parents, particularly those who recalled observations from a few years back.
2. No control group.
3. Despite a relatively large sample size, subgroups were too small for reliable statistical analysis. The patients' population was homogeneous and did not include ethnic minorities.

Conclusions

Various unspecific late complications may emerge after an acute phase of KD. Although possible explanations of observed abnormalities are numerous, our data may enhance clinicians' insight into frequent and poorly understood findings observed after KD in children.

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ROBOTIC RADICAL GASTRECTOMY – OUR OWN EXPERIENCE AND A REVIEW OF THE LITERATURE

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Abstract:

Introduction

Gastric cancer is the fifth most common cancer worldwide. Surgery or endoscopic treatment is essential in all stages of the disease. The most common procedure is total gastrectomy with D2 lymphadenectomy. Removal of stomach and lymph nodes can be performed using minimally invasive techniques. These include laparoscopic gastrectomy, present in gastric cancer surgery since 1994, and robotic gastrectomy, which appeared for the first time in 2003. The last-mentioned method is the newest and the most technically advanced form of surgical treatment for gastric cancer. The first laparoscopic robot-assisted total gastrectomy in Poland was reported by Marek Zawadzki. In this paper we present the technique of totally robotic total gastrectomy.

Aim

Presentation of our experience in robotic radical gastrectomy. Description of the first totally robotic gastrectomy in Poland. Review of the literature assessing this novel minimally invasive technique in gastric cancer treatment - robotic gastrectomy.

Material and methods

Presentation of our own experience in robotic surgery. Review of literature.

Results

Robotic gastrectomy as an alternative to the laparoscopic technique is associated with the earlier return of bowel motility after surgery and the earlier introduction of a liquid diet. In terms of perioperative and postoperative complications, morbidity and mortality, as well as the need to convert to open surgery, the laparoscopic and robotic techniques do not really differ from each other. For the first time in Poland, we performed totally robotic radical gastrectomy in our department, using the da Vinci Xi ® Surgical System (Intuitive Surgical). No postoperative complications were observed.

Conclusions

Totally robotic radical gastrectomy is a safe alternative to classic and laparoscopic surgery, and can have additional benefits, both for the surgeon (less exhaustion, ergonomics, lack of hand tremor on instruments) and for the patient (earlier tolerance of oral diet, earlier hospital discharge). Further study is needed to assess the relevance of the potential benefits and the cost-effectiveness of this novel technique.

Keywords: gastric cancer, robotic gastrectomy, da Vinci, lymphadenectomy D2.

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Introduction

Gastric cancer is the fifth most common cancer worldwide, responsible for 7.7% of cancer deaths [1]. Surgical or endoscopic treatment is essential in all stages of the disease [1]. The most common procedure is total gastrectomy with D2 lymphadenectomy. In stage IA-III B (T1N0M0 - T3N2M0) there is a possibility of subtotal gastrectomy depending on the tumour location, while with stage 0 cancers (TisN0M0) a neoplastic tumour can be removed by endoscopic mucosectomy [2]. Endoscopic resection is also possible in early T1 stages; however not all patients will benefit from this treatment. Survival outcomes in T1a gastric cancers vary significantly, depending on race. For example the rate of lymph node metastasis in T1a gastric cancers in the United States is higher than the rates reported in Asia [3], thus local endoscopic resection is inferior to gastrectomy for early clinical stage T1a and T1b gastric adenocarcinoma in the United States [4].

Apart from the first method used historically, open gastrectomy, removal of the stomach and lymph nodes can be performed with the use of minimally invasive techniques. These include laparoscopic gastrectomy, present in gastric cancer surgery since 1994 [5] and robotic gastrectomy, which appeared for the first time in 2003 [6-7]. The last-mentioned method is the newest and the most technically advanced form of surgical treatment for gastric cancer. The first laparoscopic robot-assisted total gastrectomy in Poland was reported by Marek Zawadzki [8]. The laparoscopic part of the procedure involved opening the lesser sac, mobilization of the greater curvature and transection of the duodenum. A robot was used for D2 lymphadenectomy and the creation of anastomosis. In this paper we present the technique of totally robotic total gastrectomy.

Aim

To present and assess novel minimally invasive technique in gastric cancer treatment, using robotic gastrectomy.

Material and methods

We present our experience in robotic surgery which led to the first in Poland totally robotic gastrectomy with lymphadenectomy D2, as well as a review of the literature.

Results

Our own experience

A 55-year-old man was admitted on 29 September 2021 for the surgical treatment of gastric cancer. In the gastroscopic examination, crater-like ulcers with raised, sharply delimited walls of about 4 cm were observed in the gastric cardia area. The walls and base of the lesion were described as hard, brittle, and flaky. The histopathological examination of the samples showed the presence of high-grade G3 adenocarcinoma. After the diagnosis was made, the patient was under the care of the Department of Oncology, where further treatment was planned. Before elective gastrectomy, the patient received 4 cycles of FLOT chemotherapy. A CT scan of the chest, abdominal cavity and pelvis with contrast showed thickening (with a maximum vertical dimension of 16 mm) of the walls of the abdominal oesophagus and stomach around the cardia, fundus and a partially lesser curvature with smoothing of the stomach folds. Three lymph nodes sized < 5 mm were visible in the gastric cardia area. There was no infiltration of the surrounding organs and vessels, no visible metastases, and no destructive changes in the bones. In a CT scan after four cycles of neoadjuvant chemotherapy, a marked reduction in the thickening of the gastric cardia wall was observed. The lymph nodes did not enlarge.

The patient was previously diagnosed with arterial hypertension and had not undergone any surgical procedures before.

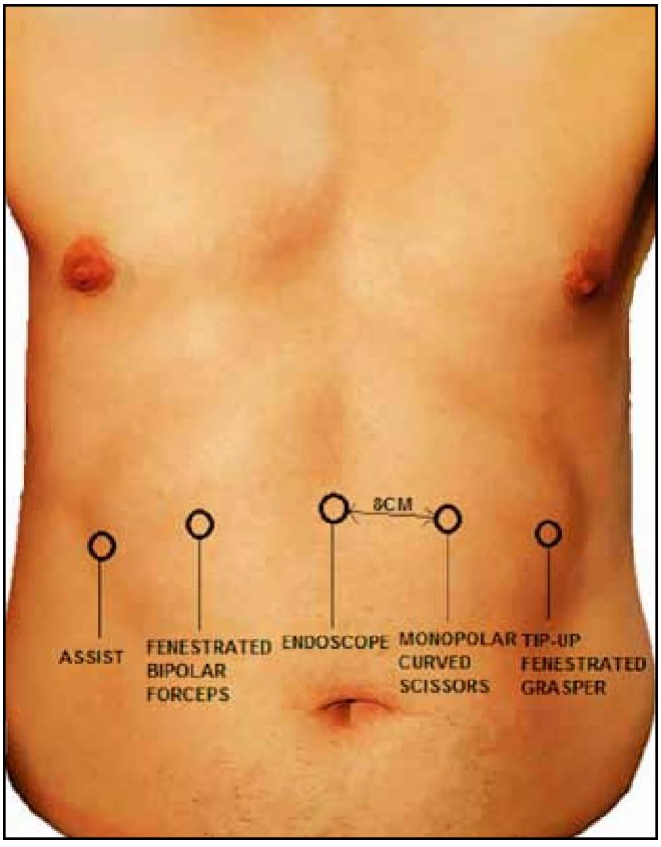
Laboratory tests on admission showed no abnormalities in the electrolyte balance, renal or coagulation system parameters. The peripheral blood count was normal.

Based on the histological type of the lesion, location, clinical stage, and the lack of metastases, the patient had been qualified for robotic gastrectomy with the use of the da Vinci Xi® Surgical System (Intuitive Surgical).

Procedure description

Robotic gastrectomy was performed on 30 September 2021. After disinfection and sterile draping of the operating field, under general anaesthesia, a Veress needle was inserted at the Palmer's point. Pneumothorax was set to 12 mm Hg. The first 8 mm robotic trocar and endoscope were introduced. Under visual control, another three 8 mm robotic trocars and an assistant trocar were introduced (Fig. 1).

Figure 1. Trocar placement.



The appropriate position of the operating table was set. The intestines were arranged, revealing the operating field. Robotic trocars were attached to the robot's "patient cart". The trocars were placed at the correct depth under visual control, and the tension was released. The robotic tools were installed: Tip-up Forceps, Fenestrated Bipolar Forceps and Monopolar Scissors. The stomach and the greater omentum were dissected, the blood vessels supplying the organ were clipped with polymer clips and cut. The duodenum was divided distally to the pylorus with the use of the iDrive Ultra ® (Covidien) stapler (45 mm gold cartridge) (Fig. 2). A D2 lymphadenectomy was performed (Fig. 3-4) and the resected tissues were sent for histopathological examination. The jejunum was cut with the stapler (60 mm white cartridge) about 15 cm from the Treitz ligament. The mesentery was divided, and a Roux en Y loop was created. The distal part of the intestine was moved through a pre-made opening under the mesocolon and the intestine was mechanically anastomosed with the oesophagus (45 mm gold cartridge) with the use of the self-pulling technique (SPLT). The oesophagus was cut with a stapler (60 mm purple cartridge) just above the gastric cardia (Fig. 5). The remaining opening in the anastomosis was sutured (Fig. 6). A functional end to end anastomosis (FETEA) was created (Fig. 7). The proximal part of the jejunum was mechanically anastomosed side-to-side with the small intestine about 60 cm from the esophagojejunal anastomosis (Fig. 8). The remaining opening in the anastomosis was closed by double layer running suture (Fig. 9). The leak test of the esophagojejunal anastomosis was performed with the use of methylene blue solution. No leak was detected. The afferent loop was fixed to the opening in transverse colon mesentery and the remaining opening in the small bowel mesentery was closed. A Pfannenstiel incision was made in the lower abdomen, and the edges of the wound were secured with an Alexis Wound Protector ® (Applied Medical). The stomach, the greater omentum and the other excised tissues were removed from the abdominal cavity and sent for histopathological examination. Two 16F drains were left in the peritoneal cavity.

Figure 2. The duodenum was divided distal to the pylorus.

Figure 3. A D2 lymphadenectomy was performed.

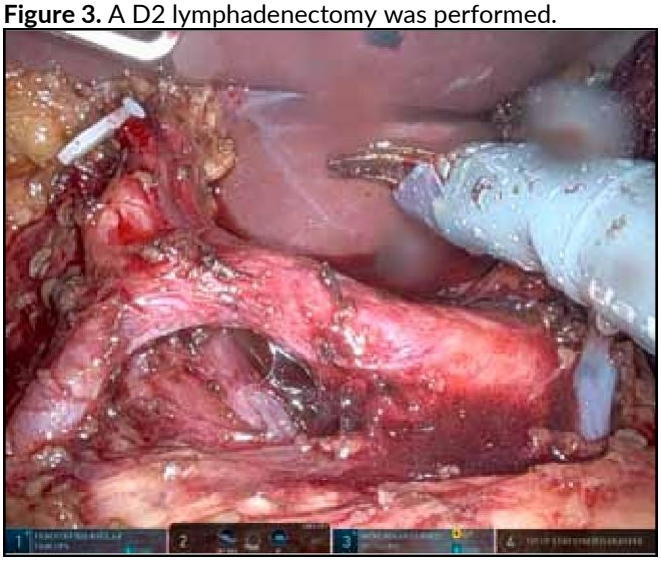


Figure 4. A D2 lymphadenectomy was performed.

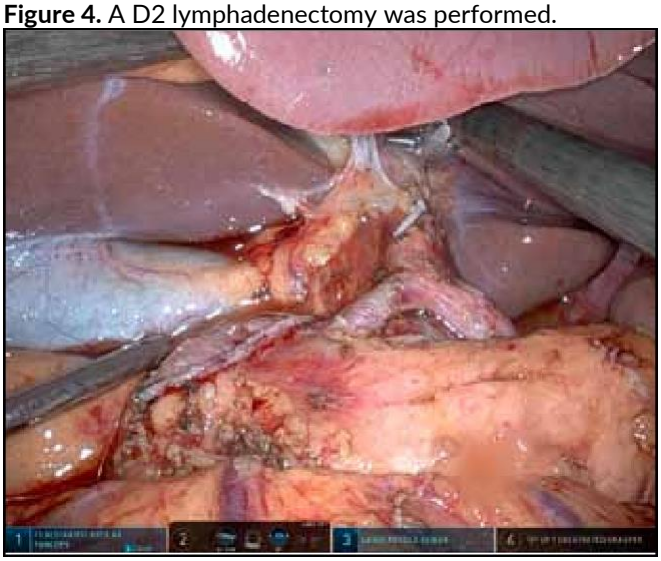


Figure 5. The oesophagus was cut with a stapler just above the gastric cardia.

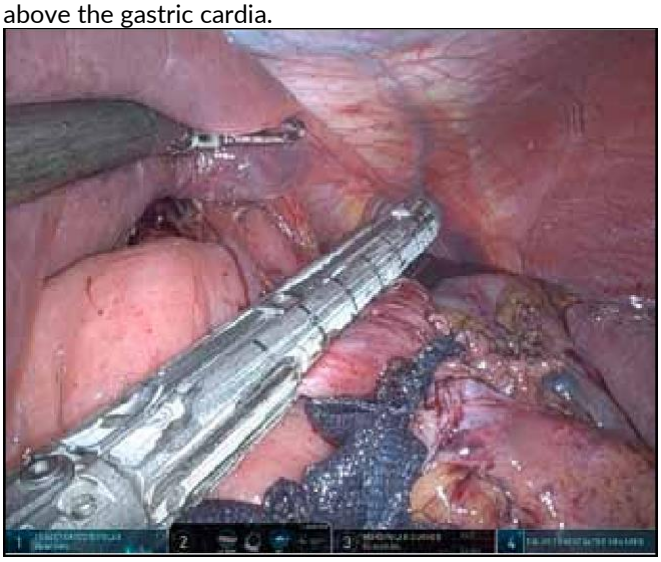


Figure 6. The opening in the anastomosis was sutured.

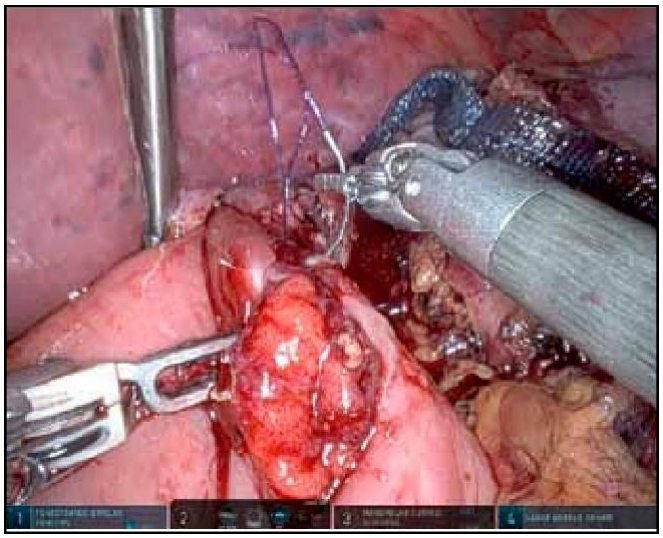


Figure 7. A functional end to end anastomosis was created.

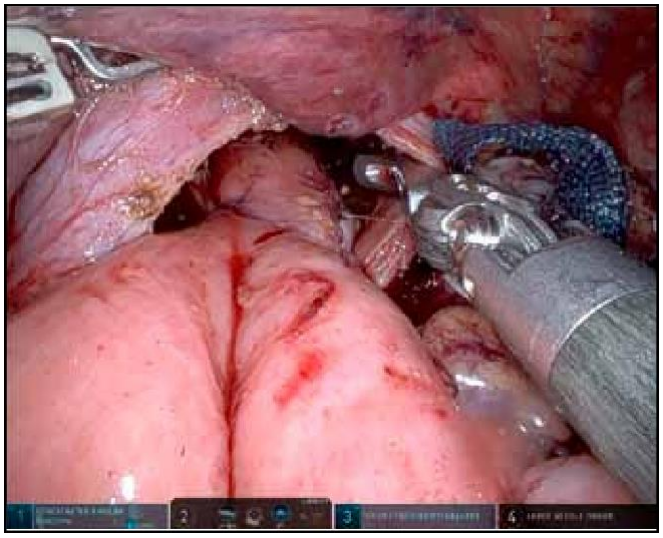


Figure 8. The proximal part of the jejunum was mechanically anastomosed side-to-side with the small intestine.

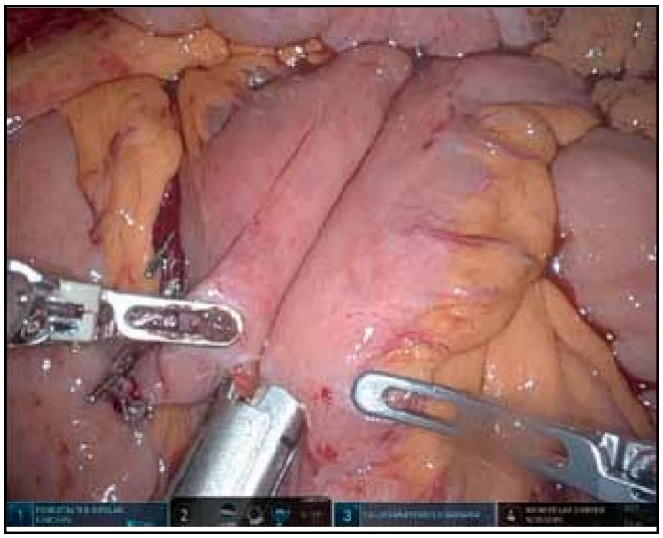
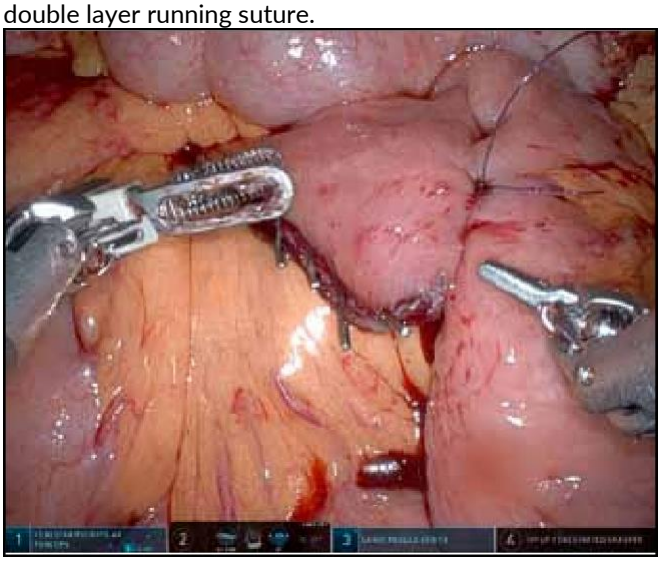


Figure 9. The opening in the anastomosis was closed by a double layer running suture.



Postoperative care

In the early postoperative period the daily fluid balance, basic vital signs and the volume and appearance of fluid collected by the drains were monitored. The patient did not have a fever. There were no signs of surgical site infection.

In laboratory tests, a slight decrease in haemoglobin concentration to 10 g/dl was observed (preoperative haemoglobin concentration was 11.9 g/dl), clinically with no evidence of active bleeding. The serum levels of α-amylase, urea and creatinine remained within the normal range. The concentration of C-reactive protein was 2.3; 5.6 and
3.6 mg/dl on the first, second and fourth postoperative days, respectively. On the first postoperative day, an increased concentration of creatine kinase was noted (it normalized in the days following the procedure).

In the histopathological examination of the excised tissues (stomach with the greater omentum, mediastinal site, common hepatic artery site, hepatoduodenal ligament site, celiac trunk sit, upper edge of the pancreas site, lesser curvature and the greater curvature site), no cancer cells were found. The biopsy obtained from the ulcer found in stomach in the preoperative gastroscopy was again examined. The primary diagnosis was confirmed (high grade cancer, G3). Taking into account that the patient had received four cycles of chemotherapy prior to the gastrectomy, a complete response to this treatment was observed (according to UICC CR). In the current study, according to the TNM classification, the tumour was assessed as an ypT0CR ypN0 (0/29) R0 tumour.

The patient was discharged home in good general condition on the sixth day after surgery.

Discussion

Nowadays there is no metaanalysis which compares the amount of minimally invasive procedures conducted in Asia

and in Europe. Most of the clinical trials are based on the experience gathered from the Asian centres. This phenomenon is caused by the higher incidence of gastric cancer in Asian countries, such as Japan or South Korea [9-11]. In Europe gastric cancer is less frequent; however there are also some analyses focused on minimally invasive procedures in gastric cancer treatment. In 2015 a registry known as IMIGASTRIC was established [12-13]. The purpose of this clinical trial was to create a "multi-institutional database comprising of information regarding surgical, clinical and oncological features of patients undergoing surgery for gastric cancer with robotic, laparoscopic or open approaches, and subsequent follow-up at participating centres" [13]. The data about different types of gastric surgery was collected from North America, Europe, and Asia, but the results are not yet available [14].

In a meta-analysis, Jianglei Ma et al. [15] compared laparoscopic and robotic gastrectomy. It showed that perioperative blood loss can be reduced in the robotic gastrectomy group (WMD: 28.66; 95% CI 18.59 - 38.73, p < 0.001). Meta-analysis by Xinsheng Zhang et al. showed that robotic gastrectomy with D2 lymphadenectomy required a longer operating time (WMD = 29.78, 95% confidence interval (CI): 15.97–43.59), but it had less operative blood loss (WMD = −31.93, 95% CI: −44.03 to −19.83), shorter time to first flatus (WMD = −0.13, 95% CI: −0.22 to −0.04), as well as shorter time to liquid diet (WMD = −0.20, 95% CI: −0.28 to 0.12), fewer severe complications (RR = 0.62, 95% CI: 0.43–0.90) and overall complications (RR = 0.75, 95% CI: 0.62–0.91) compared with laparoscopic gastrectomy with D2 lymphadenectomy [16].

A statistically significant difference was also obtained in the studies by Binghon Xiong et al. [18], Leonardo Solaini et al. [19] and Li-Dong Hu et al. [20].

Similar conclusions were obtained on the basis of a retrospective analysis by Weisong Shen et al. [17], but only in the subgroup of patients whose tumour did not infiltrate the serosa (176.6 ± 217.2 ml for robotic gastrectomy vs. 212.5 ± 198.8 ml for laparoscopic gastrectomy, P = 0.001). In the subgroup of patients with serosa involvement, no statistically significant difference was found in the amount of blood lost perioperatively.

In a retrospective analysis by Taeil Son et al. [21], in which both techniques were compared (total gastrectomy with limadenectomy D2), no statistically significant difference was noticed in the amount of blood lost perioperatively (163 vs. 210 ml; P = 0.360). Data collected by Hong-Bin Liu et al. [22] and J. M. Park et al. [23] also showed no differences in this parameter for both techniques. In the case of a gastrectomy performed without D2 lymphadenectomy, then perioperative blood loss also did not differ for both the robotic and laparoscopic gastrectomy [23].

It should be emphasized that the BMI in patients with gastric cancer does not affect the amount of estimated blood loss, which was shown in a prospective study by J.M. Park et al. [23] and Juhan Lee et al. [24].

Another analysed parameter is the number of lymph nodes removed during the operation. It is an important issue for further oncological treatment and the overall patient survival. Most of the studies conducted so far have reported a greater number of obtained lymph nodes for robotic rather than laparoscopic gastrectomy (Weisong Shen et al. for the subgroup of patients without serosa involvement [17]: 33 ± 8.5 vs. 31.3 ± 9.5, P = 0.047; Taeil Son et al. al. [21] 47.2 vs. 42.8, P = 0.210; Hong-Bin Liu et al. [22] 40.9 ± 13.1 vs. 35.4 ± 15.8; P = 0.004; Li-Dong Hu et al. [20]). On the other hand, in the studies by Jianglei Ma et al. [9], Binghong Xiong et al. [18], Taeil Son et al. [21], Liang Zong et al. [25] there were no significant differences in the number of obtained lymph nodes. Weisong Shen et al. also did not show such a difference for the subgroup of patients with sera involvement [17].

Taeil Son et al. [21] showed that although the total number of lymph nodes did not differ for both techniques, more lymph nodes were obtained from the area of splenic artery, spleen hilum and abdominal aorta. The retrospective analysis by Myung-Han Hyun et al. [26] showed that in obese patients, the number of lymph nodes obtained during robotic gastrectomy was lower (23.4 ± 7.0) than during laparoscopic gastrectomy (32.2 ± 12.5, P = 0.006). The same conclusions were obtained in the prospective study of Juhan Lee et al. [24] for the group of patients undergoing subtotal gastrectomy with D2 lymphadenectomy.

The duration of the gastrectomy performed with the robotic technique is longer compared to the laparoscopic technique (according to Weisong Shen et al. [17] 257.1 ± 74.5 min vs. 226.2 ± 61.3 min respectively, p < 0.001; according to Kuo-Hung Huang et al. [27] 357.9 ± 107.8 min vs. 319.8 ± 113.7 min respectively, p = 0.040; according to Leonardo Soilani et al [19] 327 min (297-358) vs. 248 min (222-275) respectively, p = 0.001) [9, 18, 20, 23, 24]. In studies by Hong-Bin Liu et al. [22] and Myung Han Hyun et al. [26] there was no difference in the time for surgery for both techniques. However, it should be emphasized that these studies are based on data from procedures performed by a single surgeon. In a prospective study by Juhan Lee et al. [24] the effect of obesity on the difference in surgery time was not confirmed for either minimally invasive technique.

A factor that may influence further oncological treatment is the time from surgery to hospital discharge, because the shorter this time, the sooner the patient can receive adjuvant chemotherapy. In the studies of Hong-Bin Liu et al. [22] and Weisong Shen et al. [17] this time for robotic gastrectomy was shorter compared to laparoscopic gastrectomy (Hong-Bin Liu et al.: 11 days (9-13) vs. 12 days (10-14) respectively, p <0.0001; Weisong Shen et al.: 9.4 ± 7.5 days vs. 10.6 ± 10.9 days respectively, p = 0.41). Binghong Xiong et al. did not observe significant differences in the length of hospital stay after surgery (WMD: 0.42, 95% CI: -1.87 to 0.79; P = 0.42) [18].

Robotic gastrectomy as an alternative to the laparoscopic technique is also associated with an earlier return of bowel

motility after surgery and the introduction of a liquid diet [20,22].

In terms of perioperative and postoperative complications, morbidity, and mortality, as well as a need to convert to open surgery, the laparoscopic and robotic techniques do not differ from each other [9, 17, 18, 20, 21, 22, 24, 27, 28].

In the meta-analysis by Jianglei Ma et al. [9] there were no statistically significant differences in overall survival (HR = 0.95, 95% CI 0.76 ~ 1.18, P = 0.640), relapse-free survival (HR = 0.91, 95% CI 0.69 ~ 1.21, P = 0.530) and the recurrences (OR = 0.90, 95% CI 0.67 ~ 1.21, P = 0.500). Similar results for overall survival and disease-free survival are described in the retrospective analysis of Taeil Son et al. [21].

Based on the literature, robotic gastrectomy also has no advantage over laparoscopic gastrectomy in terms of the R0 resection rate [17] and in terms of resection margins free of neoplasm [9, 20, 28].

Robotic gastrectomy is one of the most advanced surgical methods in the treatment of gastric cancer. The learning curves have also been studied over the past decade. Kuo-Hung Huang et al. [27, 29] in both the 2012 and 2014 analyses, observed the plateau phase of the learning curve in terms of operating time and the time needed to apply the necessary equipment after 25 robotic gastrectomy procedures. In the study of Hong-Bin Liu et al. [22] after adopting the cut-off point of 25 treatments as a learning curve, no significant differences were observed in duration of surgery and installation of equipment after another 75 treatments. Kuo-Hung Huang et al. [27] determined the learning curve for 41 performed procedures for laparoscopic gastrectomy in patients with gastric cancer. Operation time and perioperative blood loss decreased with experience. These conclusions, however, require verification in subsequent studies, as the current data are insufficient to estimate the learning curve for robotic gastrectomy and to conclude that this curve is shorter compared to the learning curve for laparoscopic gastrectomy. There have also been reports that experience in laparoscopic gastrectomy positively influences the learning curve in robotic gastrectomy [30-31].

As presented above, there is a lack of clear consensus regarding both minimally invasive techniques. There is no such discrepancy when comparing robotic gastrectomy to open surgery. Data from retrospective studies and meta-analyses are consistent. Robotic gastrectomy is associated with a longer duration of the procedure [25, 32, 33], perioperative blood loss is lower than in classic surgery [25, 32, 33], and the stay in a hospital ward is also shorter in the group of patients undergoing robotic surgery. In a meta-analysis by M. H. Hyun et al. [33] this period was shorter by an average of 2.18 days (P < 0.001). There are no significant differences in postoperative complications, such as bleeding, wound infection, or anastomotic leakage [32-33]. There are also no differences in the number of removed lymph nodes [25, 32-33]. The length of resection margin also does not differ between the two techniques [33].

Comparing postoperative mortality and morbidity for classic and robotic surgery, based on the meta-analyses quoted above [25, 32], it can be concluded that both methods are equally safe.

Conclusions

To sum up, robotic gastrectomy is a safe alternative to classic and laparoscopic surgery. In addition to the high-resolution three-dimensional image of the operating field, the da Vinci Xi® Surgical System provides various amenities, such as surgeon's hand vibration filter and wrist instruments that provide seven degrees of freedom, which gives greater scope and precision to manoeuvres in a narrow operating field.

Robotic surgery compared to open surgery, apart from a better cosmetic effect, has an advantage in terms of the time from surgery to discharge from hospital. Comparing it with laparoscopic surgery, it is difficult to demonstrate additional benefits for the patient. According to the experience of the authors of the publication, work ergonomics during robotic procedures (compared to open and laparoscopic techniques) has improved for both the operator and the assistant, and thus long surgical procedures have become less physically demanding. In addition, da Vinci Xi® Surgical System connects wirelessly with TruSystem 7000dV Operating Table so that a patient can be dynamically positioned while the surgeon operates (Integrated Table Motion).

A certain limitation, when it comes to the availability of this modern technology, may be the cost of purchasing the robotic system itself and the cost of its further operation.

Further research and postoperative supervision are needed to verify whether robotic gastrectomy will improve the patients' quality of life of and extend disease-free survival.

Disclosures section

The authors have nothing to disclose.

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CASE REPORT

46 XY, FEMALE. COMPLETE ANDROGEN INSENSITIVITY SYNDROME

46 xy, kobieta. Zespół całkowitej niewrażliwości na androgeny

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Abstract: Androgen insensitivity syndrome (AIS) is an inherited disorder of sexual development caused by mutations in the androgen receptor encoding gene. A female patient, at the age of 17 years, was diagnosed with complete androgen insensitivity syndrome, during the diagnosis of primary amenorrhoea. Cytogenetic analysis showed a 46 XY karyotype. A gynaecological examination revealed a blind-ending vagina and a lack of a uterus. A physical examination revealed normal breast development and scanty pubic and axillary hair. At the age of 18, the patient underwent laparoscopic gonadectomy. Before the surgery, the testosterone level was 5.6 ng/ml, and after 0.6 ng/ml. Histopathological examination of the gonads revealed a cyst and many lumps and, in one of them, a tubular adenoma was diagnosed. After the procedure, the patient was under medical supervision and was taking 1 mg of estradiol daily, orally. At the age of 24 the patient was diagnosed with osteoporosis, T-SCORE was -2.6 SD, and 3 years later -2.76 SD. The patient received sodium alendronate and ibandronic acid. At the age of 34, she was diagnosed with type 2 diabetes, therefore she started receiving metformin and was under diabetological supervision. Quigley grades 6 and 7 correspond to complete androgen insensitivity. The genitals are completely feminized, and newborns at birth are assigned as females. The diagnosis is usually established during the diagnostics of primary amenorrhoea. CAIS is associated with high risks of gonad carcinogenesis and therefore a gonadectomy must be performed. Hormone replacement therapy (HRT) is required after gonadectomy to maintain secondary sexual characteristics. Due to the high risk of osteoporosis, the patient requires calcium and vitamin D supplementation as well as bone density control. The prognosis is good, and gonadectomy and HRT usually give satisfactory long-term results.

Streszczenie: Zespół niewrażliwości na androgeny (AIS) to wrodzone zaburzenie rozwoju płciowego spowodowane mutacjami w genie kodującym receptor wiążący androgeny. U pacjentki w 17 rż., podczas diagnostyki pierwotnego braku miesiączki, rozpoznano zespół całkowitej niewrażliwości na androgeny. Badania cytogenetyczne wykazały kariotyp 46 XY. W badaniu ginekologicznym narządu rodnego wykazano ślepo zakończoną pochwę, nie stwierdzono obecności macicy. W badaniu przedmiotowym stwierdzono prawidłowo rozwinięte gruczoły piersiowe oraz skąpe owłosienie pachowe i łonowe. W 18 rż. chora przeszła obustronną gonadektomię metodą laparoskopową. Przed operacją poziom testosteronu wynosił 5,6 ng/ml, a po 0,6 ng/ml. Badanie histopatologiczne wykazało obecność tkanki jąder w usuniętych gonadach, a w jednej z nich wykryto gruczolaka cewkowego. Po zabiegu pacjentka pozostawała pod kontrolą lekarską i przyjmowała 1 mg estradiolu dziennie, doustnie. W 24 rż. zdiagnozowano osteoporozę, T-SCORE wyniósł -2,6 SD, natomiast 3 lata później -2,76 SD. Pacjentka przyjmowała alendronian sodu oraz kwas ibandronowy. W 34 rż. rozpoznano u chorej cukrzycę typu 2, włączono leczenie metforminą i zalecono opiekę diabetologiczną. Stopień 6. i 7. w skali Quigleya odpowiada całkowitej niewrażliwości na androgeny. Narządy płciowe są całkowicie sfeminizowane, a noworodkom nadaje się płeć żeńską. Rozpoznanie zazwyczaj ustala się w trakcie diagnostyki pierwotnego braku miesiączki. CAIS wiąże się z koniecznością usunięcia nieprawidłowych gonad z powodu podwyższonego ryzyka wystąpienia zmian nowotworowych. Po gonadektomi niezbędne jest stosowanie substytucji estrogenowej m.in. w celu utrzymania drugorzędowych cech płciowych. Wysokie ryzyko rozwinięcia osteoporozy wymaga suplementacji wapnia i witaminy D oraz kontroli gęstości kości. Rokowanie jest dobre, a gonadektomia i estrogenowa terapia hormonalna dają zadowalające estrogenowa terapia hormonalna dają zadowalające wyniki długoterminowe.

Keywords: androgen insensitivity syndrome, Morris syndrome, CAIS, primary amenorrhea.

Słowa kluczowe: zespół niewrażliwości na androgeny, zespół Morrisa, CAIS, pierwotny brak miesiączki.

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Introduction

Androgen insensitivity syndrome (AIS, Morris syndrome) is an inherited disorder of sexual development caused by mutations in the androgen receptor encoding gene. It is located on the X chromosome (locus Xq11-q12), and hence it is inherited in the X-linked recessive manner [1]. The Morris syndrome can be divided into three phenotypes: complete (complete AIS, CAIS), partial (partial AIS, PAIS) or mild (mild AIS, MAIS) [2-3]. The seven-grade Quigley scale is used for classifying a patient based on the appearance of the external genitalia, where grade 7 corresponds to fully feminised reproductive organs. Complete and partial androgen insensitivity syndrome affects 2–5/100,000 individuals born with the XY karyotype. The mild form, on the other hand, is much less frequent [4].

The androgenic action can be seen when the androgens are connected with a receptor protein (AR). Mutations within this receptor gene cause a wide range of abnormalities in male sexual development. They range from complete androgen insensitivity, with individuals presenting the normal development of the mammary glands and external female reproductive organs to those with a male phenotype with only partial virilization or infertility [2]. During foetal development in individuals with the 46XY karyotype, the SRY gene located on the Y chromosome initiates testicular development. In turn, as the testicles develop, testosterone is produced, which triggers the development of the external reproductive organs. In addition, the antimullerian hormone (AMH) is produced, which is supposed to inhibit the development of the Müllerian ducts (which form the female reproductive organs, such as the fallopian tube, uterus, and upper vaginal fragment) [5]. Despite the high concentration of androgens, the complete AIS cells are not stimulated with testosterone, which leads to the development of external female organs. The action of the AMH hormone in such individuals is not impaired, causing the inhibition of the Müllerian duct development. Endogenous oestrogen production (by the testes and through peripheral androgen aromatization) results in the development of external reproductive organs, including a blind-ending vagina and phenotypically female mammary glands [6]. Below we present a case of a patient with complete androgen insensitivity syndrome, who was classified as grade 7 on the Quigley scale.

Case study

The patient, born in 1984, weighing 68 kg and measuring 171 cm, was diagnosed with complete androgen insensitivity syndrome at the age the 17 during the process of diagnosing primary amenorrhoea. Cytogenetic analysis showed a 46 XY karyotype, but the patient perceived herself as a female. At the age of 18, (2002) the patient underwent a bilateral laparoscopic gonadectomy. Before the surgery, the testosterone level was 5.6 ng/ml, and after (in 2011) it was 0.6 ng/ml (N 0.11-0.78 ng/ml). A histopathological examination revealed the presence of testicular tissue in the removed gonads. A cyst about 4 cm in diameter and nodules about 2 cm in diameter were visible on one of the gonads. In addition, both gonads contained a stroma with a tubular structure, lined with Sertoli cells and clusters of Leydig cells. Consequently, a suspicion of tubular adenoma was raised. After the procedure, the patient remained under medical care and took 1 mg of oral estradiol daily. In 2009, estradiol was discontinued, and the patient was started on estradiol transdermal patches with norethisterone (Systen Sequi), but due to periodic pain in the mammary glands, the drug was changed to Systen Conti ½.

In 2009, the patient was diagnosed with osteoporosis. In densitometry, the T-SCORE was -2.6 SD, osteocalcin concentration was at the level of 25 ug/dl (N), calcium at the level of 9.1 mg/dl (N) and phosphate at the level of 3.7 mg/d (N). In 2012 the T-SCORE was -2.76 SD and the Z-SCORE was -2.92. The patient received 70 mg of sodium alendronate and ibandronic acid.

In 2019, the patient was admitted to the Department of Gynaecological Endocrinology at the A. Mazowiecka Hospital in Warsaw for appropriate diagnostic tests for endocrine and insulin-glucose metabolism, as well as control of general and gynaecological condition. In the patient's history: nicotinism, varicose veins of the lower extremities, and an appendectomy at the age of 7. Family history: the mother was diagnosed with hyperthyroidism (the patient's TSH, fT4, anti-TPO, anti-TG levels were normal), and one of her three sisters was also diagnosed with CAIS. No specific androgen receptor mutation was found in the patient or her sister due to the family's refusal to perform genetic testing.

Gynaecological examination of the reproductive organs showed a blind-ending vagina and no uterus (its absence had been confirmed earlier via ultrasound and laparoscopy). The physical examination revealed normally developed mammary glands: Tanner stage ¾, while axillary and pubic hair were very sparse: Tanner stage ½.

Laboratory tests revealed an abnormal fasting blood glucose level of 113 mg/dl (6.25 mmol/l). After an oral glucose load test, the blood glucose value was 272 mg/dl (15.1 mmol/l (N:<7.8 mmol/l)). The cortisol level at 08:00. was 2.31 ug/dl (N: 5–25 ug/dl), while the measurement at 23:00 indicated a normal value of 3.58 ug/dl (N: 0–5 ug/dl). The folliculotropic hormone (FSH) level was 35.50 mIU/ml and the luteinizing hormone (LH) level was 13.05 mIU/ml. Due to a persistently elevated alanine aminotransferase level of 55.2 U/l (N:0–33 U/l), the patient remains under the supervision of a hepatologist; HBV and HCV infection were ruled out.

Discussion

Complete androgen insensitivity syndrome corresponds to grades 6 and 7 on the Quigley scale: the reproductive organs are those of a typical female, and a child is assigned female sex. Due to the normal picture of the external reproductive organs, complete androgen insensitivity syndrome is rarely diagnosed in infancy. At puberty, characteristic features include: the absence of pubic and axillary hair, well-developed mammary glands (due to peripheral conversion of testosterone to estradiol) and a blind-ending vagina. In most cases, as in the described patient, a diagnosis of CAIS is established in girls only at puberty, during the diagnosis of primary amenorrhoea. Very rarely, the complete androgen resistance syndrome is diagnosed prenatally, based on inconsistencies between genetic sex determined by amniocentesis and the structure of the external reproductive organs visualized in ultrasound [7]. The karyotype must be mapped to distinguish it from other genetic disorders.

The physical examination of such patients reveals a short vagina, no uterus, and imaging techniques (ultrasound, CT, MRI) confirm the absence of uterus and ovaries and the presence of testicles [8]. In two-thirds of patients with CAIS, the testicles are located within the inguinal canal or vulva, and in 15% they are located in the peritoneal cavity. Diagnosed CAIS requires treatment consisting in the removal of testicals, located outside the scrotum, due to the increased risk of malignant lesions [7]. A laparoscopic procedure is preferred because of its minimal invasiveness and low associated mortality [9].

Among gonadal neoplasms, the most common are seminomas, and less common are gonadoblastomas, syncytiomas, teratomas or Sertoli cell tumours. The risk of developing germinal neoplasms in the androgen insensitivity syndrome increases with the age of the patient: from 3.6% at the age of 25 to 33% after the age of 50. The incidence rate of these neoplastic lesions in CAIS ranges from 0.8% to 2% [7]. The patient described above underwent gonadectomy at the age of 18, and histopathologically the removed tissues were suspected to contain tubular adenoma. Delaying the elective surgery until post-pubertal status allows for developing spontaneous puberty through testosterone aromatization, while also remaining a safe option, as the risk of developing a malignant tumour before puberty is low. In addition, thanks to this procedure, patients can take an active role in the decision-making [9]. After surgical gonadectomy, oestrogen replacement therapy is necessary to maintain secondary sex characteristics and normal body proportions, prevent a decrease in bone mineral density, and ensure normal psychosocial development and well-being. Patients with CAIS are usually treated with oral oestrogen, less often with a transdermal supply. Treatment begins with low doses, which are increased gradually, while observing the advancement of bone age. In women with CAIS due to uterine agenesis, progesterone replacement therapy is not recommended [7].

The described patient was diagnosed with osteoporosis (T-SCORE -2.96SD), which may be related to the moderate decrease in bone mineral density in patients with CAIS, and in addition to the irregular intake of HRT. Patients with CAIS are advised to take calcium and vitamin D supplementation, take part in regular physical activities, and monitor bone density and BMI [10-11].

It is important to include the patient and their family in psychological care early in the diagnosis. While most patients, like the patient described above, perceive themselves as women, understanding that their genetic sex is male and that they are unable to have children can be very difficult. Therefore, comprehensive evaluation and possible psychological and psychiatric intervention contribute substantially to alleviating the associated stress and improving the quality of life.

Conclusions

In conclusion, the androgen insensitivity syndrome, although rare, is a very distressing condition for the patient and family members. The prognosis of this condition is generally good, especially when the syndrome is diagnosed early, and appropriate management is implemented. Gonadectomy and HRT usually give satisfactory short- and long-term results. However, long-term follow-up of patients is necessary to avoid bone demineralisation, the adverse effects of HRT and to ensure psychological well-being [12]. The patients with androgen insensitivity syndrome should remain under multidisciplinary care. Close cooperation between the surgeon, gynaecologist and psychiatrist is essential for proper treatment.

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CASE REPORT

A CASE OF A PATIENT WITH A SUSPICIOUS, RAPIDLY GROWING THYROID TUMOR, WITH A SHORT REVIEW OF THE THYROID NODULAR DISEASE GUIDELINES

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Abstract:

Thyroid nodules, also known as goitre, are the source of the most common thyroid disease. Its prevalence depends on age, iodine supply, and the availability of an ultrasonography examination. The manuscript presents a case of a patient with a fast-growing thyroid nodule, with ultrasonographic and cytological features suggesting a high probability of malignancy, which finally turned out to be a benign one. In addition to the presented case, the EU-TIRADS guidelines and indications for hemithyroidectomy are briefly discussed.

Keywords: goitre, thyroid nodule, FNA, EU-TIRADS, BETHESDA.

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Introduction

Thyroid nodular disease, commonly known as thyroid nodules or goitre (ICD-10: E04), is a frequent condition with the prevalence dependent on the examination type, with rates ranging from 2%-7% (palpation) to 19%-67% (ultrasonography – USG). [1.2]. Due to the high percentage of the disease in the population, and the increasing availability of ultrasound examination, the diagnosis of thyroid nodules is increasing yearly. The prevalence of the disease is correlated mostly with iodine supply (has U-shape distribution – increases both with iodine deficiency and excess), and advanced age [2, 3]. Proper interpretation of neck USG examination is crucial for accurate diagnosis and appropriate recommendations. Ultrasonographic features of nodules can suggest the need for performing fine-needle aspiration (FNA) to differentiate between benign and malignant characteristics of the lesion [4]. Many ultrasound images, despite suggesting the possibility of malignancy, can be misleading and force unnecessary procedures. This often leads to overtreatment and life-long complications. Thus the most important aspect of assessing thyroid nodules is the good qualification for FNA, which gives the most probable answers and suggests treatment or active surveillance.

Case presentation

A 66-year-old woman with no chronic diseases was referred for endocrinological assessment due to a rapidly growing neck nodule. She had no family history of cancer, radiotherapy, or any other factors increasing the risk of cancer. The first USG of the neck showed a thyroid nodule almost fully filling the right lobe. She was urgently admitted to the nearest oncological centre where FNA was performed, and the cytological result was the *Bethesda IV* category, with the commentary: "Suspicious of follicular neoplasm". Hormonal evaluation showed euthyreosis (calcitonin concentration was not measured). The patient was referred to a local surgery department, with a diagnosis of "thyroid cancer", but due to the long waiting time for admission she looked for help and consultation in another reference centre. At this stage of the diagnostic process she was redirected to our centre. In the physical examination we confirmed a clearly palpable nodule of the right lobe, with "soft consistency" in palpation. USG showed 30 x 30 x 36 mm (H x W x L) sized solid, hypoechogenic nodule of the right thyroid lobe, with an irregular shape, mixed type of vascularity, and no "halo" sign (Fig. 1, 2, 3). The only ultrasonographic feature that spoke against the high risk of malignancy was Shear Wave Elastography (SWE), which

showed similar elasticity to a normal thyroid tissue (in this case the left lobe). Due to ultrasonographic features suggesting possible malignancy, the fine needle aspiration cytology results, and most importantly the clinical aspect (rapid growth), the patient was referred to an experienced oncological surgeon, and underwent surgery a week later. During the surgery, the operator decided to perform hemithyroidectomy, due to palpable features of the lesion, and the low "intraoperative visual probability" of malignancy. The pathological results confirmed that the lesion was a follicular adenoma [Fig.4]. The patient received 50 ug levothyroxine a day, and remains euthyroid.

Figure 1. Right lobe of thyroid.

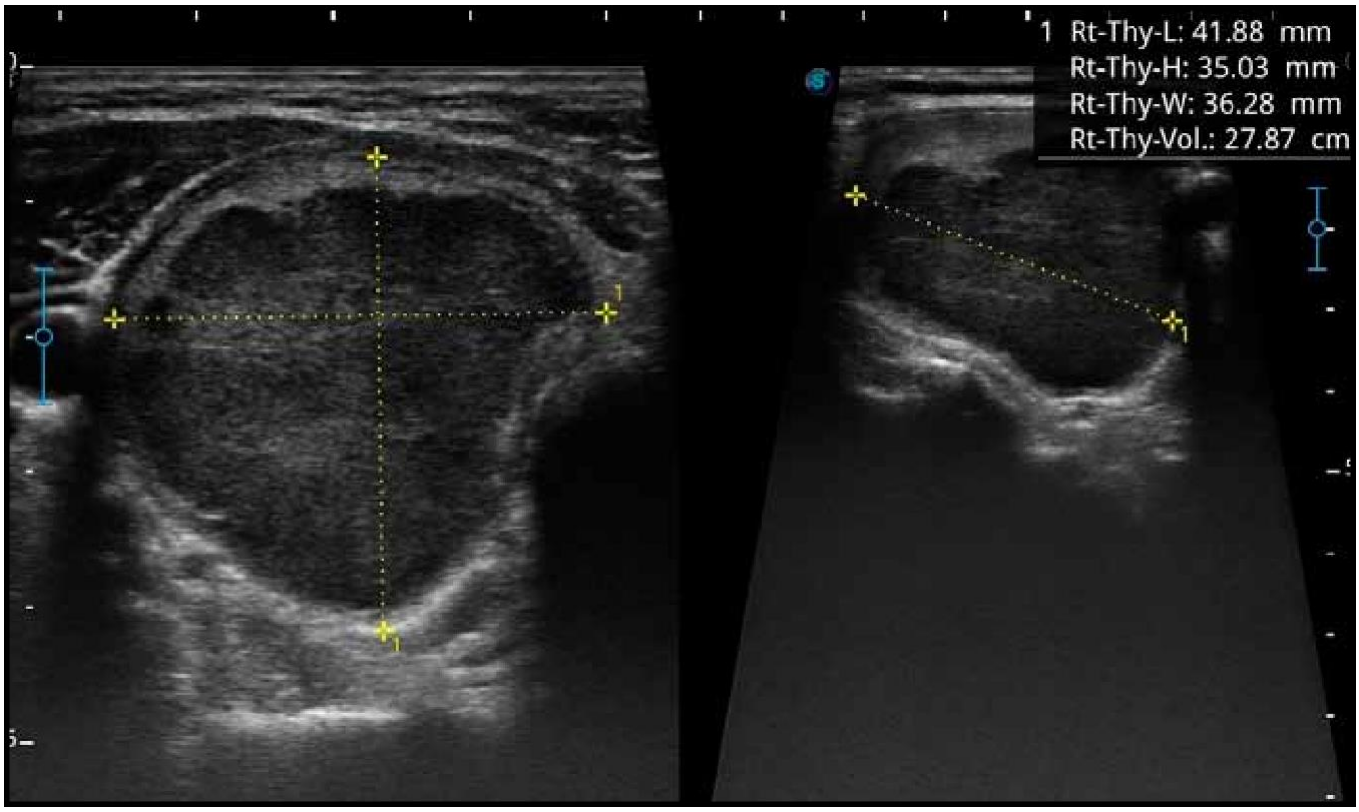


Figure 2. Left lobe of thyroid.

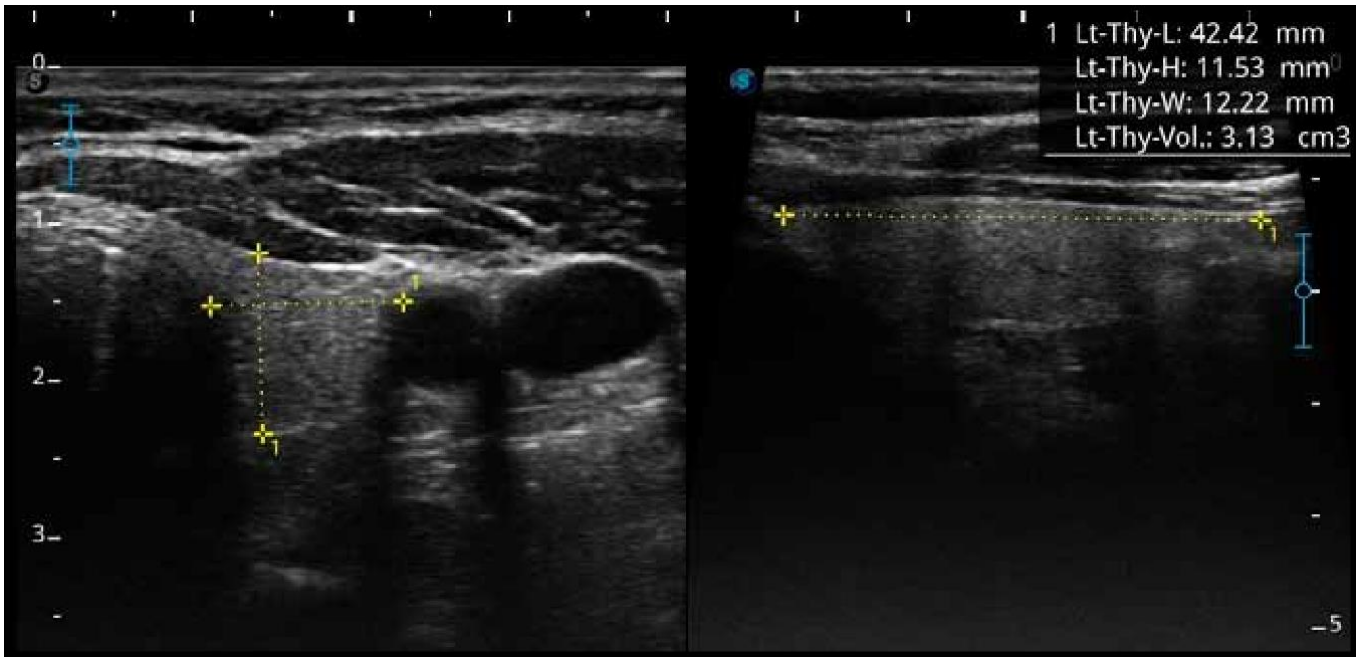


Figure 3. Hypoechogenic nodule in right lobe.

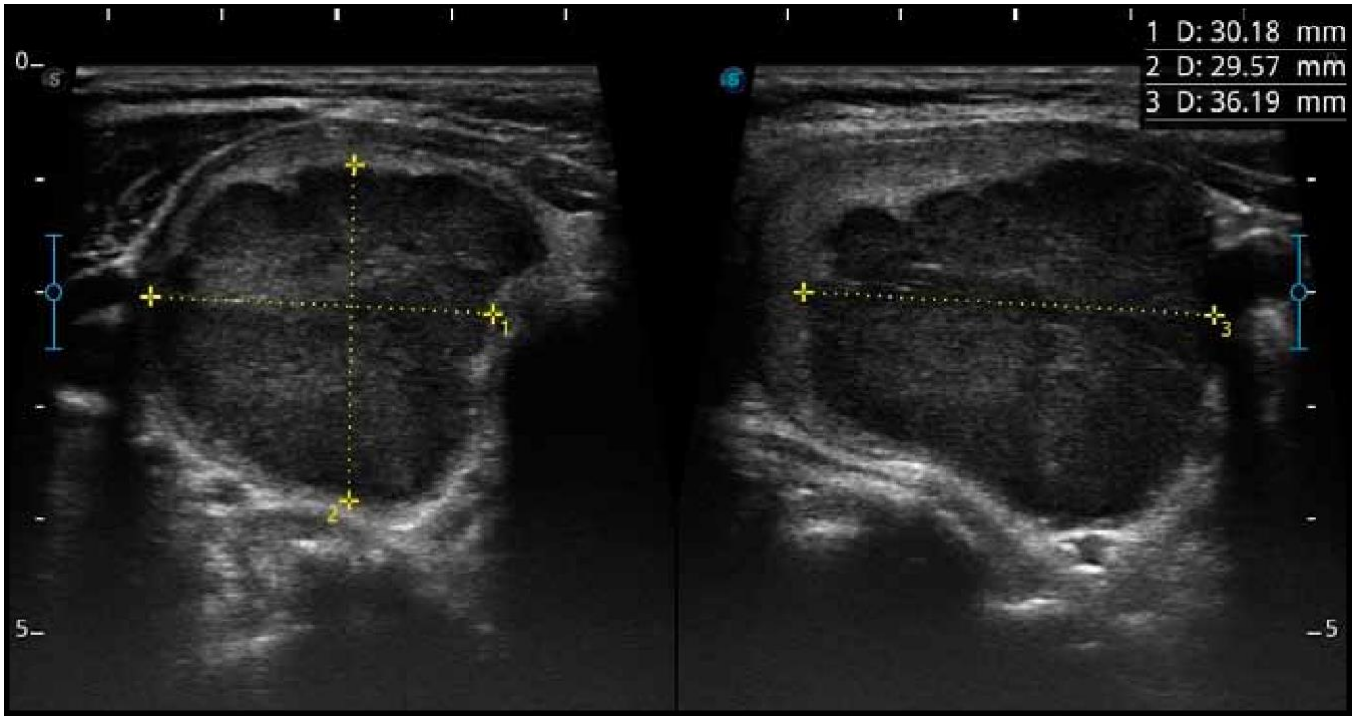
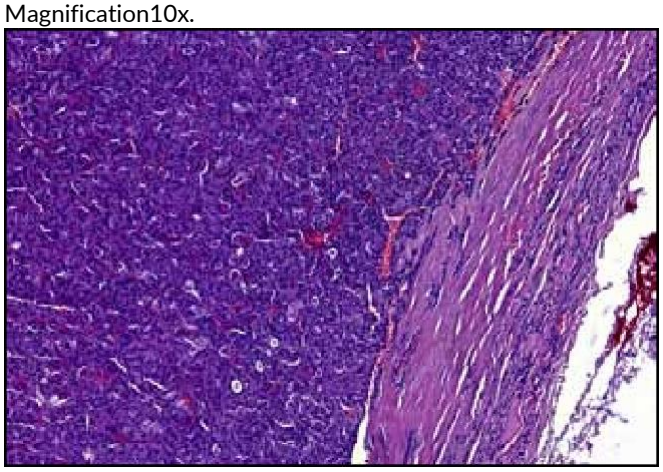


Figure 4. Histopathological result of the surgery – follicular adenoma. Hematoxylin & Eosine (HE) staining. Magnification10x.



Discussion

The interpretation of ultrasound thyroid examination and biopsy qualification should be performed using local guidelines. The European Thyroid Association in 2017 published Guidelines for Ultrasound Malignancy Risk Stratification of Thyroid Nodules in Adults, known as EU-TIRADS [4]. The most important summaries of those guidelines are presented in Table 1. The aim of the guidelines is to help in properly qualifying patients to the FNA or an observation group. The diagnosis of malignancy should never be stated only on the basis of an ultrasound examination. There are some ultrasound features that can suggest the potential malignant character of the nodule, but the patient never should be told that the diagnosis is certain. Some ultrasound features, including the SWE method where ultrasound waves are used to estimate density and elasticity of the tissues, can help to set up a diagnosis (malignant nodules tend to be stiffer than benign ones). Several studies proved the utility of using SWE in the diagnosis of thyroid nodules [5]. The results have shown that this method can improve the accuracy of the diagnosis, especially in inconclusive or ambiguous cases; however, the examination should always be used in combination with other imaging modalities (and clinical data), and the interpretation should be done by an experienced ultrasonographer. Only the cytological examination of cells harvested during the FNA can give the answer on the true potential risk of the lesion. According to the above, the FNA is a basic examination which can answer the most important question for the patient and the doctor: “Is surgery needed?”. Decisions about surgical intervention and its range are based on cytological results, and a summary of the guidelines is presented in Table 2. In the table, the differences in the malignancy percentage in the European and the Polish population, due to the published studies are presented in separate columns [6, 7]. The most appropriate suggestion for the patient about thyroid surgery is when the result of the FNAC shows Bethesda V or Bethesda VI. If the nodule is below 10 mm in every diameter then surgery on one lobe can be considered. This recommendation of hemithyroidectomy seems to be most advantageous with a FNAC of Bethesda IV, although in those cases total thyroidectomy is also an option. Bethesda III results suggest repeating FNAC after 3 months (to avoid false positive results which repairing tissue may suggest). A triple result of Bethesda III leads to the suggestion of surgery, especially if an ultrasound shows the features of malignancy.

Table 2. FNA results and follow-up procedure recommendations.

FNAC Category "Bethesda"	Description	Malignancy probability [%] EU	Malignancy probability [%] PL	Indication for FNA repeat	Most common histological results	Recommended procedure
I	Non-diagnostic	5–10	5–10	Repeat FNA after 3–12 months depending on risk	N/A	Another FNA or observation
II	Benign	0–3	< 1	Yes, if ultrasound suspicion of malignancy or the nodule enlarges its size significantly	• Nodular goiter • Thyroiditis, including chronic inflammations • Hyperplastic nodule • Colloid nodule (lots of colloid, sufficient cellularity) • Cytological findings suggest colloid nodules (lots of colloids, insufficient cellularity) • Thyroid cyst	Observation
III	Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS)	6–18	2.4–5.2	• **Yes,** repeat FNA after 3–12 months depending on risk • **USG** every six month is indicated	This category should be used in rare cases when it is not possible to state a precise cytological diagnosis	Consider surgical treatment in the presence of significant risk features in the US image or repeat FNA
IV	Follicular neoplasm or suspicious for a follicular neoplasm	10–40	19	• **No,** but if surgery is planned another pathologist confirmation is necessary • **USG** every six month is indicated, with decision of FNA repeat every 3-12 months	At least 25% of lesions belonging to this category are not neoplastic tumours (hyperplastic nodules, inflammation). This category should not be diagnosed when nuclear features of papillary thyroid cancer are present	In nodules < 10 mm in diameter, if they do not show risk features, a conservative strategy is acceptable (ultrasound observation); in larger nodules or presence of risk features, surgical treatment is generally indicated.
V	Suspicion of malignancy	45–60	75	No, but another pathologist confirmation is necessary	• **papillary** thyroid cancer • **medullary** thyroid cancer • **lymphoma** • **metastatic** carcinoma • **anaplastic** thyroid cancer/vascular sarcoma due to the presence of necrotic tissues • **hyalinizing** trabecular tumour	Thyroidectomy (consider hemithyroidectomy if tumour < 10 mm)
VI	Malignant	94–96	95–100	No, but another pathologist confirmation is necessary	• **papillary** thyroid cancer • **medullary** thyroid cancer • **lymphoma** • **metastatic** carcinoma • **anaplastic** thyroid cancer/vascular sarcoma	Thyroidectomy (consider hemithyroidectomy if tumour < 10 mm)

Bethesda I and Bethesda II results are considered to be low probability of malignancy, so observation or repeating FNA after 3-12 months is considerable. Surgery can be proposed to patients with a family history of thyroid cancer or in cases of compressive goiter [8]. Hemithyroidectomy compared to total thyroidectomy is associated with a smaller number of possible complications, like vocal cord impairment or hypoparathyroidism. It can be proposed to almost every patient, even with high-risk cancers [9-11]. Decisions should be made by the patient and surgeon together, and possible outcomes of every decision should be discussed before the surgery. Patients and physicians should remember that if histopathological diagnosis of thyroid cancer confirms a TNM classification higher than pT1aN0M0, a second operation and radioiodine treatment might be necessary. Nevertheless, a high cytological possibility of malignancy (Bethesda V and Bethesda IV), especially with a tumour size of ≥ 10mm in any diameter, should suggest total thyroid removal [7].

Conclusions

The majority of suspicious nodules diagnosed in thyroid ultrasound examinations are not malignant, even when “they look suspicious”.

If there is ultrasonographic or clinical risk of malignancy, or any uncertainty in obtained results, the patient should be referred to an experienced endocrinologist for proper diagnosis.

Fine needle aspiration with cytological examination should be the only test that can confirm the possibility of malignancy, and practitioners should not set up a diagnosis based only on the ultrasound image.

Hemithyroidectomy is a treatment option, with a lesser number of complications, but cannot be offered to every patient.

Indication for the surgery should be made individually regarding patient needs and expectations.

Fine needle aspiration results for Bethesda V and Bethesda VI should suggest total thyroidectomy.

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RENAL AMYLOIDOSIS IN ANKYLOSIS SPONDYLITIS – AN UNUSUAL INDICATION FOR A RENAL REPLACEMENT THERAPY

Amyloidoza nerek w przebiegu zesztywniającego zapalenia stawów kręgosłupa – nietypowy powód leczenia nerkozastępczego

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Abstract: AA amyloidosis might be a serious complication of chronic inflammatory diseases. One of the possible causes of AA amyloidosis is ankylosing spondylitis (AS). Amyloidosis is a rare complication of AS. However, delayed diagnosis and therefore delayed treatment of the underlying disease may even lead to organ dysfunction, which is a result of extracellular deposits of the acute-phase reactant – serum amyloid A (SAA). Renal involvement is the most common with clinical presentation characterised by proteinuria, nephrotic syndrome, and chronic kidney disease. We present the case of a 45-year-old man with a 25-year history of untreated AS which has led to AA amyloidosis and a necessity for renal replacement therapy. On admission the patient denied arthralgia. Following further investigation, AS was diagnosed as the underlying cause of amyloidosis manifesting as a nephrotic syndrome.

Streszczenie: Amyloidoza AA stanowi potencjalnie poważne powikłanie przewlekłych chorób zapalnych. Jedną z możliwych przyczyn tej choroby jest zesztywniające zapalenie stawów kręgosłupa (ZZSK). Amyloidoza to stosunkowo rzadkie powikłanie wspomnianej spondyloartropatii. Opóźnienie diagnozy i wdrożenia leczenia choroby podstawowej może prowadzić do uszkodzenia przez złogi amyloidu wielu narządów – najczęściej nerek. Zajęcie nerek, które zwykle objawia się białkomoczem oraz zespołem nerczycowym (ZN), może prowadzić do ich niewydolności. Przedstawiamy opis przypadku 45-letniego pacjenta, u którego 25-letni wywiad nieleczonego ZZSK skutkował rozwojem amyloidozy nerek i koniecznością terapii nerkozastępczej. W trakcie diagnostyki pacjent początkowo negował dolegliwości ze strony stawów. Rozpoznanie ZZSK postawiono dopiero w ramach poszukiwania przyczyn amyloidozy AA przebiegającej pod postacią zespołu nerczycowego.

Keywords: haemodialysis, nephrotic syndrome, AA amyloidosis, ankylosing spondylitis, heparin induced thrombocytopenia (HIT).

Słowa kluczowe: dializoterapia, zespół nerczycowy, amyloidoza AA, zesztywniające zapalenie stawów kręgosłupa (ZZSK), małopłytkowość poheparynowa (HIT).

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Introduction

AA amyloidosis is the second most common type of systemic amyloidosis in Western countries, resulting from chronic inflammation. Its etiopathogenesis is not yet well understood. It is assumed that abnormal protein deposits build up in the extracellular matrix, the precursor of which in this case is the acute phase protein serum amyloid A (SAA). These deposits can disturb the function of many organs: usually the kidneys, then sequentially the gastrointestinal tract and the heart [1]. In a nationwide Japanese study involving 199 patients, as many as 76.4% developed a kidney failure, 39.7% presented gastrointestinal symptoms, and 11.6% suffered from a heart failure [1]. The symptoms most often result from kidney involvement and progress to nephrotic syndrome and progressive kidney failure. An important cause of inflammation leading to AA amyloidosis is the range of rheumatic disorders, especially rheumatoid arthritis (RA) [1].

Data on the incidence of AA amyloidosis and the assessment of how various aetiologies contribute to it vary depending on the region of origin. In Japan, rheumatic disorders accounted for nearly 70% of AA amyloidosis cases in 2012–2014 [1]. In developing countries, it is more

often caused by infectious diseases [2]. A greater association of rheumatic diseases with the incidence of amyloidosis results also from the limited availability of modern therapies for these diseases. In Europe, the epidemiology of the disease has changed over the last quarter century, which is attributable to the spread of effective treatment, including biological treatment [3]. The data from a British reference centre show that there has been a significant decline in the contribution of rheumatic disorders, such as RA and juvenile idiopathic arthritis, due to the incidence of AA amyloidosis over the past quarter century [3].

Renal diseases are thought to be more common in patients with AS than in the general population [4]. A retrospective study using data from the Quebec Provincial Patient Registry (1996–2006) found that these diseases occurred in 3.4% of men and 2.1% of women with AS, with a risk approximately 70% higher than in the control group (95% confidence interval (CI): 1.5-2.0). Renal amyloidosis occurred about six times more often in patients with AS than in the general population (95% CI: 2.0-18.0), while still remaining a relatively rare complication (prevalence was 0.1%) [5]. Similarly, in a retrospective study based on patient databases in Israel, amyloidosis was over six times more common in AS patients than in the general population (95% CI: 2.43-15.60), while remaining a rare complication, with an incidence rate of 2.15/10,000 patient years [6].

Case study

A 45-year-old man, a refugee from Ukraine, was admitted to the Department of Nephrology at the Military Institute of Medicine (WIM) in March 2022 for massive oedema and urosepsis of *Escherichia coli ESBL* aetiology. Incomplete history taking showed that the patient had had a cystoprostatectomy performed in Ukraine in January 2022 for an unclear reason. The procedure was complicated by a suprapubic abscess with a fistula. Then the patient required bilateral nephrostomies in February 2022 due to urinary retention. The patient had very sparse documentation and denied the conditions suggested in it. During the rheumatology consultation, he also reported reactive arthritis, although he initially denied joint complaints.

During the stay at the Department, the patient was diagnosed with the nephrotic syndrome and G4 stage chronic kidney disease with secondary complications in the form of anaemia and calcium-phosphate disorders.

The patient underwent the targeted anti-infective treatment (urine cultures showed growth of *E. faecium* and *E. faecalis*, blood cultures showed *E.coli ESBL*+) as well as symptomatic treatment for nephrotic syndrome and renal failure. Due to increasing renal parameters and persistent profound hypoalbuminemia, a decision was made to administer 6 pulses of 250 mg of Solu-Medrol intravenously, with continued oral prednisone at a daily dose of 30 mg. Since no satisfying effect was achieved, cyclosporine was added at a dose of 250 mg/day (the determined cyclosporine concentration was 68 ng/ml). Throughout the diagnostic process, elevated serum levels of SAA protein (32.2 mg/dl with laboratory norm < 0.64 mg/dl) and B2-microglobulin (7.2 ug/ml with norm 1.09-2.53 ug/ml) were detected.

During a subsequent stay at the Department, the diagnosis of amyloidosis was continued. A biopsy of the lower lip with salivary gland was performed, and histopathological examination confirmed the presence of amyloid deposits. The tests did not detect any elevated concentrations of immunoglobulin light chains in the serum or urine, or the presence of monoclonal protein in the serum and urine immunofixation, which excluded monoclonal gammopathy and AL amyloidosis. A diagnosed elevated serum SAA protein level was indicative of AA amyloidosis, being a complication of a long-term inflammatory process.

Given the 25-year history of reactive arthritis without any treatment, the rheumatology diagnostic process was broadened to include imaging examinations. X-rays showed calcifications in the ligaments in the neck, status post compression fracture of the Th12 vertebra and signs of bilateral *sacroilitis*. Since the imaging raised the suspicion of AS, the HLA B27 was also determined, giving positive

Table. Panel of laboratory tests during the patient's first and second stay at WIM.

	1st hospital stay (March)	2nd hospital stay (May)	Reference normal range
Protein in daily urine collection [mg/24h].	16184	9904	< 150
Serum albumin [g/dl]	1.4	1.6	3.9–4.9
Total cholesterol [mg/dl]	347	291	35–165
Triglycerides [mg/dl]	184	319	120–200
Creatinine [mg/dl]	3.1	4	07–1.2
EGFR [ml/min/1.73 m2]	23	17	
Uric acid [mg/dl]	8	10.6	3.4–7
Urea [mg/dl]	48	176	18–55
Ionized calcium [mmol/l]	1.1	1.11	1.15–1.29
Serum phosphate [mg/dl]	6.2	7.6	2.6–4.5
Haemoglobin [g/dl]	9.5	10.2	13.5–17

results. The presence of sacroilitis symptoms and a positive HLA B27 test allowed the diagnosis of AS according to the ASAS 2010 criteria.

Due to the progression of the chronic kidney disease, persistent destructive proteinuria and lack of effective therapeutic options, a renal replacement therapy was implemented in the form of haemodialysis. The patient required modification of the anticoagulant treatment due to suspected heparin-induced thrombocytopenia (HIT): enoxaparin was discontinued and fondaparinux was included. Due to the patient's tendency to persistent hypotension, midodrine was introduced. Due to persistent hyperuricemia a decision was made to add allopurinol. Cyclosporine was discontinued, and a dose of prednisone was reduced until it was discontinued. The consulting rheumatologists considered including a TNF-*alfa* inhibitor drug after controlling the nephrotic syndrome, recurrent urinary tract infections and improving renal function, which they ultimately decided not to do.

Discussion

AS is more common in men, and symptoms tend to appear in young adults, which is consistent with the history of the patient, who admitted that his joint pain had appeared around the age of 20. It is not known whether from the beginning the complaints had been caused by AS, which had been misdiagnosed as reactive arthritis. Indeed, it is estimated that about 20% of patients with reactive arthritis and HLA B27 develop AS within 10 years of onset [7].

The reason for the Ukrainian patient's decision to undergo such a radical urological procedure is unknown and may have significantly influenced the rapid course of the disease. The patient claimed to have been treated for a bladder tumour. He did not have a histopathological examination result. He also did not know whether such a test had been performed at all. Radical cystectomy, which includes resection of the prostate, is performed in the case of muscle-invasive bladder cancer (MIBC) at stages T2-T4a, N0-Nx, M0 and some other forms of bladder cancer when less invasive methods have failed [8]. A neoplasm of this organ affects patients over 55 years of age in more than 90% of cases. [9]. In a Swedish study of a patient registry, only 5.6% of patients with bladder cancer infiltrating the muscularis were younger than 50 [10]. This type of cancer is therefore diagnosed rarely in the age group to which the patient in question belonged.

Another possible explanation for radical cystectomy in a relatively young patient with advanced renal amyloidosis could be the involvement of the lower urinary tract. Amyloidosis of the urinary bladder is rare, more often in the primary form of the disease. Its first symptom is usually haematuria [11]. The radiological and cystoscopic picture may resemble a bladder neoplasm [12]. Cases of amyloidosis of the ureter, urethra, prostate, and seminal vesicles have also been described [11]. Droghetti et al. state that only 34 cases of AA bladder amyloidosis have been described to date (as of 2020), including two coexisting with AS [13]. Theoretically, the patient's renal amyloidosis could also be accompanied by the involvement of other genitourinary organs and mimic cancer. However, bladder or prostate involvement is very rare, more often associated with the primary form of the disease, and its treatment usually begins with less radical methods, including trans urethral resection of the lesion (TUR) or dimethyl sulfoxide (DMSO) therapy [14]. A possible history of bladder amyloidosis is therefore unlikely in the patient and would only explain radical cystoprostatectomy if other therapeutic approaches were exhausted or the disease were significantly advanced. In the absence of a histopathological result, it cannot be definitively determined why this procedure had been performed on the patient. It cannot be ruled out that the procedure was inappropriate.

The best standard of AA amyloidosis treatment is the treatment of the underlying disease. Since there are no drugs available for amyloid deposits, the main therapeutic goal is to inhibit the production of the amyloidogenic protein: SAA. SAA is produced by hepatocytes, macrophages, endothelial and smooth muscle cells under the influence of pro-inflammatory cytokines, especially tumour necrosis factor (TNF) alpha, interleukin 1 (IL-1) and interleukin 6 (IL-6) [15]. Although treatment is primarily aimed at inhibiting the formation of new deposits, some studies indicate that such deposits may undergo partial regression in patients with maintained low levels of the SAA protein and that such patients live longer [16].

Anti-TNF-*alfa* antibodies and anti-receptor antibodies for IL-6 (tocilizumab) are used in amyloidosis in the course of rheumatic disorders. Studies indicate that these drugs effectively lower serum SAA protein concentrations [17, 18]. Their use in amyloidosis in the course of AS is based on case reports of the improvement in renal function in patients with amyloidosis in the course of AS [19, 20] and on extrapolation of the results of patients with AA amyloidosis in the course of rheumatoid arthritis, whose contribution to the epidemiology of this disease is greater than that of AS [16]. Unfortunately, in the patient described, recurrent urinary tract infections and the stage of the disease are contraindications to biological treatment.

In the era of biological treatment, renal amyloidosis is a rare complication of AS. Within a single-centre Finnish retrospective study the researchers analysed the causes of death in patients with AS between 1961 and 1969, before the introduction of biological medications, and found that renal amyloidosis had accounted for as many as 13% of deaths in AS [21]. In a more recent Finnish study, it was observed that in the first years of the 21st century, there had been a decrease in the number of new patients requiring renal replacement therapy due to amyloidosis in the course of rheumatic disorders [22]. In the described case, the diagnosis of AS was given as a result of searching

for the cause of nephrotic syndrome, a long-term complication of the underlying disease. The patient's 25-year history of untreated ankylosing spondylitis resulted in chronic kidney disease with the need to implement renal replacement therapy. The course of the patient's disease shows how extremely important it is to diagnose this disease early and implement appropriate effective treatment.

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INTRACRANIAL STENTING AS A RESCUE THERAPY AFTER UNSUCCESSFUL MECHANICAL THROMBECTOMY FOR AN INTRACRANIAL ATHEROSCLEROSIS-RELATED ACUTE ISCHEMIC STROKE

Wewnątrzczaszkowa implantacja stentu jako metoda ratunkowa po nieskutecznej trombektomii mechanicznej u pacjenta z podejrzeniem miażdżycowego zwężenia tętnicy mózgowej

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Abstract: Mechanical thrombectomy is a highly effective stroke therapy. Nonetheless, the routine methods (aspiration and/or stent retriever) sometimes fail to achieve satisfactory reperfusion. The treatment strategy in such cases is not yet strictly defined. This is a case of an unsuccessful mechanical thrombectomy for an intracranial atherosclerosis--related ischaemic stroke with an occlusion in the M1 segment of the left-middle cerebral artery. During the procedure, a full reperfusion was reached, but a persistent narrowing of the artery with a subsequent reocclusion was observed. The operator decided to perform rescue intracranial stenting combined with the administration of glycoprotein IIb/IIIa inhibitor (GPI). The procedure resulted in a full and lasting reperfusion. On discharge the patient presented a significant neurological improvement. At a 3-month follow-up, he only had minor neurological symptoms that did not result in a disability of any kind (mRS 1) and at the 1-year follow-up he showed no neurological symptoms at all (mRS 0). This case indicates that rescue stenting combined with GPI administration might be safe and beneficial in patients treated for an intracranial atherosclerosis-related acute ischaemic stroke with an unsuccessful mechanical thrombectomy.

Streszczenie: Trombektomia mechaniczna jest zabagliem o wysokiej skuteczności w leczeniu udaru mózgu. Mimo to, zdarzają się przypadki, kiedy użycie standardowych metod, czyli aspiracji i/lub stent retrievera, nie pozwala na osiągnięcie rekanalizacji. Obecnie brakuje jednak wytycznych postępowania w przypadku nieskutecznej trombektomii. Prezentowany przypadek dotyczy nieskutecznej trombektomii u pacjenta z udarem niedokrwiennym na tle miażdżycowego zwężenia tętnicy środkowej mózgu lewej w jej segmencie M1. W trakcie zabiegu, mimo udanego udrożnienia naczynia, obserwowano przetrwałe zwężenie z postępującą stopniową reokluzją w kontrolnych badaniach angiograficznych. W trakcie zabiegu, mimo udanego udrożnienia naczynia, obserwowano przetrwałe zwężenie z postępującą stopniową reokluzją w kontrolnych badaniach angiograficznych. Osiągnięto całkowitą i trwałą rekanalizację lewej tętnicy środkowej mózgu. Pacjent do wypisu ze szpitala osiągnął znaczną poprawę stanu neurologicznego. W badaniu kontrolnym po 3 miesiącach obecne były jedynie nieznaczne deficyty neurologiczne niewpływające istotnie na jakość życia pacjenta (mRS 1), a po roku od udaru objawy wycofały się całkowicie (mRS 0). Przedstawiony przypadek wskazuje, że u pacjentów z miażdżycopochodnym tłem udaru i nieskutecznością trombektomii, ratunkowa implantacja stentu połączona z infuzją GPI może być skuteczną i bezpieczną metodą postępowania.

Keywords: ischaemic stroke, mechanical thrombectomy, intracranial stenting, intracranial atherosclerosis.

Słowa kluczowe: udar niedokrwienny mózgu, trombektomia mechaniczna, stentowanie wewnątrzczaszkowe, miażdżyca tętnic wewnątrzczaszkowych.

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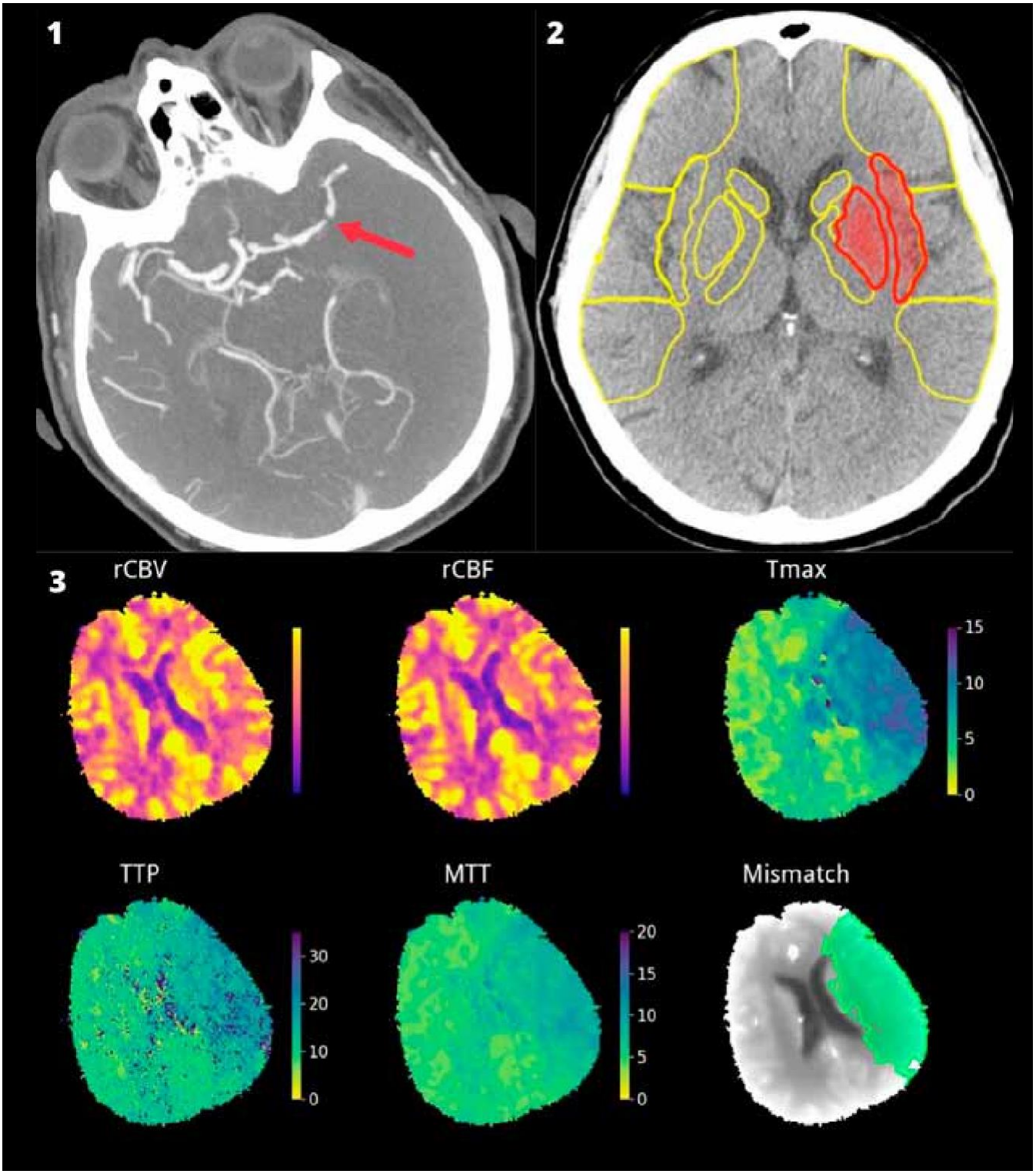
Introduction

In addition to thrombolytic therapy, a mechanical thrombectomy (MT) is the first-line treatment for patients with an ischaemic stroke secondary to a large vessel occlusion [1-3]. Successful recanalization is defined as procedures completed with a flow rated 2b or 3 on the *modified treatment in cerebral ischaemia* (mTICI) scale [2]. According to various data, up to 25% of the procedures performed with the routine methods (aspiration and/or

Figure 1. (1) Axial view of an CT angiography examination performed during establishing MT eligibility. A short segment of contrast loss (red arrow) is visible, which corresponds to a permeable thrombus located in the midsection of the M1 segment of the left middle cerebral artery. (2) Axial view from computed tomography (CT) in the native phase. Areas highlighted in red indicate structures of possible ischaemic lesions (ASPECTS 8). (3) Computed tomography: brain perfusion examination analysed with the Brainomix 360 software. The areas of the left cerebral hemisphere marked in green as *mismatch* were recognized by the program as a penumbra area (Tmax > 6 seconds) of 157 millilitres. Explanation of abbreviations: CBV: *cerebral blood volume*; CBF: *cerebral blood flow*; TTP: *time to peak*; MTT: *mean transit time*.



stent retriever) fail to achieve this result [4–7]. At the same time, there are no clear guidelines as to what treatment should be used in cases of an unsuccessful MT, which is associated with a significantly worse prognosis for patients [8]. Studies confirm that long-term success for an MT depends mainly on the effectiveness of blood flow

restoration and the duration of the ischaemia [9]. A failed thrombectomy may result from atherosclerosis of the cerebral arteries, and balloon angioplasty, stent implantation, glycoprotein IIb/IIIa inhibitor (GPI) delivery or various combinations of these methods are used as a rescue therapy after a failed MT [10-11].

Case study

A 71-year-old man was admitted to the Invasive Stroke Treatment Centre on an emergency basis due to symptoms of left hemisphere stroke lasting for 2 hours in the form of moderate motor aphasia, central palsy of nerve VII of the right hemisphere, right-sided unilateral hemiamblyopia and moderate right limb paresis. The neurological condition on admission was assessed as score 8 on the National Institute of Health Stroke Scale (NIHSS). Imaging diagnostics included head computed tomography without contrast enhancement (CT), CT angiography of the cephalic and intracranial arteries and CT perfusion study. The CT scan excluded intracranial haemorrhage and showed no ischaemic lesions: score 10 on the Alberta Stroke Program Early CT Score (ASPECTS). The CT angiography showed subtotal occlusion of the left middle cerebral artery (LMCA) in the M1 segment (Fig. 1).

Assessment of the extent of the stroke focus was supported by the use of Brainomix 360 e-Stroke Suite (Brainomix Limited, Oxford, UK) software using artificial intelligence. On the basis of the CT in the native phase, the program rated the ischaemic lesions as 8 on the ASPECTS scale (the volume of deeply hypodense areas was 12 ml), while the CT perfusion highlighted an extensive penumbra area of 157 millilitres covering the frontal lobe, parietal lobe, temporal lobe and nucleus accumbens without ischaemic lesions made (core 0 ml) (Fig. 1). The collateral circulation was scored as 2 on the CTA-CS scale (*Computed Tomography Angiography– Collateral Score*) [12]. A positive history was present of hypertension, chronic ischaemic heart disease, hypercholesterolemia, and paroxysmal atrial fibrillation. Due to chronic anticoagulant therapy with apixaban, the patient was disqualified from thrombolytic therapy. At the same time, the patient was qualified for MT.

On baseline cerebral angiography, a permeable thrombus was observed in the M1 segment of the left middle cerebral artery (LMCA) (Fig. 2).

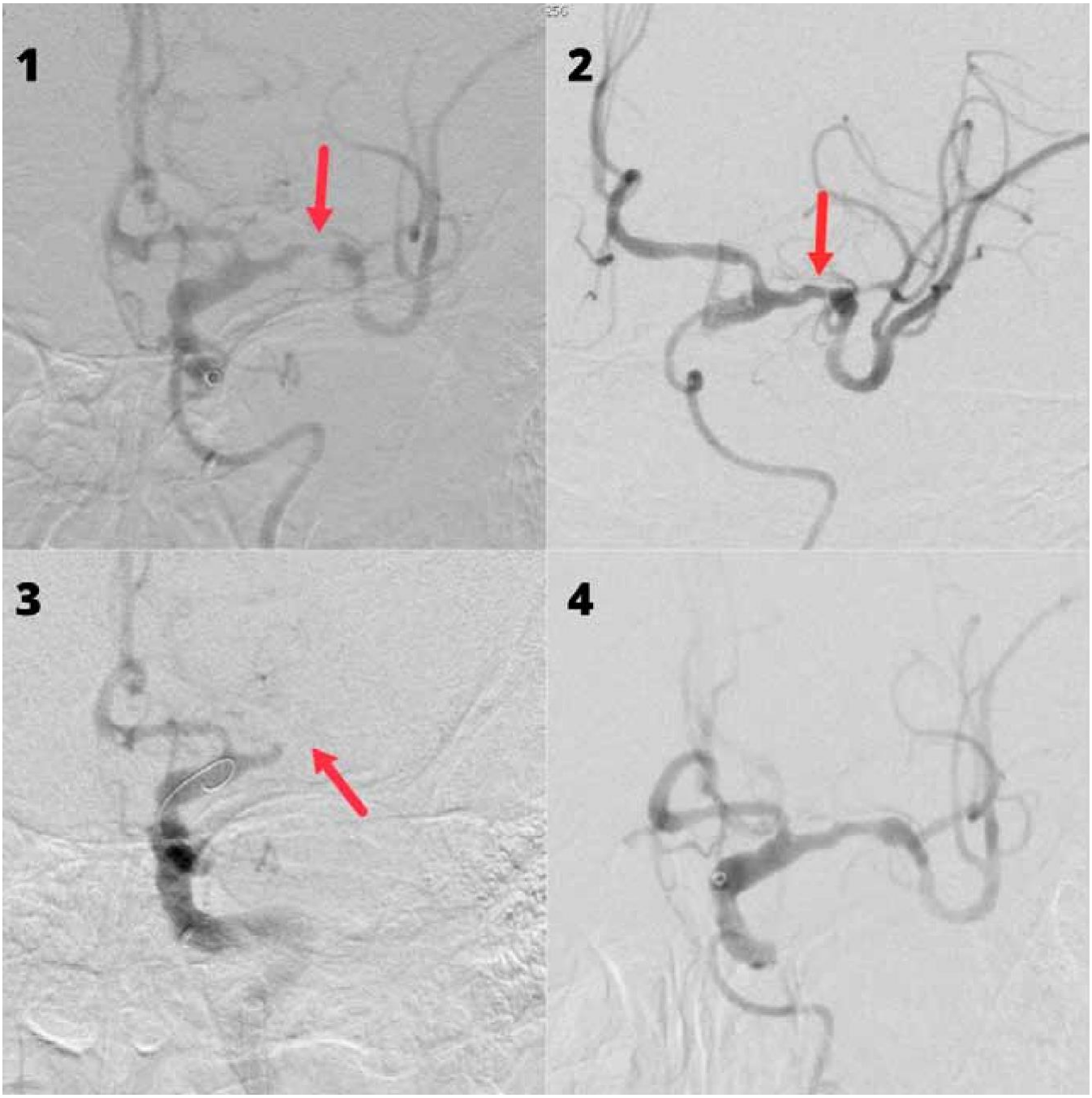
In the first stage of the procedure, the Solumbra technique was performed twice, using a React 71 aspiration catheter (Medtronic, CA, USA) and a stent retriever (SR) Tigertriever XL (Rapid Medical, Israel). Subsequently, a decision was made to change the instrumentarium and perform an MT with a Catalyst 5 aspiration catheter (Stryker, MI, USA) and a 4x20mm SR Solitaire (Medtronic, CA, USA) achieving vessel occlusion – mTICI 3. On the follow-up angiography, persistent stenosis with progressive gradual reocclusion was observed at the site of the performed MT (M1 segment of the LMCA) (Fig. 2). There was a suspicion of *intracranial atherosclerosis* (ICAS) of the middle segment of the M1 LMCA. Trial catheter deployment at the site of the stenosis resulted in an improved flow on the follow-up examination. A follow-up 3D CT scan excluded the presence of MT haemorrhagic complications. A decision was made to perform salvage implantation of a 4x30 mm Acclino flex radial-expandable cerebral stent (Acandis GmbH, Germany). The patient was then administered an intra-arterial bolus of the antiplatelet drug Integrilin (eptyfibatide) at a dose of 180 ug/kg b.w. and an intravenous infusion of 2 ug/kg b.w./min was started. Eventually, complete and permanent recanalization of the LMCA was achieved: mTICI 3. After the procedure, the intravenous infusion of eptyfibatide was continued for 24 hours. After its completion, the patient was ordered dual antiplatelet therapy with acetylsalicylic acid (150 mg 1x1) and clopidogrel (75 mg 1x1). A follow-up CT scan performed within 24 hours of the procedure showed no haemorrhagic complications. Dual antiplatelet therapy was maintained for 3 months after stent implantation, then one antiplatelet drug was continued permanently.

During the follow-up in the Stroke Subdepartment, the patient's neurological condition improved significantly. At discharge, only nominal aphasia persisted (NIHSS 1). A good long-term treatment effect was also achieved. In a follow-up neurological examination 3 months after the treatment, only minor neurological deficits, which did not significantly affect the patient's quality of life, persisted, corresponding to grade 1 on the modified Rankin Scale (mRS), and in a follow-up examination 12 months after the ischaemic stroke, the patient showed no neurological symptoms (mRS 0). Due to the good clinical outcome, no further follow-up imaging studies were performed.

Discussion

In this case, the standard methods of mechanical thrombectomy with aspiration and stent retriever using the SOLUMBRA technique provided only temporary blood flow restoration. Reocclusion of the treated vessel and gradual thrombectomy occurred at the site of stenosis of the left middle cerebral artery. In the literature, there are descriptions of a similar course of MT with only temporary unblocking of the cerebral artery [9, 10]. Such a situation most often results from the presence of atherosclerotic plaque at the site of occlusion or local endothelial damage [10]. The atherosclerotic background of the stroke in the described case is evidenced by the uneven stenosis of the middle M1 segment of the left middle cerebral artery visible in angiographic images with its subsequent poststenotic dilatation (Fig. 2). It should be mentioned that there were no signs suggestive of the presence of a calcified atherosclerotic plaque in this location on the CT in the native phase or the CT angiography. Instrumentarium deformation (compression of stent retrievers) was also observed at the site of vessel occlusion during the thrombectomy procedure. Due to the lack of randomised

Figure 2. Angiographic images obtained during the procedure. (1) Initial angiographic image showing a "permeable" thrombus in the M1 segment of the LMCA (red arrow). (2) Image after mechanical thrombectomy showing the transiently achieved recanalization of the vessel: mTICI 3. The red arrow points to the site of stenosis with postenotic dilatation of the vessel present immediately behind. (3) Image of spontaneous complete occlusion of the LMCA at the site of the previously observed stenosis. (4) Final result of the procedure (mTICI 3) after implantation of the Acclino flex cerebral stent.



trials, no clear guidelines are available for the management of an ischaemic stroke secondary to ICAS and ineffective MT, but some studies, as well as expert consensus from the *European Stroke Organisation* (ESO), indicate that rescue intracranial stenting and administration of a GPI, such as eptifibatide, may be beneficial in similar cases [9-10, 13]. However, such management requires intraoperative confirmation of the absence of haemorrhagic complications. Rescue intracranial stenting produces good clinical outcomes as long as complete and durable recanalization is achieved. The risk of thrombosis in a cerebral stent implanted as a rescue therapy is also an important limitation [9]. Temporary IV or IA GPI infusion and appropriate long-term antiplatelet therapy are required to maintain stent patency. There are no published guidelines on this issue. Determining the optimal model of both perioperative and long-term antiplatelet therapy presents a multifaceted clinical challenge. This is influenced both by the complex profile of patients with ischaemic stroke (multiple co-morbidities and medications taken), as

well as by stroke treatment that includes fibrinolytic therapy in the first line. The use of additional antiplatelet drugs may be associated with an increased risk of haemorrhagic complications. In the available literature, we can find data indicating the benefits of perioperative GPI administration in terms of both the technical success of the procedure and long-term outcomes. Rescue intracranial stenting in combination with intraoperative intra-arterial bolus, 24-hour IV GPI infusion of and subsequent oral antiplatelet therapy leads to a significantly higher rate of successful recanalization and a favourable clinical outcome, including maintenance of patency of the implanted stent into the cerebral artery. At the same time, such management does not cause a statistically significant increase in the rate of intracranial bleeding [10]. In the case described above, the use of a non-standard surgical technique allowed the achieving of a permanent reperfusion during a procedure which, if only standard methods and techniques had been used, would have ended in complete occlusion of the middle cerebral artery and extensive ischaemic stroke. A very good angiographic effect of the procedure was finally achieved (mTICI 3), which directly influenced the patient's subsequent treatment and rehabilitation process, allowing a satisfactory clinical outcome in the form of the disappearance of the most neurological symptoms and no disability in the follow-up after 3 months (mRS 1) and after one year (mRS 0)

Conclusions

In patients with atherothrombotic stroke, rescue intracranial stenting combined with GPI administration appears to be a rational management method in the case of unsuccessful mechanical thrombectomy. The appropriate regimen of perioperative antiplatelet therapy must be selected individually, due to the considerable diversity of patients undergoing the procedure and the possibility of MT haemorrhagic complications.

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REPORT FROM THE CONFERENCE: "NATIONAL FORUM FOR THE EXCHANGE OF EXPERIENCE AND GOOD PRACTICES BETWEEN THE MILITARY INSTITUTE OF MEDICINE AND ENTITIES COOPERATING WITH IT IN COMBATING THE EFFECTS OF COVID-19"

Sprawozdanie z konferencji pn. „ogólnopolskie forum wymiany doświadczeń i dobrych praktyk między wojskowym instytutem medycznym a współpracującymi z nim podmiotami w zwalczaniu skutków covid-19"

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Abstract:

On 17 November 2022, the Warsaw conference "National Forum for the exchange of experiences and good practices between the Military Institute of Medicine and entities cooperating with it in combating the effects of COVID-19" was organized by the Department of Public Health of Epidemiology and Vaccinology together with the Vaccination Centre and the Regional Medical Supply Base of the Military Institute of Medicine - National Research Institute.

Streszczenie:

17 listopada 2022 r. odbyła się w Warszawie konferencja pn. „Ogólnopolskie Forum wymiany doświadczeń i dobrych praktyk między Wojskowym Instytutem Medycznym a współpracującymi z nim podmiotami w zwalczaniu skutków COVID-19" zorganizowana przez Zakład Zdrowia Publicznego, Epidemiologii i Wakcynologii z Poradnią Szczepień i Rejonową Bazą Zaopatrzenia Medycznego Wojskowego Instytutu Medycznego – Państwowego Instytutu Badawczego.

Keywords: medicine, conference, COVID-19, vaccinations.

Słowa kluczowe: medycyna, konferencja, COVID-19, szczepienia.

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In Warsaw, on 17 November 2022, there took place the "National Forum for the exchange of experience and good practices between the Military Institute of Medicine and entities cooperating with it in combating the effects of COVID-19" conference, organized by the Department of Public Health, Epidemiology and Vaccinology with the Vaccination Outpatient Clinic and the District Medical Supply Depot of the Military Institute of Medicine – National Research Institute.

The conference was held under the Honorary Patronage of Mariusz Błaszczak, Deputy Prime Minister, Minister of National Defence, and Małgorzata Gosiewska, Deputy Speaker of the Sejm of the Republic of Poland.

The conference aimed at sharing experience and good practices between the Military Institute of Medicine and the entities cooperating with it in combating the effects of COVID-19 during the subsequent waves of the epidemic from March 2020 to the present. As a leader in the fight against the effects of COVID-19, the Military Institute of Medicine – National Research Institute has established effective cooperation during the epidemic with a number of medical entities from the 1st Preventive and Curative Division.

Figure 1. Speech by Lt Gen. Prof. Grzegorz Gielerak MD, PhD, Director of the Military Institute of Medicine – National Research Institute.

The forum provided an opportunity to present the achievements of Military Institute of Medicine – National Research Institute in the fight against COVID-19. We presented the self-designed projects and solutions that we had put into practice during the 2-year epidemic experience:

- strategy and organization of vaccinations against COVID-19 in the 1st Preventive and Curative Division,
- medical experience gained during the COVID-19 epidemic in Lombardy (Italy), Slovenia and the USA,
- principles of operation of the opened Modular and Temporary Hospital and Isolatorium of the Military Institute of Medicine,
- organisation and supervision of vaccinations against COVID-19 in mobile centres in the 1st Preventive and Curative Division within the framework of the Ministry of National Defence campaign "Become a soldier of the Republic of Poland" at military picnics (12 locations),
- a concept of cooperation with medical entities, Provincial Occupational Medicine Centre Modlin, military clinics from the area of the 1st Preventive and Curative Division in combating the effects of COVID-19,
- identification of the most appropriate tools and strategies that were used to combat the effects of COVID-19 in the 1st Preventive and Curative Division after analysis of the content presented by the invited entities.

The subject areas included:

1. The epidemic situation in Poland and around the world.
2. Participation of the Preventive and Curative Divisions of the Armed Forces in combating COVID-19 in areas of responsibility.
3. Vaccinations as an important link in combating and reducing the spread of COVID-19.
4. Participation of the Military Institute of Medicine in the Polish Medical Mission in Italy, USA, and Slovenia during the epidemic crisis.
5. Modular and Temporary Hospital Okęcie of the Military Institute of Medicine as a tool in combating COVID-19.
6. Participation of the Outpatient Specialist Care and Primary Health Care during subsequent waves of the COVID-19 pandemic.
7. Medical support of the Polish Military Contingents during the COVID-19 epidemic.
8. Provincial Occupational Medicine Centres and Epidemiological Response Centres of the Polish Armed Forces as an important link in the fight against infectious diseases.
9. Involvement of the Territorial Defence Forces in combating the effects of COVID-19.
10. Did the current structure of Sanitary and Epidemiological Stations work well during the COVID-19 pandemic?

Figure 2. From the left: Col. Alicja Trochimiuk MD, PhD, (Director of the Military Institute of Aviation Medicine), Col. Artur Bachta (Deputy Head of the Military Institute of Medicine – National Research Institute, Commandant of the Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine – National Research Institute), Małgorzata Złotkowska MA (Head of the Director's Office of the Military Institute of Medicine – National Research Institute), Col. Jarosław Kowal MD (Deputy Director of the Military Institute of Medicine – National Research Institute in charge of the 1st Preventive and Curative Division), Reserve Col. Barbara Betiuk MD, PhD (Head of the Vaccination Outpatient Clinic of the Military Institute of Medicine – National Research Institute), Col. Tadeusz Nierebiński MD (Chief Sanitary Inspector of the Polish Armed Forces), and Col. Michał Marciniak MSc, Eng (Junior Assistant at the Military Institute of Medicine – National Research Institute).

11. Activities of the Field Ordinariate during the COVID-19 epidemic.
12. The fight against COVID-19 in the context of public health.

The event was attended by: Małgorzata Gosiewska (Deputy Speaker of the Polish Sejm), Lt Gen. Wiesław Kukuła (Armed Forces Branches General Commander), Minister Krzysztof Saczka (Chief Sanitary Inspector), Under-secretary of State Maciej Merkisz (Deputy Chief Sanitary Inspector), Col. Tadeusz Nierebiński (Chief Sanitary Inspector of the Polish Armed Forces), Col. Alicja Trochimiuk MD, PhD (Director of the Military Institute of Aviation Medicine), Prof. Marek Sobczak (Director of the Military Institute of Hygiene and Epidemiology), Col. Aleksander Michalski PhD in Biology (Commander of the 1st Military Teaching Hospital with Polyclinic of Independent Public Health Care Unit in Lublin), Maciej Oleszczak MD, PhD (Representative of the 7th Naval Hospital with an Outpatient Clinic in Gdańsk), and Col. Robert Gregulski (Commander of the 6th Military Hospital in Dęblin), Władysław Wójcik MD (Director of the Central Military Health Service Centre "CePeLek"), Magdalena Kaczmarek MSc (Director of the Provincial Sanitary and Epidemiological Station in Warsaw), and Col. Przemysław Makowski (Commander of the Military Preventive Medicine Centre in Modlin).

"We hope that this pandemic has passed into history. We remember our 2-year struggle from the moment the virus was detected, the trauma we all experienced, the reorganisation of the state functioning, but also the tragic dimension of this epidemic related to the excessive number of deaths. We still suffer the consequences of the pandemic, known as the "health debt", which we will face and pay off for many years to come. The most important thing is the ability to draw conclusions. We cannot predict what the next crisis will look like. The old truth says that 'generals are always prepared to fight the last war'. I hope that with this conference we will prove that the current generals are ahead of the reality, said Lt Gen. Prof. Grzegorz

Gielerak MD, PhD, Director of the Military Institute of Medicine – National Research Institute.

“What was lacking in the discussion about lessons learned after the COVID-19 pandemic was the elevation of health care professionals, and a demonstration of their role. We are not able today to count the lives you saved but be sure that we remember and will not forget,” said Lt Gen. Wiesław Kukuła, Commander of the Territorial Defence Forces.

“We all had to fight this battle,” said Minister Krzysztof Saczka, Chief Sanitary Inspector.

“The whole battle for human life and health is an incredible effort of medical and non-medical personnel,” stressed Col. Tadeusz Nierebiński, Chief Sanitary Inspector of the Polish Armed Forces.

Representatives of military hospitals, military institutes of medicine, the Armed Forces Central Epidemiological Surveillance Centre, Military Centre for Preventive Medicine, Territorial Defence Forces, and the Field Ordinariate discussed about tools and methods in the fight against the COVID-19 epidemic, as well as the support structure for combating the COVID-19 epidemic.

Analysis of the experience of a number of entities led to the identification of effective and implementable optimal strategies in a public health emergency. This scope of the debate made it possible to develop modern tools for responding to a public health emergency as fully and comprehensively as possible, which may help limit the spread of future health crises.

REPORT FROM THE SCIENTIFIC AND TRAINING CONFERENCE NEPHROCARDIOLOGY 2023

Sprawozdanie z konferencji naukowo-szkoleniowej Nefrokardiolgia 2023

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Abstract: The scientific and educational conference, Nephrocardiology 2023, took place on April 21-22 at the Branicki Palace in Białystok. The conference consisted of six sessions, involving discussions related to the pathomechanisms and the latest therapeutic possibilities for cardiovascular complications in patients with chronic kidney disease. During the conference, non-renal aspects of sodium-glucose cotransporter 2 (SGLT2) inhibitors were presented, new methods of hyperlipidemia treatment were discussed, and the issue of obesity and metabolic syndrome in the context of qualification for kidney transplantation was addressed. There were also topics presented related to genetics - the genetic causes of obesity and the issue of metabolism programming. The relationship was discussed between dysbiosis and arterial hypertension, as well as the pathomechanism and the consequences of congestive nephropathy. Additionally, estimates of the costs of cardiovascular care in dialysis patients were presented, as well as the potential for individualizing haemodialysis therapy in the future. New methods of vasculitis treatment were also presented.

Streszczenie: Tegoroczna konferencja naukowo-szkoleniowa Nefrokardiologia 2023 odbyła się w dniach 21-22 kwietnia 2023 r. w Pałacu Branickich w Białymstoku. Składała się z sześciu sesji, podczas których omówiono patomechanizmy i najnowsze możliwości terapeutyczne powikłań sercowo-naczyniowych u pacjentów z przewlekłą chorobą nerek. Podczas konferencji przedstawiono pozanerkowe aspekty działania inhibitorów kotransportera glukozowo-sodowego 2 (SGLT2), omówiono najnowsze dostępne metody leczenia hyperlipidemii, poruszono problem otyłości i zespołu metabolicznego w kontekście kwalifikacji do przeszczepienia nerki. Nie zabrakło również tematów dotyczących genetyki – przedstawiono genetyczne przyczyny otyłości i problem programatyki metabolizmu. Omówiony został również związek dysbiozy z nadciśnieniem tętniczym oraz patomechanizm i konsekwencje nefropatii zastoinowej. Ponadto przedstawiono szacunkowe koszty opieki kardiologicznej u pacjentów dializowanych oraz możliwości indywidualizacji hemodializoterapii w przyszłości. Przedstawiono również nowe metody leczenia zapaleń naczyń.

Keywords: nephrocardiology, conference.

Słowa kluczowe: nefrokardiologia, konferencja.

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On 21–22 April 2023, a scientific and educational conference concerning nephrocardiology was held in the beautiful scenery of the Branicki Palace in Białystok. The meeting was held under the scientific patronage of: His Magnificence, Rector of the Medical University of Białystok Prof. Adam Krętowski PhD and the Department of Nephrology and Transplantation with Dialysis Centre of the Medical University of Białystok, whose Head is Prof. Barbara Naumnik PhD, holding the function of Chairwoman of the Conference's Scientific Committee.

The scientific meeting in Białystok consisted of six sessions devoted to current issues in nephrocardiology. Since the main cause of morbidity and mortality in patients with renal dysfunction is cardiovascular complications, cooperation between cardiologists and nephrologists, setting common goals of therapy and guidelines for management, are becoming indispensable in modern medicine. The combination of these two very difficult and extensive specialities is extremely useful in the management of patients with chronic kidney disease, which usually causes multiple cardiovascular complications, such as hypertension, heart failure, atherosclerosis and its consequences, namely coronary heart disease, atherosclerosis of the cerebral and peripheral vessels.

Genes and inhibitors

The opening lecture on obesity was delivered by Prof. Adam Krętowski (Department of Endocrinology, Diabetology and Internal Medicine, University Clinical Hospital in Białystok), who, among other things, presented the characteristics of monogenic obesity (caused by a single mutation in 1 gene) and polygenic obesity, the most common form of obesity, associated with more than 1000 identified gene loci. It seems very important to emphasize the influence of chronobiology, or biological rhythm, on the development of obesity. It turns out that individuals with an evening chronotype, i.e., those who go to bed late, are at higher risk of developing obesity. Prof. Krętowski also discussed the impact of obesity and increased amount of visceral adipose tissue on the development of kidney failure, but also the beneficial effect of the so-called reverse epidemiology, i.e., the positive effect of being overweight on reducing mortality in a group of patients with chronic kidney disease.

The presentation by Prof. Andrzej Więcek (Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland) was devoted to extra-renal aspects of SGLT2 inhibitors (Sodium-glucose Cotransporter-2 inhibitors), whose main mechanism of action is based on inhibition of glucose reabsorption by the proximal tubule, resulting in increased urinary glucose excretion and decreased serum glucose levels. Prof. Więcek discussed the mechanisms of the hypotensive effects of SGLT2 inhibitors, including reduced fluid volume, reduced body fat, reduced central sympathetic overactivity, as well as improvement of the vascular endothelial function due to its anti-atherosclerosis and anti-inflammatory effect. In addition, the speaker analysed possible cardioprotective mechanisms of the SGLT2 inhibitor, including improved cardiac remodelling, reduced myocardial hypertrophy, and reduced epicardial adiposity, which in turn is associated with decreased production of pro-fibrotic and procytokine factors. In addition, the increased sodium excretion observed during SGLT2 inhibition and the resulting reduction in sodium concentration contributes to the reduction in vascular stiffness. Decreased body weight of the perinephric space during SGLT2 inhibition leads to improved renal function. Other positive aspects of SGLT2 inhibition include reduction of hepatic steatosis, symptoms of sleep apnea or polycystic ovary syndrome, but also an increase in erythropoietin secretion and improvement in blood count. In addition, studies were presented that confirm the beneficial effects of SGLT2 inhibition on energy and metabolic processes, including improved insulin resistance, reduced inflammatory processes and a positive influence on the gastrointestinal microbiota. Another particularly important part of the presentation was related to the neuroprotective effects of SGLT2 inhibition, which improve cognitive function and reduce the risk of stroke and progression of Alzheimer's disease due to its anti-atherosclerosis anti-inflammatory effect.

Metabolic programming and microbiota

An extremely interesting and surprising lecture was given by Prof. Ryszard Grenda (Department of Nephrology, Kidney Transplantation and Hypertension, Children's Memorial Health Institute, Warsaw) on what is known as metabolism programming. It turns out that certain behaviours during pregnancy, such as smoking, improper diet or stress, induce epigenetic changes, which are observed in the third generation and which, regardless of behavioural influence, can disrupt metabolic processes and induce the development of obesity. In the era of the popularity of caesarean sections, it is worth noting and considering that caesarean delivery significantly and even completely alters the intestinal flora of the newborn. Analysing the behavioural elements of the impact on metabolism, it seems beneficial to eat meals regularly and always at the same time.

During the conference, the available hyperlipidemia treatment methods were presented. Another discussed issue was the possible benefits of preventive lowering of the uric acid levels, which have not yet been proven.

Prof. Alicja Dębska-Ślizień (Department of Nephrology, Transplantology and Internal Medicine, University Clinical Centre, Gdańsk) raised the issue of obesity and metabolic syndrome in the context of establishing eligibility for kidney transplantation. At present, the acceptable BMI in obese patients qualified for kidney transplantation is 30–34 kg/m^2, and there are insufficient data to make recommendations for higher BMI values. During her presentation, the speaker discussed the data confirming that individuals with a BMI of up to 40 kg/m^2 who have undergone kidney transplantation may have a higher survival rate compared to obese patients awaiting transplantation. Therefore, it is suggested to consider referring patients with BMI up to 39 kg/m^2 for the kidney transplant waiting list and not excluding this group of patients from transplantation due to obesity.

Another interesting topic focused on the relationship between dysbiosis, and hypertension was raised by Prof. Marcin Adamczak (Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland). Patients with hypertension present a reduced variety of gut microbiota. Significant differences in the number of bacteria of the intestinal microbiota have been shown between patients with normal and elevated blood pressure. Dysbiosis influences the development of arterial hypertension through multiple mechanisms. Short Chained Fatty Acids (SCFAs), such as acetic acid, propionic acid, and butyric acid, are formed during bacterial fermentation of carbohydrates in the colon. SCFAs regulate the normal functioning of the intestinal barrier, have anti-inflammatory effects, and inhibit the growth of other pathogens. SCFAs not metabolised in the colonocytes are transported into the plasma and bind to receptors located on the smooth muscle cells and sympathetic ganglia. In animal experiments, SCFAs have been shown to lower blood pressure. Gut dysbiosis may be associated with impaired SCFA synthesis and thus with

increased blood pressure. Trimethylamine (TMA) is synthesized in the large intestine mainly by dysbiotic bacteria. An increase in concentrations of TMA in the plasma result in increased sensitivity to angiotensin II and thus the development of hypertension. In addition, when lipopolysaccharide (LPS), which is a membrane component of gram-negative bacteria, crosses the intestinal barrier and binds to Toll-like receptor 4 on the surface of macrophages, it stimulates the processes leading to increased blood pressure. Damage to the intestinal barrier and the signs of inflammation seen in gut dysbiosis promote the passage of LPS through the intestinal barrier. Prof. Adamczak also raised the issue of possible modification of the gut microbiota in the treatment of hypertension with pre-and probiotics.

Cardiovascular risk and cost of cardiac care

On the second day of the conference, Prof. Bożena Sobkowicz (Department of Cardiology, Medical University of Białystok) discussed cardiovascular risk assessment in light of the new ESC 2021 guidelines. The assessment of the 10-year risk of cardiovascular episodes using SCORE cards does not apply to patients with chronic kidney disease, as these patients are classified as high or very high risk, but not only on the basis of eGFR values, as was recommended in the 2016 guidelines, but also on the basis of the albumin/creatinine ratio. The speaker also presented the value of specific imaging tests in assessing cardiovascular risk. Another highlighted issue was the new elements of the guidelines in cardiovascular risk prevention, such as air pollution and climate warming.

Prof. Szymon Brzósko (Department of Nephrology and Transplantation with Dialysis Centre, University Clinical Hospital in Białystok) discussed the positive and negative aspects of sauna, cold water swimming, running in marathons, yoga, and alcohol consumption in patients with chronic kidney disease.

Prof. Magdalena Durlik (Department of Transplantation Medicine, Nephrology and Internal Medicine, University Clinical Centre of the Medical University of Warsaw) gave a lecture on increasing the pool of deceased donors. A deceased expanded criteria donor is a donor over the age of 60 or a donor aged 50–59 who meets at least 2 of the following diagnostic criteria: history of hypertension, serum creatinine concentration above 1.5 mg% and/or death from stroke. Transplantation from an expanded criteria donor is associated with a 70% higher risk of graft loss within a year compared to an ideal donor. Nevertheless, kidney transplantation from expanded criteria donors is recommended, as it extends recipient survival by about 5 years.

Prof. Przemyslaw Rutkowski (Department of Nephrology, Transplantology and Internal Medicine, Medical University of Gdańsk) discussed the problem of cardiac care participation in the cost of dialysis therapy. Cardiovascular complications are a major cause of morbidity and mortality in a group of patients with chronic kidney disease and increase in the progression of kidney failure, being most advanced in dialysis patients. Due to complaints reported during dialysis, these patients often require cardiology consultation at the dialysis unit, which increases the hidden costs of dialysis therapy. It has been calculated that the cost of cardiac care accounts for a large share of the cost structure of haemodialysis, and simply providing regular and relatively frequent cardiac care to dialysis patients would reduce dialysis unit costs.

Prof. Monika Lichodziejewska-Niemierko (Department of Palliative Medicine, Medical University of Gdańsk) raised the topic of lowering sodium levels as one of the goals of therapy for patients with chronic heart and kidney disease. The adverse effects of excess sodium are observed both in patients with heart failure and in those with kidney failure. The mechanism of damage to cardiac and renal tissue by sodium ions is similar: sodium ions combine with proteoglycans, stimulate the release of proinflammatory cytokines by macrophages, cause excessive fluid accumulation in the intravascular and extravascular space, resulting in the increased volume overload, increased blood pressure, and increased symptoms of heart and kidney failure. Excessive sodium also induces metabolic dysfunction, including development of subclinical inflammation, loss of muscle tissue and development of insulin resistance. Hypernatraemia is greater in older patients, in men and in African Americans. In patients with heart and kidney failure, sodium can be reduced through a well-balanced diet and the use of diuretics in the case of patients with preserved diuresis. In peritoneal dialysis patients, increased glucose concentrations in the dialysis solution results in more intense sodium flow into the dialysate. The role of haemodialysis in removing excess sodium cannot be overlooked. Flozins are written into the records as sodium-lowering medications in patients with preserved diuresis. The lecture also included new imaging techniques, such as sodium MRI, which help to assess tissue sodium stores and the effectiveness of excess sodium removal.

Prof. Tomasz Hryszko (Department of Nephrology and Hypertension with Dialysis Unit, Medical University of Białystok) presented aspects of diuretic treatment in nephrocardiology. The speaker presented arguments against the use of furosemide together with torasemide and stated that furosemide should be changed to torasemide if it fails to cause increased diuresis. In some patients, furosemide does not significantly increase diuresis, which is related to the greater variability in the bioavailability of furosemide compared to torasemide. The addition of acetazolamide to the treatment increases the diuresis effect. SGLT2 inhibitors should not be overlooked either since they also enhance diuresis.

Individual revolution

A very interesting lecture on congestive nephropathy was given by Prof. Michał Nowicki (Department of Nephrology, Hypertension and Kidney Transplantation, Medical University of Łódź). The term congestive nephropathy was introduced in 2022, and refers to the renal dysfunction associated with venous stasis and reduced renal perfusion.

It is especially observed in patients with heart failure. Fluid retention in heart failure and low renal capsule elasticity result in the accumulation of the interstitial fluid, increased pressure inside the capsule and venous compression. A so-called “renal tamponade” occurs with compression of the renal sinus, which is not covered by the renal capsule, leading to impaired venous outflow and arterial inflow. At the same time one may observe activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, sodium retention, endothelial dysfunction, increased secretion of inflammatory cytokines and decreased eGFR. At present, it is not fully known whether the renal function impairment in congestive nephropathy is fully reversible. Renal function in patients with congestive nephropathy improves after intensive dehydration of the patient, and in patients with end-stage heart failure after implantation of a left ventricular assist device. Methods used when diagnosing congestive nephropathy include echocardiography to assess the degree of heart failure, ultrasound with Doppler evaluation, concentration of natriuretic peptides and Ca-125, which is secreted by serum membrane cells in response to mechanical stress and an increase in cytokines, as well as bioimpedance analysis to estimate the degree of the patient's overhydration. It is important to determine the serum sodium concentration and the presence of dilutional hyponatraemia.

Prof. Katarzyna Krzanowska (Clinical Department of Nephrology, Dialysis and Transplantation, University Hospital in Krakow) presented new treatment methods for vasculitis, including avacopan, the medication which inhibits the C5a receptor and may become an alternative to corticosteroids. Additionally, the speaker discussed the SPARVASC open-label recruitment trial of sparsentan, a dual endothelin-A receptor/angiotensin type 1 receptor antagonist, and irbesartan, an angiotensin type 1 receptor antagonist.

At the end of the conference, Prof. Beata Naumnik (Department of Nephrology and Transplantation with Dialysis Centre, Medical University of Białystok) delivered a lecture on individualised haemodialysis therapy, which could be a kind of revolution in the work of dialysis stations. Individualisation of haemodialysis therapy may be possible in the future, thanks to the use of a special device that measures the concentration of uraemic toxins in the dialysate every few minutes and thus adjusts the time of dialysis and its frequency to the individual needs of the patient. Thanks to the use of modern applications, the course of dialysis and biochemical parameters will be monitored over time, not only by the health care professional, but also by the patient.

Numerous discussions were held between cardiologists and nephrologists between the conference sessions and behind the scenes, centring on aspects of treating patients with heart and kidney failure.

At the Versailles of the north

The conference was held in the unique scenery of the palace and garden complex of the Branicki Palace in Białystok. The palace, which is called the “Versailles of the north”, is a late Baroque residence dating back to the early 16th century. It was built at the request of the owners of Białystok, the Wiesiołowski family. In the 17th century it became the seat of the Branicki family. Destroyed during World War II, it was rebuilt in 1946–1960. Since 1950, the palace has been owned by the Medical University of Białystok and is the seat of the university's authorities. It also houses the Museum of the History of Medicine and Pharmacy.

Right after crossing the impressive gate of the complex, the conference participants were surprised by the captivating beauty of the palace and the garden located at the back of the building. Thanks to the feast of colours, greenery and the scent of spring flowers, the participants could combine gathering knowledge during the conference with rest and relaxation. During the conference we had a chance to participate in a guided tour of the Museum of History of Medicine and Pharmacy, where we were introduced to the history of drug production. We were also able to see numerous exhibits used to make pharmaceuticals and dental instruments as well as a field hospital room from the early 20th century. After such a content-rich conference in such a beautiful place, we are looking forward to the next edition of Nephrocardiology, which will hopefully be held next year.

Figure 1. Nephrocardiology 2023 Scientific and Training Conference.

Figure 2. Branicki Palace in Białystok.

Figure 3. Branicki Palace in Białystok.

Figure 4. Museum of the History of Medicine and Pharmacy of the Medical University of Białystok.

Figure 5. Museum of the History of Medicine and Pharmacy of the Medical University of Białystok.

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