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   Książki:
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   Wantz GE. Groin hernia. In: Cameron JJ, ed. Current surgical theraphy. St Louis, Mosby, 1998: 557–561

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   Journal articles:
   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 . doi: 10.1016/s0091-6749(97)70134-9

   Books:
   Rudzki E. Alergia na leki: z uwzględnieniem odczynów anafilaktycznych i idiosynkrazji. Lublin, Wydawnictwo Czelej, 2002

   Chapter of a book:
   Wantz GE. Groin hernia. In: Cameron JJ, ed. Current surgical therapy. St Louis, Mosby, 1998: 557–561

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Letter from the Editor-in-Chief

Dear Readers,

We are pleased to present the second 2025 issue of the quarterly Military Physician. It is with keen interest and anticipation that we await the announced changes in the scoring of scientific journals and the criteria for evaluating scientific personnel and institutions. The depth and complexity of these reforms make their implementation more time-consuming. Nevertheless, we trust that our Journal – published continuously since 1920 – will gain recognition among experts, especially as it addresses broadly interpreted health security and presents the latest developments in therapy, offering considerable educational value.

Authors submitting to Military Physician have likely observed a new functionality in the submission system: the obligation to provide their affiliation in both Polish and English. This change is intended to enhance the identification of the scientific institutions behind submitted works, both in international databases and within the broader scientific community.

Among the contents of this issue are articles on military medicine, a continuation of our aerosol therapy series, and a discussion of mushroom poisoning – a topic of particular relevance during the holiday season and the approaching autumn. The case report section includes, among other subjects, outcomes of plastic surgery interventions and noteworthy nephrological case studies.

The issue closes with an extensive report on the 6th Scientific Meeting of the Polish Society of Medical Biology.

I invite you to explore this issue and wish you enriching experiences along with many sunny days throughout your summer break. I also look forward to your continued collaboration with our Journal.

Prof. Bolesław Kalicki, MD, PhD

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TABLE OF CONTENTS

ORIGINAL ARTICLE

CASE REPORTS

REPORT

CONCLUSIONS ON BATTLEFIELD MEDICINE FROM THE UKRAINIAN THEATRE OF OPERATIONS BASED ON A STUDY BY THE MEDICAL SERVICE OF THE INTERNATIONAL LEGION OF THE ARMED FORCES OF UKRAINE

Wnioski płynące z ukraińskiego teatru działań w zakresie medycyny pola walki w oparciu o opracowanie stworzone przez Służbę Medyczną Międzynarodowego Legionu Sił Zbrojnych Ukrainy

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Abstract

In February 2022, a full-scale Russian-Ukrainian war began, reshaping strategic thinking about how future combat operations might be conducted. The ongoing armed conflict has prompted a reassessment of the methods used to provide battlefield care. Lessons from the Ukrainian theatre of operations may be also used to develop medical equipment and determine the scope of training of both soldiers and medical personnel. Most data on casualties, including the primary causes of preventable injuries and deaths, remain classified. This makes it significantly difficult to collect and interpret research data and draw conclusions. A position paper entitled "War in Ukraine: TacMed Lessons Identified. International Legion Medical Service: Proposal of changes", published by the Medical Service of the 1st International Legion of the Armed Forces of Ukraine, which discusses the conclusions drawn from the Russian-Ukrainian conflict regarding battlefield medicine training and equipment, is the main source of data.

Streszczenie

W lutym 2022 roku rozpoczęła się pełnoskalowa wojna rosyjsko-ukraińska. Zmieniło to sposób myślenia odnośnie do możliwych scenariuszy prowadzenia działań bojowych w przyszłości. Trwający konflikt zbrojny zrewidował sposoby udzielania pomocy poszkodowanym w warunkach taktycznych. Wnioski płynące z ukraińskiego teatru działań możemy także odnieść do wyposażenia medycznego oraz zakresu wyszkolenia żołnierzy i personelu medycznego. Większość danych liczbowych dotyczących strat, dominującego mechanizmu możliwych do uniknięcia urazów oraz zgonów jest utajniona. Utrudnia to znacznie zebranie materiału badawczego, jego analizę i wnioskowanie na jej podstawie. Głównym źródłem informacji jest dokument *War in Ukraine: TacMed Lessons Identified. International Legion Medical Service: Proposal of changes* – opracowany przez Służbę Medyczną 1. Międzynarodowego Legionu Sił Zbrojnych Ukrainy, omawiający wnioski płynące z wojny rosyjsko-ukraińskiej dotyczące sposobu szkolenia i wyposażenia w zakresie medycyny pola walki.

Keywords: Ukraine; war; traumatic injury; Tactical Combat Casualty Care; war-related injuries

Słowa kluczowe: Ukraina; wojna; uraz; Tactical Combat Casualty Care; obrażenia wojenne

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In early January 2024, the Medical Service of the 1st International Legion of the Armed Forces of Ukraine (MSIL) published a paper entitled "*War in Ukraine: TacMed Lessons Identified. International Legion Medical Service: Proposal of changes*" [1]. MSIL is composed of doctors, nurses, and other medical professionals with competencies equivalent to those of paramedics. Its role is to provide medical support to Ukrainian troops in key operational areas. The authors of the paper highlight the importance of the guidelines developed by the Committee on Tactical Combat Casualty Care (CoTCCC), while noting that some aspects are outdated due to the realities of frontline operations in the Russian-Ukrainian war. They further identify specific areas where revisions and updates are needed.

Military medical lessons from Ukraine's battlefield

The first part of the paper discusses changes that need to be introduced in medical training. For about a decade, Ukrainian troops trained using translated CoTCCC guidelines for the standard of battlefield care. These were frequently adapted to local needs, and sometimes internally developed guidelines were issued, bearing only the CoTCCC logo.

The need to train many soldiers in basic battlefield medicine is a major factor prompting changes in the training system. According to the model used by the US Armed Forces, basic training lasts 10 weeks, with battlefield medicine included in the "yellow phase," i.e. between the first and second week of training [2]. Due to the ongoing Russian-Ukrainian conflict, the duration of basic course has been reduced, necessitating modifications to battlefield medicine training.

According to MSIL, the basic battlefield medicine course for all soldiers should last three days. An additional three days should expand the training to the Junior Combat Medic (JCM) level. The term Junior Combat Medic does not appear in official U.S. or NATO medical training guidelines, with Combat Lifesaver (CLS) being its closest equivalent.

According to the recommendations outlined in the MSIL paper, each combat team should have two JCMs. The competencies for basic soldier and JCM levels are presented in a table, structured according to the MARCH algorithm (which stands for Massive Haemorrhage, Airway, Respiration, Circulation, Hypothermia/Head injury). The source document extends the MARCH framework by introducing an additional acronym - PAWS (Painkillers; Antibiotics; Wounds; Splinting) (Fig. 1).

The document published by MSIL further expands the framework to include monitoring, pharmacotherapy, burn and fracture management, communication and documentation, as well as evacuation procedures (Tab. 1) [1].

For massive haemorrhages, MSIL (aligned with CoTCCC guidelines) recommends a rapid assessment to identify major limb bleeding (blood sweep), followed by the application of a tourniquet and wound packing. A soldier trained in JCM can also use the iTClamp device (MED Alliance Group, Oakland Drive, Sycamore, IL, USA) [1].

The recommended airway management procedures include manual manoeuvres to maintain airway patency, such as the head-tilt and jaw thrust, placing the casualty on their side with the head tilted back, and, in conscious patients with facial trauma, positioning them seated with the torso leaning forward. A nasopharyngeal airway (NPA) can be used at the JCM level. In their docu-

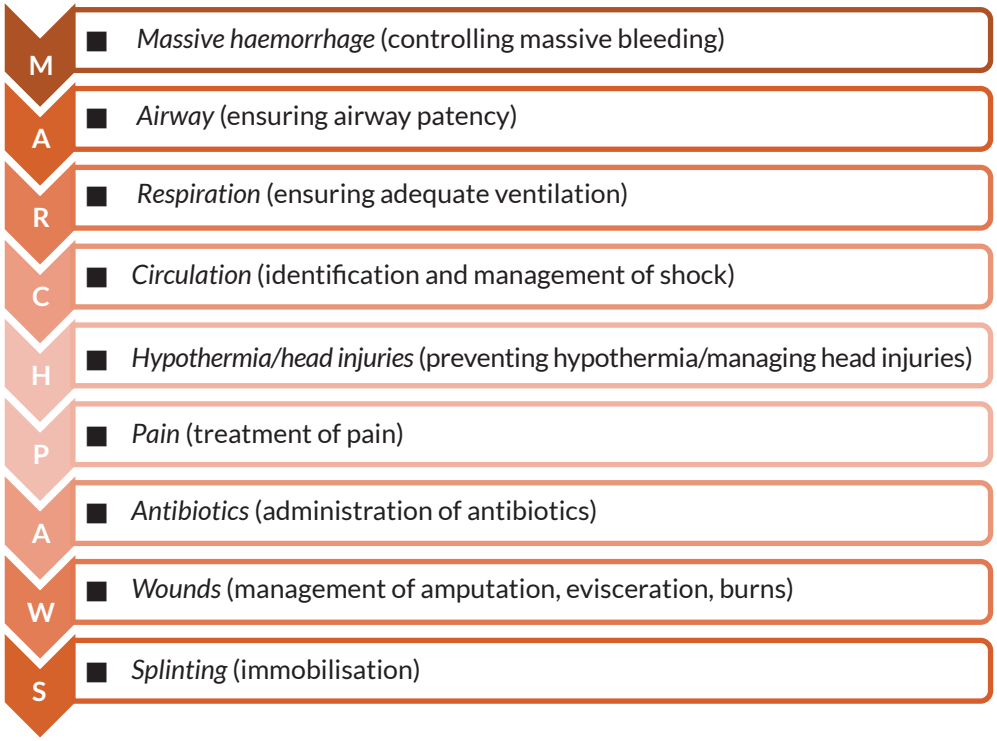

Figure 1. Explanation of the MARCH-PAWS acronym. Source: Zachaj [3]

Table 1. Comparison of the scope of competencies acquired after basic (S) and extended (JCM) training, in accordance with the assumptions of the Medical Service of the International Legion of the Armed Forces of Ukraine

Skill	Basic training (S)	Extended training (JCM)
General		
The principles for providing care to battlefield casualties	×	×
The scope of CUF and TFC	×	×
Rapid MARCH trauma assessment	×	×
Detailed examination of the casualty	-	×
Massive haemorrhage		
Principles for controlling massive haemorrhage in a battlefield setting	×	×
Identifying the symptoms of massive haemorrhage	×	×
Applying a tourniquet (high and tight)	×	×
Blood sweep	×	×
Targeted application of a tourniquet (5–7 cm above the upper edge of the wound)	×	×
Wound packing	×	×
The use of iTClamp	-	×
Direct pressure	×	×
Securing a packed wound	×	×
Airways		
Assessment of airway patency	×	×
Non-instrumental airway management (lateral position, sitting position with forward lean)	×	×
Head-tilt and jaw thrust	×	×
Nasopharyngeal airway (NPA) insertion	-	×
Respiration		
Breath assessment	×	×
Application of a vented chest seal to chest wounds	-	×
Needle decompression of tension pneumothorax	-	×
Circulation		
Assessment and control of bleeding wounds	×	×
Identification of symptoms of hypovolemic shock	×	×
Tourniquet conversion/approximation	×	×
Hypothermia & head injury		
Prevention of hypothermia	×	×
Active warming of the casualty (using chemical warmers – author's note)	×	×
Identification of head and eye trauma	×	×
Consciousness evaluation using the AVPU scale	-	×
The use of eye shield	×	×
Monitoring of basic vital signs		
Assessment of vital signs	×	×
Reassessment of the casualty's condition	×	×
Administration of pharmacological agents		
Administration of pharmacological agents included in CWMP	×	×
Administration of pharmacological agents (not included in CWMP)	-	×
Administration of oral agents	×	×
Administration of intramuscular agents	-	×
Burns & fractures		
Assessment of the severity and extent of burns	×	×
Use of a dressing intended for burns	-	×
Assessment of limbs for possible fractures	×	×
Use of splints for immobilization	-	×
Communication & documentation		
Principles for tactical medicine radio communication	×	×
Communication with the casualty	×	×
Reporting of casualties to superiors	×	×

Table 1 (continued). Comparison of the scope of competencies acquired after basic (S) and extended (JCM) training, in accordance with the assumptions of the Medical Service of the International Legion of the Armed Forces of Ukraine

Skill	Basic training (S)	Extended training (JCM)
Initiating evacuation	×	×
Completion of Tactical Combat Casualty Care Card	×	×
Evacuation		
Techniques for towing and carrying the casualties	×	×
Stretcher transportation	×	×
Preparing the casualty for evacuation	×	×
CUF – care under fire; TFC – tactical field care; MARCH – Massive hemorrhage, Airways, Respirations distress, Circulation, Head injury and hypothermia; NPA – nasopharyngeal airway; AVPU – Alert, Verbal, Pain, Unresponsive; CWMP – combat wound medication pack		
Source: Own elaboration based on: 1st International Legion Medical Service Armed Forces of Ukraine. Recommended knowledge & skills standard Tactical Medicine – Warfighter (W) & Junior Combat Medic (JCM) – Assault Unit		

ment, the MSIL emphasised that NPAs were applied incorrectly. It was also noted that NPAs of the same size can vary by 2–3 cm between different manufacturers. The recommendation to limit NPA use in basic soldier-level training corresponds with updated CoTCCC guidelines, which prioritise bag valve mask (BVM) ventilation with an NPA for cases of respiratory failure and oxygen saturation under 90% [4].

When assessing casualties for potential respiratory failure, basic soldiers should be able to accurately evaluate breathing and identify potential abnormalities, as emphasised by MSIL. Needle decompression of the chest and the use of vented seals are procedures typically performed by JCMs. This distinction is justified by the need for extended training, including hands-on learning primarily through clinical scenarios, which may be impractical given the limited time available for basic training.

For chest wounds, MSIL cited data from stabilization point records showing that 4% of casualties had chest injuries, of which 0.75% were penetrating wounds. Only 20% of vented chest seals were applied to open and sucking chest wounds [1]. However, no information on exclusions was provided, which is important, particularly in cases where vented seals are used for the epigastrium (a solution also recommended in battlefield medicine).

The Americans reached similar conclusions during their analysis of medical interventions in Afghanistan. Chest seals were placed in 74.2% of casualties with chest injuries; however, the majority of these dressings were not used in compliance with the guidelines that were in force at the time. Additionally, the same data indicated that 50% of casualties with clear indications for a chest seal did not receive one until reaching a stabilization point [5].

Observations by Ukrainian medics also indicate that vented seals are frequently applied to the lumbar region, thighs, and even lower extremities. In 87% of these cases, no chest seal was applied [1]. This underscores the critical importance of adequate training at the basic level, as it directly contributes to increased survival rates among the wounded and ensures optimal use of the available medical resources.

When assessing a casualty for hypovolemic shock, both soldiers and JCMs should be able to identify its symptoms (based on altered consciousness, the presence of central and radial arterial pulse, skin colour and temperature, and the presence of clammy skin), manage all bleeding wounds, and make any necessary modifications in tourniquet placement (approximation, i.e., placing the tourniquet as close to the wound as possible for targeted application, or conversion, i.e., switching from one method of controlling bleeding to another, e.g. switching to a tourniquet or a haemostatic compression dressing).

MSIL places particular emphasis on educating every soldier about the potential negative consequences of prolonged tourniquet use, describing the tourniquet as a "traumatic yet necessary tool for saving lives", which is like "a ticking bomb with a timer set for two hours." [1].

High limb amputations due to prolonged tourniquet use are frequently reported in the Ukrainian conflict. MSIL members have emphasized that many of these outcomes could have been prevented by proper approximation or conversion.

Head injuries and hypothermia, the last two components of the MARCH algorithm, significantly raise mortality among both combat and civilian trauma cases [6, 7]. Preventing hypothermia should be a core skill for all soldiers. According to the concept developed by MSIL, individual medical kits should include four chemical warmers (of unspecified type) to supplement personal equipment during the fall, winter, and spring seasons. These are to be used with a thermal blanket, preferably in olive green, khaki, or camouflage to minimize the risk of detection [8].

In the event of head trauma, every soldier, regardless of their level of medical training, should be able to identify typical symptoms and appropriately manage injuries involving the eyes. Consciousness assessment using the AVPU scale (Alert, Verbal, Pain, Unresponsive) is to be performed by JCMs [9].

The MSIL paper further details skills related to managing fractures and burns. Soldiers after elementary training are expected to identify both these types of injuries and apply basic measures to reduce their negative sequelae. Interventions involving the use of dedicated burn dressings and splints for fracture stabilization are assigned to JCMs [1].

Proper documentation should be the final step in tactical casualty care. In NATO forces, this is standardized through the use of DD Form 1380, which must accompany a wounded individual during evacuation. Data from Iraq and Afghanistan have shown that prehospital documentation was completed in only18.6% and 25.4% of cases, respectively [10]. As emphasized by MSIL, relying on verbal reports in the absence of written records increases the risk of errors, potentially compromising treatment decisions and lowering survival rates [1].

The Ukrainian Armed Forces utilize Form 100 as the standard document for recording combat injuries (Fig. 2). The International Legion has developed its own version of the DD Form 1380, replacing the traditional CABC framework (Circulation [specifically massive haemorrhage], Airway, Breathing, Circulation) with the MARCH protocol. This aligns the documentation with the CoTCCC guidelines. Additionally, the new form allows for recording tourniquet application, including approximation and conversion.

Further letters were added in the form proposed by the International Legion to denote different components of the casualty condition reporting protocol, following the MIST template (Mechanism of injury, Injuries, Symptoms [including observations and monitoring], and Treatment given), similar to the format used in the DD Form 1380 (Fig. 3) [11]. As set out in the CoTCCC guidelines, Each soldier should carry a Combat Wound Medication Pack (CWMP), and use it after sustaining an injury. CWMP typically contains paracetamol (650 mg, two extended-release tablets), meloxicam (15 mg), and moxifloxacin (400 mg).

According to MSIL, JCMs are responsible for the intramuscular administration of tranexamic acid (TXA), meloxicam, and nefopam, as well as for administering pharmacological agents identical to those contained in CWMP. Additionally, JCMs should be prepared to administer ondansetron in the form of orally disintegrating tablets. It is worth noting that ondansetron is recommended in the CoTCCC guidelines for use by medics with the highest level of training, i.e. Combat Medic/ Corpsman (Tier 3) [11].

MIST recommendations for medical equipment

From its experience, the International Legion Medical Service has proposed a list of basic medical gear every soldier should carry, as well as extra supplies for Junior Combat Medics.

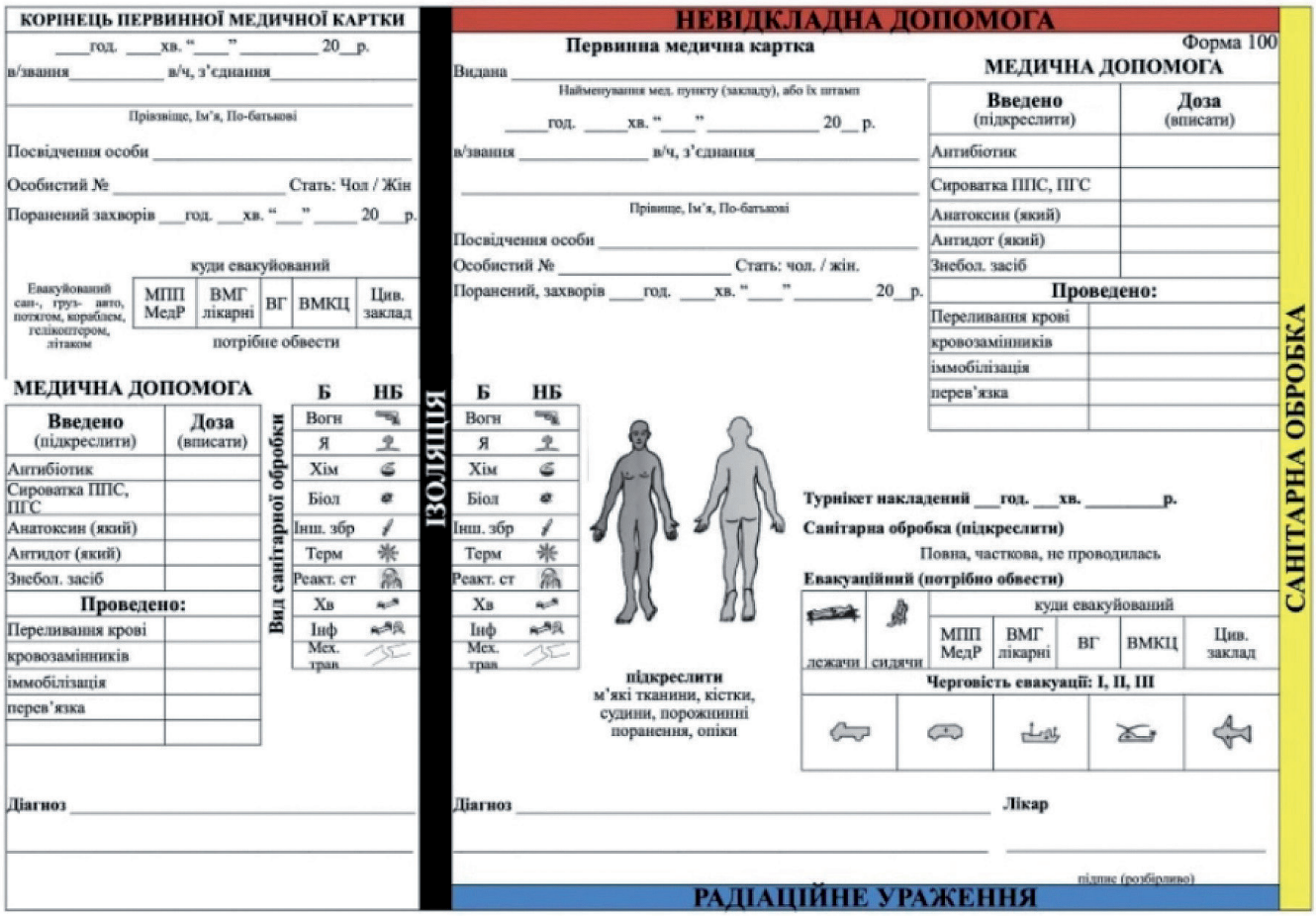

Figure 2. Form 100 used by the Armed Forces of Ukraine. Source: own elaboration

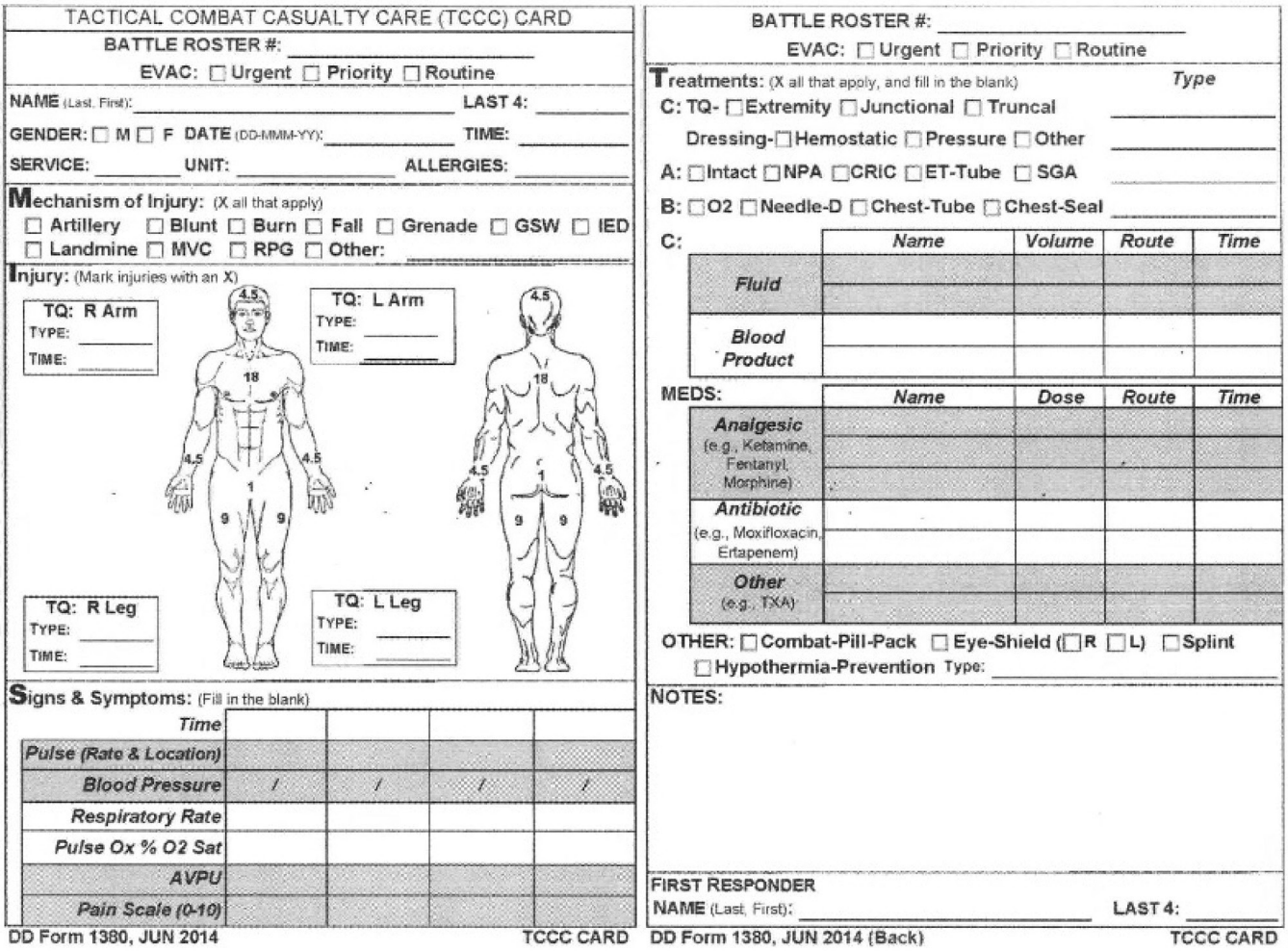

Figure 3. Tactical Combat Casualty Care Card proposed by the International Legion of the Armed Forces of Ukraine. Source: own elaboration

According to MSIL, a basic casualty kit should include a tourniquet, haemostatic dressing, wound-packing gauze, Israeli-style pressure bandages, an elastic bandage, thermal blanket, nitrile gloves, chemical hand warmers, a marker, Tactical Combat Casualty Care Card (TCCC card), a patch with a strip of duct tape, and a Combat Wound Medication Pack (CWMP) containing the following pharmacological agents: 1000 mg paracetamol, 15 mg meloxicam, and 400 mg moxifloxacin.

Every soldier should carry such a kit as part of their standard gear (Tab. 2) [1].

After utilizing the casualty's medical supplies, the Junior Combat Medic typically continues rescue operations using a properly stocked medical backpack.

The JCM's backpack should include the following items: tourniquets; haemostatic dressings; gauze for wound packing; 6-inch and 4-inch Israeli-type dressings; an iTClamp; nasopharyngeal airways; vented chest seals (MSIL strongly advocates the use of CoTCCC-recommended products); needles for decompression of tension pneumothorax; elastic bandages; trauma shears; 2.5 cm wide non-adhesive patches; a permanent marker; a TCCC card; nitrile gloves; rigid eye shields for penetrating eye injuries; a soft splint; a triangular sling; adhesive tape; a thermal blanket; and chemical warmers (with no specific type indicated).

The pharmacological agents and equipment available to JCMs should at least include the Combat Wound Medication Pack (CWMP) (as part of the basic kit), tranexamic acid (TXA), ondansetron (4 mg), meloxicam (15 mg), nefopam (20 mg), a 5 mL syringe with needle, a 10 mL syringe with needle, a 21 G or 23 G needle, and an alcohol-soaked swab. This is the minimum standard. According to MSIL, JCMs should be authorized to supplement this kit with additional items as required by the operational situation.

In addition to a medical backpack and pharmacological supplies, each JCM should be equipped with a soft stretcher (canvas stretcher) or a drag stretcher for safe dragging or towing the casualty. The paper also highlights the potential role of JCMs as members of an evacuation team, in which case the equipment may be augmented with ready-to-use solutions such as the Hypothermia Prevention and Management Kit (HPMK) (North American Rescue LLC, USA), or alternative types of stretchers (Tab. 3) [1].

MIST recommendations for medical training

The document also addressed the issue of basic training conducted in the Ukrainian Armed Forces. Accord-

Table 2. Medical supplies included in the individual equipment according to the recommendations of the Medical Service of the International Legion of the Armed Forces of Ukraine

Medical agents	Quantity
Tourniquet	4
Gauze with haemostatic agent	2
Gauze for wound packing	2
Israeli bandage 6”	2
Elastic bandage	2
Nitrile gloves (medic size)	2
Rescue scissors	1
Thermal blanket (green, 210 × 160 cm)	2
Chemical warmer	4
Marker	1
Adhesive plaster 2.5 cm	1
Duct tape	1
CWMP (paracetamol 1000 mg, meloxicam 15 mg, moxifloxacin 400 mg)	1
Tactical Combat Casualty Care Card	1

CWMP – combat wound medication pack

Source: Own elaboration based on: *1st International Legion Medical Service Armed Forces of Ukraine. Recommended knowledge & skills standard Tactical Medicine – Warfighter (W) & Junior Combat Medic (JCM) – Assault Unit*

Table 3. Recommended medical equipment included in the JCM backpack according to the Medical Service of the International Legion of the Armed Forces of Ukraine

Medical agents	Quantity
Tourniquet	4
Gauze with haemostatic agent	3
Gauze for wound packing	3
Israeli bandage 6” Israeli bandage 4”	2 2
Elastic bandage	3
iTClamp	2
Nasopharyngeal airways (NPA, 28 Fr, 30 Fr and 32 Fr)	4
Vented chest seal	4
Decompression needle for tension pneumothorax	3
Thin elastic bandage	4
Rescue scissors	1
Adhesive plaster 2.5 cm (large roll)	1
Marker	1
Tactical Combat Casualty Care Card	2
Nitrile gloves (medic size)	8
Rigid eye shield	2
Soft splint	2
Triangular sling	2
Duct tape	2
Thermal blanket (green, 210 × 160 cm)	4
Chemical warmer	6
CWMP (paracetamol 1000 mg, meloxicam 15 mg, moxifloxacin 400 mg)	2
Moxifloxacin	2 (w CWMP)
Paracetamol 500 mg (PO; tablets)	10
Tranexamic acid 10% 500 mg (ampoules)	8
Meloxicam 15 mg (ampoules)	2
Nefopam 20 mg (ampoules)	2
Ondansetron 4 mg (ampoules and/or ODT)	4
Syringe (5 mL) with needle	6
Syringe (10 mL) with needle	2
21 G/23 G needle for injections	6
Gauze pads for skin disinfection	20

CWMP– combat wound medication pack

Source: Own elaboration based on: *1st International Legion Medical Service Armed Forces of Ukraine. Recommended knowledge & skills standard Tactical Medicine – Warfighter (W) & Junior Combat Medic (JCM) – Assault Unit*

ing to the current model of such training, 13 teaching hours are allocated to battlefield medicine. During this time, soldiers receive training in casualty extraction from a tank and an infantry fighting vehicle. However, MSIL finds this training inadequate for current operational realities. It recommends reallocating this time, for example, to mastering the full tourniquet application protocol, including approximation and conversion procedures.

According to the Medical Service of the International Legion, basic training on tactical medicine should last 24 hours. The proposed training plan for the first day includes instruction on providing Care Under Fire (CUF). This training should cover the principles of tourniquet application (high and tight), as well as the procedures for its approximation and conversion, which are performed as part of Tactical Field Care (TFC). The practical skills in the basic course are complemented by learning the wound packing procedure and proper wound care, trauma examination according to the MARCH algorithm and proper preparation for transport [1].

Successful completion of the basic course is the foundation of JCM training. The JCM course begins with training scenarios based on the skills acquired during the basic course. In the following days, additional elements of the MARCH protocol are introduced during the TFC phase, along with PAWS.

According to MSIL, JCM candidates should be trained in the use of iTClamps, vented chest seals, NPAs, and thoracocentesis needles, as well as in pharmacotherapy, wound protection, and fracture stabilization. The final phase of JCM training focuses on preparation for evacuation.

The course also covers elements of prolonged care during evacuation. The trainees use porcine cadavers for procedures such as needle thoracocentesis, as well as perform supervised intramuscular saline injections to one another to ensure more realistic hands-on training [1].

Discussion

In February 2022, the nature of the conflict in the Ukrainian theatre of operations shifted away from hybrid warfare strategies, which had primarily been employed in the eastern regions of the country. The current phase of the conflict is reminiscent of the First World War, with extensive networks of trenches and fortifications spanning Ukraine's eastern and southern borders. These fortifications are dominated by artillery and rocket fire, as well as unmanned aerial vehicle (UAV) operations. These developments elicit changes not only in the concept of military operations, but also in the approach to casualty care and evacuation within this type of operational environment.

The establishment of a sustainable and efficient system of casualty care in Ukraine faces several key challenges. These include staff shortages across all levels of care, large evacuation distances, operational conditions that must be met to ensure safe evacuation, communication limitations or failures, overcrowding at casualty stabilization points, lack of standardized care procedures, and shortages of essential medical equipment.

The existing assumptions regarding the organization of battlefield medical support, rooted in doctrines developed during the wars in Iraq and Afghanistan, should be critically reviewed and adapted to the evolving operational environment, and more importantly, to the specific demands of large-scale combat operations (LSCO). Sources of insight for reorganizing battlefield casualty care should be drawn from recent experiences in the Ukrainian theatre of operations, as well as from the Israeli military operations in the Gaza Strip and the ongoing civil conflict in Myanmar (formerly Burma).

The core of an effective and well-organised battlefield casualty care system, one that adheres to the highest standards, is composed of several critical components: a uniform level of basic training in battlefield medicine, with particular emphasis on the aggressive control of massive haemorrhage; resuscitation using whole blood and blood products; a standardized and sustainable casualty management system; and comprehensive planning of medical operations [12]. The document prepared by the Medical Service of the International Legion underscores the importance of standardized medical training, both at the basic and advanced levels, adapted to the current context of the Ukrainian theatre of operations. It underscores that proficient mastery of the basic curriculum is essential for progression to more advanced training. While the document clearly outlines what should be taught and how, it notably fails to address the issue of ongoing medical training for personnel once they are deployed to the frontline.

A significant portion of the document describes the individual equipment intended for use by JCMs. The medical kits include items that are familiar to battlefield medics trained in accordance with NATO standards. The document places significant emphasis on the use of approved and standardised medical agents. Particularly noteworthy is the inclusion of nefopam among the pharmacological agents authorised for use at the JCM level. This choice likely reflects its local availability on the Ukrainian market.

What is puzzling, however, is the authors' lack of reference to current trends in both civilian and tactical medicine, particularly for the potential use of methoxyflurane and ketamine.

Methoxyflurane is an inhaled analgesic [13]. The drug causes relatively mild and uncommon adverse reactions, and shows high analgesic efficacy [14]. Studies have shown that the therapeutic effects of methoxyflurane are superior to those of other commonly used analgesics, including tramadol [15].

Ketamine is a rapid-acting general anaesthetic that belongs to the group of psychodysleptics [16]. The CoTCCC guidelines recommended ketamine as an analgesic used at the highest levels of medical training, i.e. Combat Medic/Corpsman (Tier 3) and Combat Paramedic/Provider (Tier 4). There are several administration routes for ketamine: intranasal (IN), intravenous (IV), intraosseous (IO) and intramuscular (IM). In addition to its analgesic properties, the drug also exhibits sedative and antidepressant effects, which may reduce the risk of post-traumatic stress disorder (PTSD) [17].

However, it is important to acknowledge the potential adverse effects of ketamine, including dissociation (feeling detached from reality, hallucinations). However, ketamine is considered safe for use in patients with head injuries, who represent a significant proportion of cases in combat medicine [18].

The MSIL document does not address the potential use of whole blood products or blood components by battlefield medics. While such initiatives, mainly volunteer-led, have emerged periodically in Ukraine, no systemic solution has yet been proposed in this regard.

The use of whole blood and blood products in military operations is not a new concept. The first reports on plasma and whole blood use in combat settings date back to 2011 and 2014, respectively [19]. The use of these blood products is particularly justified in the Ukrainian theatre of operations, where casualty evacuation can take some time, and there is an urgent need for rapid transition to prolonged field care (PFC).

The document also lacks data on attempts to define the organisational framework for the management of casualties, or an outline of medical planning across the various levels of combat operations. Training, uniform basic training in particular, is an essential component of such a system. This aspect is comprehensively addressed by the International Legion Medical Service. What is notably missing from the document is any mention of continuing training within defined cycles, or the possibility of expanding the programme to include interventions such as establishing intravenous or intraosseous access. Maintaining situational awareness of medical activities across all operational levels is essential for the planning of medical operations.

The paper states that basic training includes a module on the principles of providing medical care within specific operational zones. This reflects a tactical and operational rather than a strategic approach. What is clearly missing in the document is any reference to the organisation of medical operations across different levels, including how these operations are adapted to the realities of the Ukrainian theatre and the specific tasks. However, information on the necessity of creating supply facilities for medics working on the frontline, but without defining the principles of their functioning.

Medical triage is one of the critical tasks to be performed by a battlefield medic immediately after moving casualties from Care Under Fire (CUF) to Tactical Field Care (TFC) zone. This process is essential in managing high numbers of casualties that can result even from a single incident during full-scale combat operations. As such, medical triage should be introduced during initial training and further expanded at the JCM level to include the field organisation of Casualty Collection Points (CCPs).

The ability to conduct medical triage is a critical competency, without which the reduction of preventable fatalities among own forces becomes unattainable. It must therefore be integrated into all training programmes and doctrinal frameworks. Unfortunately, this gap is also evident in current CoTCCC guidelines and NATO military doctrines.

Conclusions

The paper published by the Medical Service of the International Legion serves as both a foundation and a milestone in the development of battlefield medicine within the Ukrainian theatre of operations. It is an attempt to systematise and identify the key skills that need to be developed in both soldiers and battlefield medics to reduce the number of preventable deaths. These activities have been systematised not only in terms of the range of skills, but also in terms of equipment and training.

It is important to emphasise that the information presented in the paper is drawn from experience and data collected during active combat operations within a conflict environment unlike any previously encountered by NATO forces.

Despite some shortcomings in terms of management, planning, and organisation of medical operations, the document should nonetheless be regarded as a valuable source of knowledge. It can help improve the preparation of medical personnel for future armed conflicts, where the volume of casualties, the availability of resources, and the evacuation timelines may differ substantially from current doctrinal assumptions.

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ADAPTIVE CHANGES IN THE MEDICAL AND EVACUATION SUPPORT SYSTEM FOR COMBAT OPERATIONS, DEPENDING ON THE OPERATIONAL SITUATION, AS ILLUSTRATED BY THE ACTIVITIES OF THE UKRAINIAN MILITARY HEALTH SERVICE

Zmiany adaptacyjne w systemie zabezpieczenia leczniczo-ewakuacyjnego działań bojowych w zależności od sytuacji operacyjnej na przykładzie działania wojskowej służby zdrowia w Ukrainie

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Abstract

The article presents a brief history of the two-stage conflict that began in February 2014 and continues to this day. By describing four key periods of the first stage of the conflict, we highlight the problems faced by the military health service during this time. The changes in how medical and sanitary losses were managed during the various phases of the first stage of operations laid the groundwork for a unified medical support system in Ukraine during the later stage of the conflict. Modifications of the combat medical support system, aligned with Western standards, significantly enhanced the effectiveness of medical services within the Ukrainian army. Based on the experience of combat participants, necessary logistical and organizational changes that could further improve the medical evacuation system were identified. The aim of this paper was to present the evolution of the treatment and evacuation system during the course of hostilities in Ukraine. The transformations within the Ukrainian army's medical evacuation system during the armed conflict require detailed analysis, with the findings serving to guide the operations of the military health service of the Polish

Streszczenie

Artykuł przedstawia krótką historię dwuetapowego konfliktu zbrojnego, który rozpoczął się w lutym 2014 roku i trwa do chwili obecnej. Autorzy, opisując cztery kluczowe okresy pierwszego etapu działań, zwracają uwagę na problemy, z jakimi borykała się wojskowa służba zdrowia w tym czasie. Zmiany, jakie zaszły w sposobie zabezpieczenia medycznego strat sanitarnych w poszczególnych fazach pierwszego etapu działań, pozwoliły na stworzenie jednolitej przestrzeni zabezpieczenia medycznego w Ukrainie w dalszym etapie konfliktu. Wprowadzone zmiany w systemie zabezpieczenia medycznego działań bojowych, wzorowanych na rozwiązaniach zachodnich, przyczyniły się do zwiększenia skuteczności wsparcia medycznego armii ukraińskiej. Autorzy, bazując na doświadczeniach uczestników walk, wskazują na potrzebę dalszych usprawnień logistyczno-organizacyjnych, które mogą zwiększyć efektywność systemu leczniczo-ewakuacyjnego. Celem pracy jest ukazanie zmian w tym systemie w trakcie trwania działań wojennych w Ukrainie. Zmiany zachodzące w systemie leczniczo-ewakuacyjnym armii ukraińskiej w czasie trwania konfliktu zbrojnego powinny podlegać szczegółowej analizie, a wnioski z niej płynące należy wykorzystać w działalności wojskowej służby zdrowia Sił Zbrojnych Rzeczypospolitej Polskiej.

Keywords: medical treatment and evacuation system; uniform medical support space

Słowa kluczowe: system leczniczo-ewakuacyjny; jednolita przestrzeń zabezpieczenia medycznego

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Introduction

February 24, 2024 marks two years since the outbreak of a full-scale armed conflict in Ukraine. A potential scenario for preparing such an operation was outlined already in 1940 by General Georgii Isserson in his book entitled "New Forms of Combat". Analysing German military actions preceding the outbreak of World War II, Isserson emphasized the necessity of preliminary troop deployment, covert mobilization and concentration, followed by rapid, aggressive actions conducted without a formal declaration of war. Isserson developed a concept of delivering strikes across the full depth of the enemy's military formation, aiming to simultaneously engage areas far beyond the front line using all available forces. This concept was further developed by General Valery Gerasimov, the creator of the modern Russian military doctrine (often referred to as the 'theory of chaos'). In contrast to the classical approach proposed by Carl von Clausewitz, Gerasimov views war as an extension of political actions, employing all available means such as hacking, cyberattacks, media manipulation, controlled information leaks, fake news, and hybrid and asymmetric warfare. Political and disinformation campaigns are designed to create the perception of a growing security threat to Russia or its allies within the areas of Russian interest, thereby justifying preventive measures, including military actions [1–3].

Stages of the armed conflict in Ukraine

The armed conflict in Ukraine can be divided into two main stages. The first stage began in February 2014 and lasted until February 24, 2022, although its nature underwent substantial transformation during that period. By shaping the political situation in Ukraine, Russia instigated an internal armed conflict involving separatist movements in the Donetsk and Luhansk regions. Simultaneously, Russia conducted covert military operations, introducing unmarked special forces into Ukrainian territory, which culminated in the annexation of Crimea [4].

Basically, four periods of the first stage of the conflict can be distinguished:

- The initial period of the conflict (from February to September 2014) was marked by a gradual escalation of tensions. By August and September, these tensions evolved into an open, medium-intensity armed conflict. In response, the Security Service, militia, and special forces launched an Anti-Terrorist Operation (ATO) to stabilize the situation. The subsequent signing of an agreement to cease hostilities led to a marked decrease in their intensity;
- The second period (from September 2014 to February 2015) was marked by the full resurgence of military activity, with a significant escalation observed particularly between January and February 2015. This phase concluded with a resolution banning the use of heavy weaponry;
- The third period (from March 2015 to April 2018) was characterized by low-intensity military operations, with occasional escalations, as well as reconnaissance and sabotage activities;
- The fourth period (from April 30, 2018, to February 24, 2022) began with the transformation of the Anti-Terrorist Operation (ATO) into the Joint Forces Operation (JFO). Unlike ATO, JFO was a coordinated military operation aimed to stabilise the situation in the Donetsk and Luhansk regions. With the initiation of JFO, the structure of commanding all military and security units engaged in repelling the armed aggression of the Russian Federation was reorganized. Operational control was transferred to the General Staff of the Armed Forces of Ukraine [5].

Following the period of active hostilities, Ukrainian authorities undertook efforts to reinforce military cooperation with Western partners, focusing on the modernisation of the armed forces, enhancement of operational and command structures, as well as improvement of medical support systems for tactical operations. The time between 2015 and 2022 was used by both conflicting countries (Ukraine and the Russian Federation) to strengthen their positions and prepare for a future conflict. Ukraine recreated its military potential based on the experience and training centres of Western countries, and focused on the construction of fortifications in selected directions. Russia, on the other hand, in line with its doctrinal provisions, undertook political and disinformation activities aimed at creating a favourable environment to justify potential future intervention. In September 2021, Russia, in cooperation with Belarus, conducted the cyclical "Zapad 2021" manoeuvres in the border regions of Poland and Ukraine, leaving military equipment and command centres behind along the Ukrainian border. In early February 2022, Russia and Belarus launched joint military drills code-named "Allied Resolve 2022". Moscow and Minsk claimed that the number of troops involved in these exercises was limited and therefore did not fall under OSCE monitoring requirements. For this reason, it was decided not to invite external observers; unlike in previous years, the communique did not disclose the number of soldiers or equipment involved. According to available data, Russia has amassed approximately 127,000 troops along the border with Ukraine [4, 5].

Since January 2022, in line with Russian military doctrine, provocative actions have escalated in the annexed republics of eastern Ukraine, accompanied by intensified political blackmail and unrealistic demands directed at Western and NATO countries. Such actions, intended to lay the groundwork for justifying a future conflict, were detected by NATO's intelligence services as well as by US and British intelligence agencies, which issued warnings about the potential outbreak of war. However, the exact timing of the possible actions remained uncertain. On February 24, 2022, Russia launched an armed invasion termed a "special military operation".

By initiating a full-scale armed conflict, the Armed Forces of the Russian Federation aimed to conduct high-intensity kinetic operations designed to rapidly seize control of Kyiv and establish a Moscow-dependent provisional government. However, the determined actions of the Armed Forces of Ukraine in the combat zones blocked Russian advances and shifted the combat focus to eastern Ukraine, as well as changed the nature of tactical operations from high-intensity kinetic warfare to positional tactical engagements of varying intensity. Since the onset of aggression, Russian combat operations have been characterized by a high degree of brutality, inclu-

ding deliberate attacks on civilian infrastructure such as commercial, residential, cultural, and medical facilities. During the autumn-winter period of 2023/2024, attacks on Ukraine's energy infrastructure intensified significantly, further affecting the psychological well-being of its citizens. During frontline operations, the Armed Forces of the Russian Federation deliberately target rescuers, battlefield medics, evacuation vehicles, and battlefield medical equipment. Such actions have had a significant impact on the organization of battlefield medical support and the functioning of the treatment and evacuation system of the Armed Forces of Ukraine [5].

Changes in the medical and evacuation system of the Armed Forces of Ukraine in 2014–2024

The combat operations that began in 2014 caught the Armed Forces of Ukraine, including the military health service, in the midst of an organizational reform that was progressing slowly due to significant underfunding, which had led to serious shortcomings in equipment, training, and personnel.

The medical support system of the Armed Forces of Ukraine was structured around phased treatment with evacuation based on medical indications, following a model similar to that used by the Armed Forces of the Russian Federation (Fig. 1) [6]. It encompassed the personnel and resources of the military medical service deployed along evacuation routes, as well as the organization of evacuation and triage of the casualties and sick to successive medical facilities, where increasingly advanced care was provided, from basic first aid, through specialist treatment, to rehabilitation.

However, due to the aforementioned factors, the system failed to function effectively. Already the initial ATO phase, significant problems were faced in terms of medical support, stemming from deficiencies in the following areas:

- standardized personal protective equipment for soldiers, and consequently, insufficient training in its proper use;
- modern IT systems to support medical support management, digital communication, search means for casualty zones, and individual medical data carriers, etc.;
- armoured evacuation vehicles and limited capacity for air evacuation;
- mobile medical modules for establishing stages of medical evacuation and modern equipment for mobile military medical units capable of autonomous operation in field conditions;
- experienced medical personnel;
- stable organisational structures, which had been deformed as a result of personnel reductions.

Financial and organisational neglect significantly affected the implementation of medical support, necessitating the involvement of civilian healthcare system and the establishment of a unified framework for medical care. This situation, in turn, exposed the lack of preparation of civil-

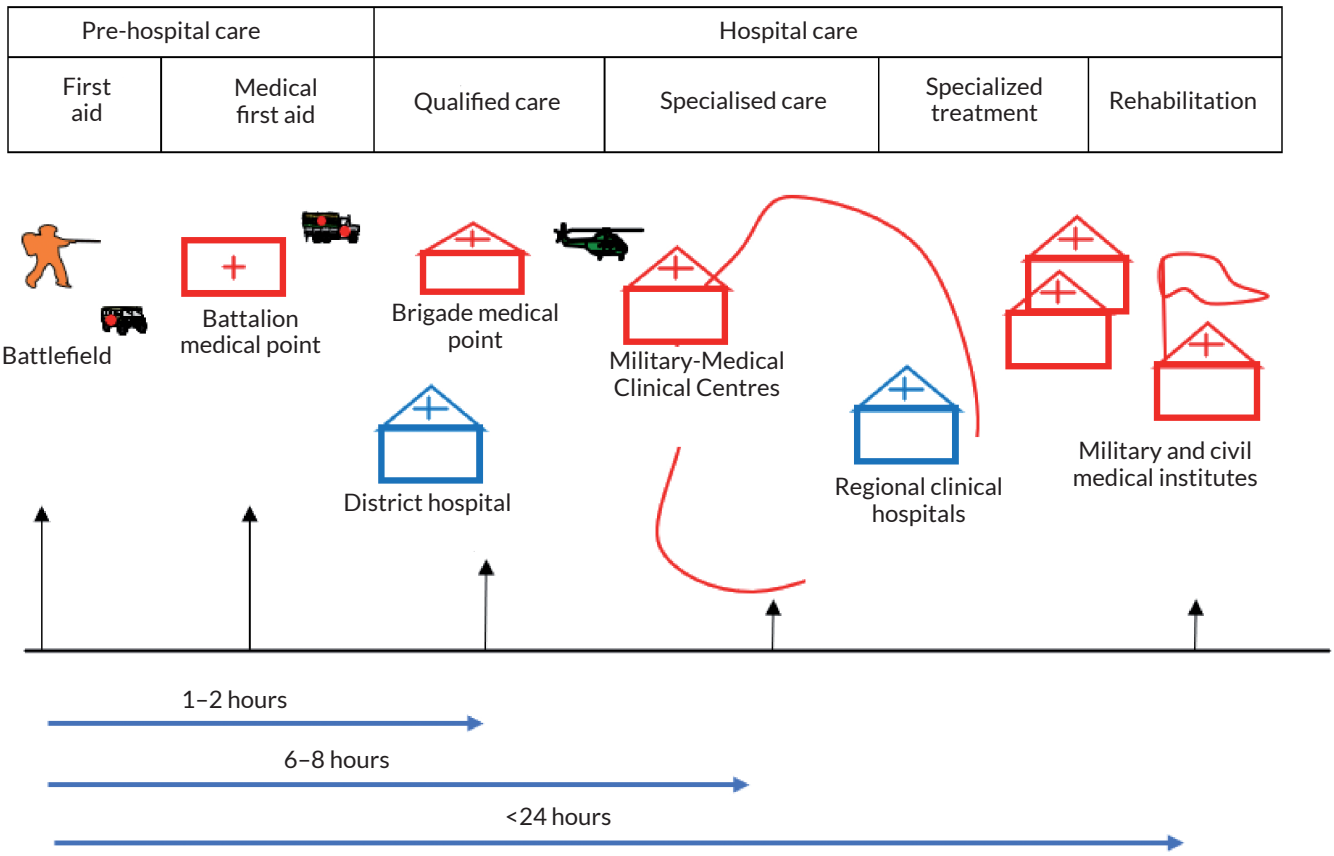

Figure 1. Medical and evacuation system of the Armed Forces of Ukraine [6]

ian healthcare personnel to manage casualties, improper treatment of combat injuries and the need to repeat surgical interventions multiple times.

The medical and evacuation system operated through organic medical units of the Armed Forces of Ukraine, supported by the civilian healthcare service and ad hoc medical and nursing brigades, which provided first aid with elements of qualified medical care in the ATO zone. A significant number of medical companies operating in the area were not fully functional due to personnel and equipment shortages. After rebuilding the medical capacity of military medical units, medical and nursing brigades were gradually withdrawn from the ATO area.

During the ATO phase, clear guidelines for management and collaboration between the military and civilian healthcare systems were missing. Despite designated military health service forces and resources, providing medical care based on post-Soviet standards proved to be a mistake. Therefore, NATO principles for organizing battlefield medical support were adopted, with timeliness, continuity, and continuity of medical care being key elements. Significant emphasis was placed on the timing of medical care: first aid should be available in the form of self aid, buddy aid, and care provided by combat medics, adhering to the principles of the "platinum minutes" (within 10 minutes of injury) and the "golden hour" (stabilization of vital functions). Furthermore, urgent surgical interventions should be performed within 2 hours of the injury. The system allowed for reducing the number of medical evacuation stages by bringing specialist medical care closer to the battlefield.

ATO stationary hospitals were arranged at three levels:

- Level 1 (30–100 km from combat zones): Mobile military and civilian hospitals, as well as designated healthcare facilities within the ATO zone, providing qualified and urgent specialist medical care and arranging further evacuation of casualties;
- Level 2 (150–300 km from combat zones): Located near the ATO zone, represented by the military hospital in Dnipro and the Dnipro Regional Clinical Hospital in the southern evacuation direction, and the Military and Medical Clinical Center of the Northern Region in Kharkiv in the northern evacuation direction. These facilities provided specialist medical care and functioned as evacuation hospitals;
- Level 3 (rear areas of the country) – the vast majority of casualties, having received medical care and having their health condition stabilised, were then transferred to evacuation hospitals in the rear areas of the country. This level was far beyond the ATO zone included the Main Military Medical Center in Kyiv, regional medical centres in Odesa, Vinnytsia, and Lviv, as well as stationary hospitals, multi-specialty hospitals of the Ministry of Health of Ukraine, and clinical institutions of the National Academy of Medical Sciences, which provided advanced specialized treatment and rehabilitation for the wounded and injured.

According to Ukrainian sources, the most severe challenges in the field of medical support faced during the first period of ATO (February–September 2014) included:

- the lack of a uniform medical support system for ATO (this system evolved during tactical operations);
- insufficient training of soldiers in administering first aid, including self-aid and buddy aid;
- insufficient personnel and material support for the military medical service and military units;
- the lack of evacuation vehicles, particularly armoured ones;
- the inability to widely use air evacuation due to the enemy's deployment of anti-aircraft missile systems;
- the lack of knowledge and training among doctors in civilian healthcare facilities and mobilized medical personnel in the conflict zone in the scope of military medicine, particularly in battlefield surgery and the treatment of combat and mine injuries;
- insufficient material support for Military Medical Clinical Centers (MMCCs), as well as stationary and mobile military hospitals, partially offset by volunteer assistance.

In the second period, following the stabilisation of tactical operations and the establishment of the demarcation line, time had come to summarise the analyses of the types and patterns of morbidities (primarily combat-related injuries), and assess medical and organisational needs.

The primary causative factors, types, topography, and severity of injuries were assessed. It was found that artillery and missile strikes accounted for the majority of injuries (56.7%), with 27.4% of the wounds classified as multiple and multi-organ. In terms of injury location, the most commonly affected areas were the limbs (57.1%), followed by the head (26.6%), chest (7.0%), and abdominal cavity (5.5%). Abdominal injuries, although accounting for a relatively low percentage of all trauma cases managed in a hospital setting, accounted for 46% of deaths. Most injuries were mild (47.3%) and moderate (42.3%) cases, while severe injuries accounted for only 10.4%. The collected data were compared with those from other conflicts involving the Armed Forces of the Russian Federation (20% in Afghanistan, 30% in Chechnya), leading to a decision to strengthen the basic level of combat medical support and to strictly enforce tactical standards regarding the timing of first aid. These measures gave rise to an increase in the proportion of seriously injured patients reaching hospitals to approximately 14.5%, which in turn led to a rise in hospital mortality within this group to 1.2%. At the same time, a significant proportion of patients were admitted to hospitals with non-combat injuries and other medical conditions. This situation arose from an inaccurate assessment of the health status of individuals included in combat units and was primarily due to military medical board doctors' insufficient knowledge of health standards required for military service.

During the third and fourth periods, low-intensity military operations were continued.

The military health service command used this time to enhance personnel and supplies, address shortages in armoured medical transport, and continuously monitor the effectiveness of the improved medical and evacuation system. Particular emphasis was placed on implementing procedures for each stage of medical evacuation, while

permitting the omission of certain stages in cases of life-threatening injuries. Given the nature and specificity of combat operations during this period, the forces and resources of brigade medical companies were mechanically allocated among the individual combat battalions.

The company elements were unable to function as a cohesive medical unit or to arrange the delivery of first aid and qualified medical care during emergencies. Second-level medical care was intended to be provided by civilian facilities. The number of beds in selected hospitals was increased, and the capacity to deliver psychological, psychiatric, and rehabilitation support was expanded (Fig. 2) [5].

Much emphasis was placed on adapting legal regulations to facilitate the process of providing medical support for combat operations. The doctrine for medical support for the Armed Forces of Ukraine was also further improved.

Following the outbreak of the full-scale conflict in 2022, the aggressor's brutality became fully apparent, marked by attacks on civilian infrastructure, deportation of children, widespread missile strikes across Ukraine, as well as the use of internationally banned weapons, including phosphorus bombs and various types of mines. Civilian and military medical facilities, medical evacuation transports, and the medics themselves became regular targets [7, 8].

It should be noted that during combat operations in eastern Ukraine, elements of tactical units and brigades are deployed as separate company- and battalion-level combat groups.

Each such combat group, typically consisting of two battalions, is supported by a dedicated stabilisation point. The stabilisation point is an element of a separate medical company, reinforced with additional personnel, including doctors. The care provided corresponds to first-level medical support, with possible extension to include qualified medical procedures. Such points are established approximately 20 to 30 kilometres from the front line, utilizing the available permanent infrastructure. Stabilisation points are rarely relocated, typically about once a month. During this time, depending on its level of readiness, a stabilisation point can receive up to 30 patients in serious condition. After stabilising their vital signs, the patients are transported to hospitals. Each hospital oversees up to six stabilization points, i.e. manages six brigades. Evacuation teams are appropriately assigned to both stabilisation points and hospitals, with evacuation conducted using the "manual drag" method. Pickup-type off-road vehicles are typically used to transport the casualties from the casualty collection point to the stabilisation point, while armoured vehicles are used less frequently due to their limited availability. In contrast, the transport between stabilisation points and hospitals is implemented using multi- or single-stretcher ambulances and buses. So far, the limited mobility of stabilisation

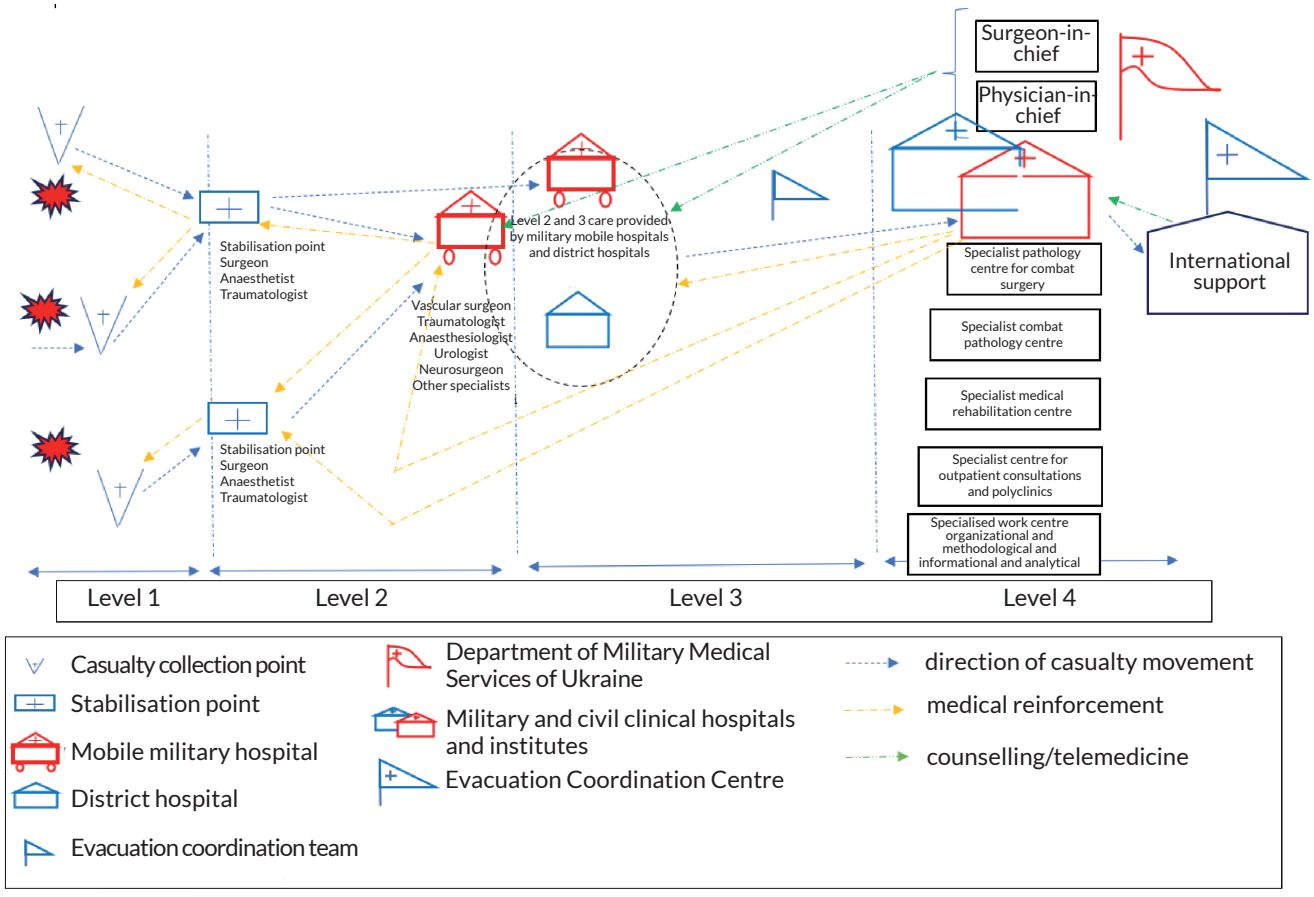

Figure 2. Medical and evacuation support of the Armed Forces of Ukraine after restructuring the medical support system [5]

points has prevented their widespread destruction by the aggressor. This may be attributed to their perceived low strategic value within the Armed Forces of Ukraine's combat structure, according to Russian military doctrine.

According to reserve colonel Viktor Kevlyuk, the head of the Organizational and Mobilization Department of the OK Zahid command (2014–2018), head of the Civil-Military Cooperation Centre at the Joint Forces Command of the Ukrainian Armed Forces (2018–2020), and expert at the Center for Defence Strategies, as well as author of the article "What Should Be Changed in the Armed Forces to Reduce Battlefield Casualties", Ukrainian military medicine has been systematically evolving and continuously improving since 2014. Owing to cooperation with NATO institutions, it is an element of the Armed Forces of Ukraine that holds a clear advantage over the military medicine of the Russian Armed Forces. The improved medical and evacuation system led to a high percentage of casualties returning to combat ranks and relatively short treatment times for those with minor-to-moderate injuries.

Drawing on his observations and experience, Colonel Kevlyuk formulated conclusions and outlined expectations regarding necessary courses of action for the Medical Command of the Armed Forces of Ukraine to enhance the efficiency of the medical support system. As pointed out by Colonel Kevlyuk:

- tactical units must be fully equipped with armoured recovery vehicles;
- given the enemy's disregard for the laws and customs of war, particularly their contempt for the Red Cross symbol, adequate stocks of such equipment should be maintained to allow for the rapid replacement of damaged vehicles;
- a stabilization point should become a full-time unit (unless it already has), fully equipped and staffed with trained personnel;
- all existing legislative restrictions and legal barriers that impede the work of combat tactical medics should be eliminated; nothing should prevent the efforts to save the casualties;
- medical reserves (reserve battalions) should be re-established; all wounded or ill personnel requiring extended convalescence should be registered in these units, assigned a position, and continue to receive full benefits as they did prior to their injury or illness;
- Purchases of medical supplies and equipment should be done under public oversight through open tenders; any quality non-compliance identified upon delivery should be treated as an act of sabotage, with both the supplier and the procuring party held accountable;
- personnel should undergo continuous training in self-aid and buddy aid techniques;
- medical helicopters should become a standard means of medical transport, comparable to routine ambulances;
- each mobile hospital should be assigned a medical aviation squadron as part of a military aviation brigade;
- the casualty evacuation process should be mechanized through the use of robotic, self-propelled, and mechanized stretchers;
- work should be completed to create a unified medical information database for military personnel and a unified DNA database for members of the Defence Forces [9].

Conclusions

The described dynamic changes in the medical and evacuation system of the Armed Forces of Ukraine should serve as the basis for detailed analyses of the activities of military and civilian health services within a unified medical framework to support a potential defence operation on Polish territory.

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THE THREAT OF WEAPONS OF MASS DESTRUCTION IN THE CONTEXT OF THE CONFLICT IN UKRAINE AND ITS IMPACT ON BATTLEFIELD MEDICINE

Zagrożenie bronią masowego rażenia w kontekście konfliktu na Ukrainie i jego wpływ na medycynę pola walki

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Abstract

The modern battlefield encompasses not only conventional operations but also the potential use of chemical, biological, radiological, and nuclear (CBRN) agents. This article focuses on two key aspects: the identification and analysis of CBRN-related threats in the context of the armed conflict in Ukraine, and the assessment of their impact on the functioning of battlefield medicine. The first part discusses possible scenarios involving the use of radiological weapons, including so-called "dirty bombs" (radiological dispersal devices, RDDs), and their potential consequences for civilian populations and the natural environment. It also outlines strategies to mitigate the effects of such attacks, including preventive measures, early warning systems, and decontamination procedures. The second part examines the challenges faced by medical personnel operating under CBRN threat conditions. Emphasis is placed on the need for rapid identification, accurate diagnosis, and effective treatment of victims of chemical, biological, or radiological attacks. The importance of adequate training for medical teams, the availability of specialized equipment, and access to personal protective gear is also highlighted. In conclusion, the article underscores the importance of an integrated approach to crisis management and medical practice as essential components of an effective response to CBRN-related threats.

Streszczenie

Współczesne pole walki obejmuje nie tylko działania konwencjonalne, lecz także potencjalne użycie broni masowego rażenia (BMR). Artykuł koncentruje się na dwóch kluczowych aspektach: identyfikacji oraz analizie zagrożeń związanych z BMR w kontekście konfliktu zbrojnego w Ukrainie, a także ocenie ich wpływu na funkcjonowanie medycyny pola walki. W pierwszej części omówiono możliwe scenariusze użycia broni radiologicznej, w tym tzw. „brudnych bomb" (radiological dispersal devices, RDD), oraz ich potencjalne skutki dla ludności cywilnej i środowiska naturalnego. Zidentyfikowano również strategie przeciwdziałania skutkom takiego ataku, obejmujące działania prewencyjne, systemy ostrzegania i procedury dekontaminacyjne. W drugiej części przeanalizowano wyzwania stojące przed personelem medycznym w warunkach zagrożenia BMR. Podkreślono konieczność szybkiej identyfikacji, trafnej diagnostyki oraz skutecznego leczenia ofiar ataków z użyciem broni chemicznej, biologicznej lub radiologicznej. Zwrócono uwagę na znaczenie odpowiedniego przeszkolenia zespołów medycznych, dostępności specjalistycznego sprzętu oraz środków ochrony osobistej. W podsumowaniu zaakcentowano rolę zintegrowanego podejścia do zarządzania kryzysowego i praktyki medycznej, jako kluczowych elementów skutecznej reakcji na zagrożenia związane z bronią masowego rażenia.

Keywords: civil protection; weapons of mass destruction; military health service

Słowa kluczowe: ochrona ludności; broń masowego rażenia; wojskowa służba zdrowia

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Introduction

The modern battlefield extends beyond conventional warfare and may involve evolving and escalating threats posed by Weapons of Mass Destruction (WMD), also known as Chemical, Biological, Radiological, and Nuclear (CBRN) weapons. They prompt modifications in tactics, strategy, and approaches to counteracting potential threats, ranging from terrorist chemical attacks to accidental radioactive leaks, the consequences of which are highly diverse and difficult to predict [1, 2]. Considerations related to the prevention, diagnosis, and treatment of the consequences of CBRN weapon use constitute a vital component of preparing all armed forces for operations in modern battlefield conditions. However, in the case of the Armed Forces of Ukraine, they take on particular significance due to the real threat of CBRN weapon deployment and the intensity of the ongoing conflict [3, 4]. The implementation of new technologies, procedures, and protocols is intended not only to minimize human casualties, but also to maintain the operational effectiveness of the armed forces and civilian emergency services. Exploring these issues will clarify the challenges of battlefield medicine in the context of rising CBRN threats and support the creation of effective countermeasures.

CBRN weapons on the modern battlefield

The classification of CBRN weapons constitutes a key element of international security strategy, enabling the identification of different types of weapons of mass destruction – namely chemical, biological, radiological, and nuclear weapons – as well as a better understanding of the consequences of their potential use. Each of these categories is associated with distinct mechanisms of action, varying degrees of destruction, and specific challenges for emergency response systems and medical services. Precise categorization allows not only for the development of appropriate countermeasure and protection procedures, but also for the adaptation of military and civilian training in responding to mass-casualty threats. Contemporary armed conflicts – such as the ongoing war in Ukraine – clearly demonstrate that the threat of CBRN weapon use is not merely theoretical, but constitutes a real challenge for national defense structures and entire international alliances. Consequently, a deeper understanding of CBRN weapon classification and its operational, logistical, and medical implications is essential, and will be discussed in the following sections of this chapter.

The concept of CBRN comprises several major threat categories:

- **chemical weapons –** toxic agents intentionally employed to contaminate large areas and target civilian populations;
- **biological weapons –** pathogenic microorganisms or toxins used to induce infectious diseases, potentially causing epidemics or pandemics;
- **radiological weapons** – improvised devices that utilize radioactive materials or isotopes; they do not cause a nuclear explosion, but disperse radioactive substances over a wide area, contaminating the environment and populations;
- **nuclear weapons** – a weapon based on an explosive nuclear reaction capable of causing massive destruction and long-lasting radioactive effects on both the environment and human populations [2].

The potential use of CBRN weapons by the Russian Federation on Ukrainian territory represents one of the most serious contemporary threats to both regional and international security. CBRN defense specialists face numerous challenges, including the ongoing identification of emerging threats and the development of effective strategies to mitigate their consequences. Among all types of weapons of mass destruction, radiological weapons draw particular attention, as their potential use is considered one of the most plausible and destabilizing scenarios in the ongoing conflict. The magnitude of possible consequences – both in terms of public health and environmental impact – demands heightened vigilance and preparedness on the part of military, medical, and civilian structures [5, 6].

Radiological weapons include, among others, the so-called "dirty bombs". A dirty bomb is an improvised explosive device designed to disperse radioactive isotopes, causing contamination of the surrounding area. During the explosion, a conventional charge detonates, while the radioactive substance itself does not undergo nuclear transformation. Radioactive isotopes can also be dispersed without the use of explosives, e.g. by means of aerosols, dropping from an aircraft or water contamination. Sources of radioactive isotopes may include nuclear power plants, radioactive waste storage facilities, and other institutions that utilize these agents for routine research and diagnostic purposes. Hazardous isotopes are characterized by a long half-life and high radioactivity. Even small amounts, e.g. 30 grams of ^{137}Cs, can cause large area contamination [5]. An attack with radiological exposure devices (RED) not only disrupts entire urban areas and critical infrastructure, but also generates enormous cleanup costs and long-term health consequences for the population.

The effectiveness of REDs depends on many factors, including:

- the force of the conventional explosive, which determines the extent of radioactive isotope dispersion;
- the type of radioactive isotopes, including their radioactive activity and half-life;
- weather conditions that influence the dispersion of isotopes following the explosion.
- The greatest threat posed by radiological weapons is their potential to contaminate vast areas and cause lasting changes to the natural environment. The use of such devices can lead to the destruction of housing, energy, and communication infrastructure, resulting in significant social, economic, and political consequences, including the evacuation and relocation of populations from affected areas.

Radiological weapons exert a profound psychological impact, often inducing panic and social chaos that surpass the immediate physical effects of the explosion. Such an attack generates fear with lasting consequences. The number of victims may increase over time due to the development of radiation sickness of varying severity and cancer among individuals exposed to contaminated areas [2, 5, 7].

The war in Ukraine has led to the loss of control over substantial amounts of radioactive materials. The location and quantity of these substances, both prior to and during the ongoing conflict, remain unknown. International organizations, including the International Atomic Energy Agency (IAEA), have documented many cases of attempted illicit trafficking of radioactive materials [5].

During the conflict in Ukraine, the Zaporizhzhia Nuclear Power Plant attracted increased attention from both the aggressor and international organizations [8, 9]. Russian troops occupying the Zaporizhzhia Nuclear Power Plant have used the threat of its potential destruction as a means of blackmail, raising fears of a nuclear catastrophe in the region. The facility is currently under the control of the Russian state-owned company Rosatom, further intensifying concerns about nuclear safety [10]. Meanwhile, international organizations are working to ensure its security, prevent a potential catastrophe, and establish protective zones around the plant.

The radiation situation in Poland is currently stable, posing no threat to public health or the environment. The National Atomic Energy Agency conducts continuous 24-hour monitoring using nearly 90 measuring devices, most of which are positioned along the country's eastern border [9].

Potential deployment of a nuclear bomb is another threat related to the Russia's use of CBRN weapons in Ukraine. Russia possesses a substantial nuclear arsenal and is the world's most powerful nuclear state alongside the United States.

European Commission representatives Hans Das and Marc Fiedrich presented an analysis of the escalating CBRN threats and the European Union's response to these challenges to a European Parliament Subcommittee. Hans Das stressed that Russia's stance on the use of nuclear weapons remains ambiguous. Earlier remarks by Russian Foreign Minister Sergey Lavrov hinted at the possibility of nuclear weapon use, although more recent statements suggest a softening of these aggressive positions [10, 11]. Nevertheless, periodic threats of tactical nuclear weapon use, voiced by Russian politicians at various levels [6], are taken seriously by the international community. These threats are closely monitored by the United Nations and the International Atomic Energy Agency, with efforts focused on dialogue, diplomacy, and peaceful negotiations to prevent escalation that could result in human tragedy and regional destabilization.

The military conflict in Ukraine has escalated to a level raising reasonable suspicion of the Russian army's use of chemical weapons, phosphorus bombs in particular [12]. Reports indicate that white phosphorus may have been used in certain engagements, notably during the battles for the city of Bakhmut in 2023. Some international organizations and eyewitnesses have reported observing the use of white phosphorus munitions by Russian forces or Russian-backed separatists. However, it should be emphasized that confirming the use of white phosphorus as a weapon in Ukraine is challenging due to limited access to conflict-affected areas and the absence of independent investigations [13]. Nevertheless, reports of the possible use of this substance are deeply concerning, as white phosphorus is highly toxic; the lethal dose for humans ranges from 50 to 100 mg. Burns caused by exposure are typically deep, affect multiple sites, and vary in size. Because elemental phosphorus reacts with skin lipids and subcutaneous fat, it penetrates deeply and can delay wound healing. Dispersed phosphorus particles are neutralized only by self-ignition, which continues until they are completely consumed. During this process, phosphorus generates temperatures of approximately 1000°C, intensifying thermal damage. As it burns, it also absorbs moisture from the tissue and produces phosphoric acid [14].

Reports related to the conflict in Ukraine have also raised concerns about the possible use of biological weapons [15]. Despite the lack of official confirmation regarding their use in combat, the Russian Defence Ministry has claimed to have found evidence that Kyiv is conducting research on components of biological weapons "with the direct involvement of the Pentagon" [16]. Russia's accusations may be intended to divert attention from its own actions against Ukraine. As with radiological weapons, the primary concern surrounding biological weapons lies in their profound psychological impact. Richard Guthrie, a British expert on chemical and biological weapons, notes that while Russia has submitted an inquiry to the UN Security Council, it has not filed a formal complaint under Article 6 of the Biological Weapons Convention. Russia has recently made similar accusations against Georgia, where the U.S. government funds the Lugar Research Center in Tbilisi. In 2018, the Georgian government invited international experts, including Russian representatives, to inspect the facility; however, Moscow declined the invitation. Following the inspection, it was confirmed that the laboratory complies with the Biological Weapons Convention. Experts recommend that Ukraine undertake similar measures; however, this would be challenging amid the ongoing conflict [17].

A new report by the Atlantic Council and the Scowcroft Center for Strategy and Security highlights the ongoing threat posed by Russian chemical weapons. The authors emphasize Russia's disregard for international arms control norms, citing, among other things, the use of Novichok in the UK in 2018. The report suggests that Moscow may resort to CBRN weapons to pursue its objectives in the conflict with Ukraine, even without large-scale deployment. Russia's military doctrine and limited conventional capabilities indicate that CBRN weapons are likely to play an increasingly important role in its defence strategy [18].

Civil-military cooperation in critical infrastructure, such as power grids and public healthcare systems, is essential for countering potential CBRN attacks. The report also recommends enhanced integration of operational planning between the United States and its European allies. At the same time, the advances in biological and chemical technologies, including genetically modified organisms, intensify the threat of highly infectious biological weapons, presenting significant challenges for societies [18].

NATO Allies have long regarded the threat posed by CBRN weapons with utmost seriousness, placing strong emphasis on preparing their armed forces to effectively respond to such challenges. This approach is driven primarily by concerns over the potential use of CBRN agents by terrorist organizations. At the same time, it is essential to closely monitor countries such as Russia and their stance on WMDs, as reflected in the largest Allied exercises in years, conducted in 2024 to enhance preparedness for CBRN threats [19].

Effective management of these threats in the context of the conflict in Ukraine requires coordinated international action. Joint efforts are essential to control, monitor, and prevent the illegal proliferation of such threats. Such actions may include information exchange, joint operational activities and the development of preventive and crisis response strategies. Support from international partners may be crucial to effectively manage the situation and minimise the risk. Poland, like many other countries, requires a comprehensive security strategy, particularly regarding threats to energy infrastructure and other critical sectors. Sharing information with international partners and drawing on the experiences of other nations can be highly valuable in shaping such a strategy.

Threats posed by weapons of mass destruction and the challenges of battlefield medicine

The growing risk of CBRN weapon use compels healthcare systems to implement comprehensive response strategies. A key priority is the establishment of interdisciplinary teams composed not only of medical personnel, but also of experts in radiobiology, toxicology, and epidemiology. Such collaboration enables faster threat assessment, more accurate clinical decision-making, and more effective preventive actions. On the battlefield – where response time is critical – integrated efforts can significantly improve casualty survival rates and help mitigate the long-term health consequences resulting from exposure to weapons of mass destruction.

Integrated medical response, supported by specialized expertise, constitutes the foundation of an effective reaction to CBRN threats. Nevertheless, even the most well-prepared healthcare system may become overwhelmed in the event of large-scale deployment of such weapons.

WMDs may impose a significant burden on healthcare systems for several reasons:

- **Mass casualties:** an attack involving WMDs may result in a large number of fatalities and injuries, necessitating the rapid mobilization of medical services and hospitals to provide urgent care to those affected.
- **Complexity of care:** victims may need specialized medical treatment due to the diverse injuries and effects caused by chemical, biological, or nuclear weapons; managing such attacks demands specialized equipment, medications, and trained medical personnel. The need for psychological support must also be taken into account, as exposure to weapons of mass destruction can lead to severe war-related trauma, manifesting as post-traumatic stress disorder (PTSD), anxiety, or adjustment disorders.
- **Risk of contamination:** Attacks involving WMDs may lead to contamination of both population and the environment; medical services are forced to operate under high-risk conditions due to exposure to toxic substances, pathogens, or radiation.
- **Pressure on the healthcare system:** A sudden influx of casualties can overwhelm hospitals and healthcare services, compromising timely care for all patients. This may necessitate difficult decisions regarding prioritization and resource allocation.

It is therefore crucial for healthcare services to be adequately prepared to respond to such situations through thorough planning, training, access to necessary equipment, and close cooperation with crisis management agencies [3, 4, 20].

Conclusions

The threat posed by WMDs significantly affects the operational capacity of battlefield medical services. The need for rapid identification, diagnosis, and treatment of CBRN victims poses major challenges for medical personnel. In battlefield conditions, where situations are dynamic and require rapid response, trained medical personnel and access to specialized equipment and personal protective gear are essential for effective treatment and minimizing adverse outcomes. Educating medical personnel on the effects of CBRN agents and the appropriate countermeasures is essential to ensuring an effective response [20]. Such training should encompass hazard identification, crisis management, the use of specialized equipment, and procedures for personal protection and evacuation. It is essential to establish appropriate procedures for responding to radiological weapon threats and cases of acute radiation syndrome (ARS). Proper preparation of medical personnel enhances response effectiveness and ensures timely, efficient medical care for both military personnel and civilians.

In the context of an armed conflict where there is a real threat of weapons of mass destruction being used, their profound psychological impact cannot be overlooked, as it may significantly exacerbate war-related trauma and intensify symptoms of combat stress. In response to these challenges, the Military Institute of Medicine – National Research Institute (WIM-PIB) has launched a project to facilitate the exchange of experiences between Polish and Ukrainian medical professionals. WIM-PIB is currently implementing the latest edition of this project, which includes training in casualty rehabilitation as well as the diagnosis and treatment of individuals affected by war trauma [21].

Creating a medical forces component will ensure coordinated action by military medical services, critical for the swift and effective care of the wounded. These initiatives are intended to enhance the country's defence capabilities and protect the lives and health of both soldiers and civilians in the event of CBRN weapon deployment on the battlefield.

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REVIEW ARTICLE

MIXED INTESTINAL INFECTIONS IN PATIENTS RETURNING FROM TROPICAL DESTINATIONS – DIAGNOSTIC CHALLENGES

Mieszane zakażenia jelitowe u pacjentów powracających z tropikalnych destynacji – wyzwania diagnostyczne

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Abstract

The increasing popularity of travel to tropical regions has led to a rise in mixed intestinal infections among returning travelers. These infections, caused by a combination of bacterial, viral, and parasitic pathogens, present complex diagnostic and treatment challenges. Travel patterns are evolving, with a growing number of individuals venturing into tropical regions. This trend is likely to continue, highlighting the need for a greater understanding of mixed intestinal infections in this population. A diverse range of pathogens can cause mixed intestinal infections, with Enteroadherent *E. coli*, Enteropathogenic *E. coli*, the protozoan *Giardia intestinalis*, noroviruses, and the stramenopile *Blastocystis hominis* being particularly prevalent. The interplay between these organisms can lead to a broad spectrum of clinical manifestations. Co-infections with multiple pathogens are common in mixed intestinal infections and can significantly worsen the severity of symptoms. Understanding the mechanisms and interactions of co-infections is crucial for effective management. Diagnosing mixed intestinal infections requires a multifaceted approach, combining clinical presentation, stool analysis, and advanced tests such as polymerase chain reaction. Early and accurate diagnosis is essential for prompt and appropriate treatment.

Streszczenie

Rosnąca popularność podróży do regionów tropikalnych doprowadziła do wzrostu przypadków mieszanych zakażeń jelitowych wśród powracających podróżnych. Zakażenia te, spowodowane kombinacją patogenów bakteryjnych, wirusowych i pasożytniczych, stanowią złożone wyzwanie diagnostyczne i terapeutyczne. Wzorce podróżowania zmieniają się i coraz więcej osób odwiedza regiony tropikalne. Trend ten prawdopodobnie się utrzyma, co wymaga lepszego zrozumienia mieszanych zakażeń jelitowych w tej grupie pacjentów. Szeroka gama patogenów może powodować mieszane zakażenia jelitowe, przy czym szczególnie rozpowszechnione są enteroadherentne *E. coli*, enteropatogenne *E. coli*, pierowtniaki *Giardia intestinalis*, norowirusy oraz stramenopile *Blastocystis hominis*. Wzajemne oddziaływanie tych organizmów może prowadzić do różnorodnych objawów klinicznych. Koinfekcje wieloma patogenami są częste w przypadku mieszanych zakażeń jelitowych i mogą znacznie zaostrzyć nasilenie objawów. Zrozumienie mechanizmów i interakcji w przebiegu koinfekcji jest kluczowe dla skutecznego postępowania. Diagnostyka mieszanych zakażeń jelitowych wymaga podejścia wieloaspektowego, łączącego ocenę kliniczną, analizę kału oraz zaawansowane testy, takie jak łańcuchowa reakcja polimerazy. Wczesna i dokładna diagnoza jest niezbędna dla szybkiego i właściwego leczenia.

Keywords: mixed intestinal infections (MIIs); co-infections; tropical destinations

Słowa kluczowe: mieszane zakażenia jelitowe (MZJ); koinfekcje; tropikalne destynacje

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Introduction

The field of tropical medicine is continuously evolving, with new challenges emerging that require innovative solutions. Among these challenges, the diagnosis and treatment of mixed intestinal infections (MII) in patients returning from tropical destinations stand out as particularly complex. These infections, which may involve a combination of bacterial, viral, and parasitic pathogens, present a convoluted puzzle for clinicians. The pathogens responsible for these infections are as diverse as the regions from which they originate. Bacterial culprits such as *Salmonella*, *Escherichia coli*, and *Campylobacter jejuni* are frequently implicated in MII, alongside viral agents like norovirus and sapovirus, and parasites such as *Giardia intestinalis* and *Cryptosporidium parvum*. The interplay between these organisms can lead to a wide spectrum of clinical manifestations, ranging from mild discomfort to severe, debilitating illness [1]. Travel patterns play a significant role in the epidemiology of these infections. The globalization of travel has increased the number of individuals venturing into tropical regions, often for leisure or work-related purposes. This has, in turn, has led to a rise in the incidence of MIIs among returning travelers. The risk factors associated with acquiring these infections are multifaceted, encompassing the duration of travel, the purpose of the visit, and the level of exposure to local pathogens [2]. The diagnostic process for MIIs is intricate, requiring a multifaceted approach. Clinicians must rely on a combination of patient history, physical examination, and a suite of diagnostic tests, including stool analysis, culture, and molecular techniques, to identify the responsible pathogens [3]. The symptomatic overlap between different pathogens can make this process particularly challenging, as it involves the differentiation between multiple potential causes of the patient's symptoms. Treatment strategies for MIIs are similarly nuanced. The presence of multiple pathogens often necessitates a combination of therapeutic agents, each targeting a specific organism. This approach must be balanced with the need to minimize antimicrobial resistance and consider potential drug interactions. Furthermore, treatment must be tailored to the individual patient's clinical presentation and the pathogens identified, requiring a personalized approach to care [1]. In conclusion, MIIs in patients returning from tropical destinations represent a significant challenge in tropical medicine. The complexity of diagnosing and treating these infections requires a comprehensive understanding of the pathogens involved, the travel patterns that contribute to their spread, and the nuanced approach needed for effective management. As global travel continues to expand, the importance of addressing these challenges becomes ever more critical, underscoring the need for continued research and development in this field.

Travel characteristics

In recent years, there has been a steady increase in the number of people traveling abroad. It is estimated that by 2030, the number of individuals traveling outside their country of residence could exceed 1.8 billion [4]. In addition to the increasing number of travelers, travel patterns are also changing. In 2019, the number of people visiting tropical regions significantly increased. Despite the decline in air traffic caused by the SARS-CoV-2 pandemic, there is still an increase in the number of people traveling to tropical countries [5]. Also in Poland, in recent years, the habits of travelers seem to align with global trends. In 2022, the number of people traveling abroad reached 18% of the society. Of these, over a million travelers chose tropical destinations, especially the UAE, Thailand, Zimbabwe, Namibia, and Tanzania [6]. The destinations of patients seem to mirror this global trend (Fig. 1).

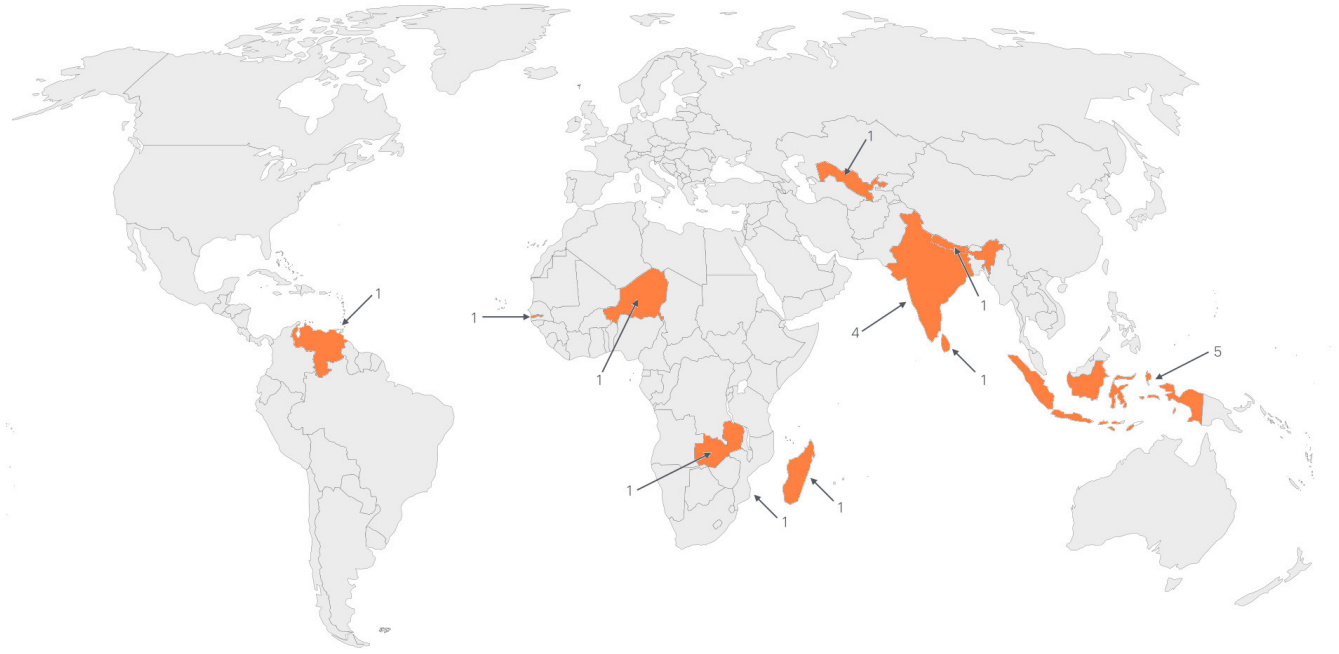

Figure 1. Patients travel destinations

Pathogens

Among the surveyed returnees from Nepal, Indonesia, Venezuela, Gambia, Zambia, Uzbekistan, India, Sri Lanka, Madagascar, Central African Republic, and Tanzania, the most common gastrointestinal infections are caused by Enteroadherent *E. coli* (EAEC) (10 cases) and Enteropathogenic *E. coli* (EPEC) (9 cases) (Tab. 1). The third most prevalent pathogens include the protozoa *Giardia intestinalis*, norovirus, and the stramenopile *Blastocystis hominis*. Enteroadherent *E. coli* colonizes the small intestine, with infection transmitted via the fecal-oral route [7]. Manifestations of infection include gastrointestinal disorders. EAEC adheres to small intestinal epithelial cells to form a biofilm and secrete enterotoxins, including thermostable enterotoxin (EAST-1) or toxin (Pet), a type V serine protease auto-transporter. The exact mechanism by which EAEC causes diarrhea remains unclear [8]. Enteropathogenic *E. coli* ranks as the second most common cause of diarrhea in hospitalized patients after rotavirus in developing countries. Infection also occurs via the fecal-oral route [7]. EPEC induces gastroenteritis, anorexia, rapid cachexia, and even death, especially in children under two years of age (constituting 10–40% of cases). EPEC virulence factors (pEAF, BFP, LEE, and Nle effectors) lead to the obliteration of microvilli, tightly adhering to intestinal epithelial cells [8]. *Giardia intestinalis* is mainly found in developing countries, with children being more commonly affected. Infection occurs through the ingestion of water or food containing cysts. The parasite inhabits the duodenum and jejunum, causing giardiasis, characterized by acute, subacute, or chronic diarrhea, nutritional deficiencies, weight loss, nausea, or vomiting. Asymptomatic cases have also been described [9]. Norovirus occurs in various geographical areas and causes seasonal epidemics, primarily affecting children. It spreads via the fecal-oral route and often causes asymptomatic infections. It is detected in fecal samples, but there have been cases of symptomatic infections where norovirus was isolated from plasma. Symptoms of infection include diarrhea, nausea, vomiting, and abdominal pain. In most patients, symptoms resolve within 1–3 days. However, in patients with co-morbidities, immunocompromised individuals, or children under two years of age, the infection may persist longer and be more severe. Necrotizing enterocolitis associated with norovirus infection has been observed in infants [10]. *Blastocystis hominis* is one of the most common zoonotic parasites, mainly found in developing, tropical, and subtropical regions. The disease predominantly affects adults aged 31–50 years [11] and children aged 10–14 years. Individuals at higher risk of infection include those in contact with animals (exposed to manure and human feces in soil), rural residents, and inhabitants of mountainous regions [12]. Infection occurs via the fecal-oral route. *Blastocystis hominis* infection can range from asymptomatic to manifesting gastrointestinal symptoms such as abdominal pain, nausea, vomiting, diarrhea, flatulence, and enteritis. In summary, the symptoms of infection by each pathogen are non-specific and similar. To identify the specific agent, it is necessary to take a comprehensive patient history and conduct appropriate stool tests. It is crucial for travelers to tropical

Table 1. Pathogens identified in patients returning from tropical destinations

Country/ Pathogens	Nepal	Indonesia	Venezuela	Gambia	Zambia	Uzbekistan	India	Sri Lanka	Madagascar	Central African Republic	Tanzania
Sapovirus	●						●				
Norovirus	●							●	●		●
Giardia intestinalis					●		●●●				
Entamoeba histolytica						●	●				
Shigella spp.			●				●				
Enteroadherent *E. coli*		●●●●		●			●	●	●	*	●
Enteropathogenic *E. coli*		●●●●			●			●	●	*	●
Enteroinvasive *E. coli*							●				
Enterotoxigenic *E. coli*		●									
Enterohemorrhagic *E. coli*		●	●								
Clostridioides difficile		●●		●							
Salmonella enterica							●				
Blastocystis hominis						●	●●●				
Rotavirus									●		
Campylobacter jejuni		●●					●				
Trichomonas hominis							●				
Yersinia enterocolitica			●								

● Patient not prepared by tropical medicine specialist
* Patient prepared by tropical medicine specialist

countries and medical practitioners to be aware of the risk of infection by each pathogen and take adequate preventive measures.

Co-infections

Travelers returning from tropical destinations often experience intestinal infections caused by not just one, but multiple pathogens (co-infections). Therefore, there is a need to analyze the specific interactions between pathogens to acquire a broader understanding of the diseases. Gastrointestinal infections can stem from various pathogens, including sapoviruses, noroviruses, *Shigella*, *E. coli*, and *Salmonella*, etc. [13]. While numerous studies have focused on the mechanisms of single infections, there is a need to concentrate on the interactions between co-infections [14]. In clinical settings, co-infections are frequent occurrences, with one pathogen potentially influencing another, either directly or indirectly. Understanding the mechanism of co-infections could significantly contribute to disease control and patient treatment. Co-infections are primarily manifested by alterations in the microbial flora: a decrease in bacterial numbers, reduced diversity, and general disturbances [15]. Studies commonly report an intra-host preference effect, suggesting that the effects of infections depend on the sequence pathogen arrival [16]. However, some argue that the severity of infection is primarily determined by the number of pathogens present, although the regulatory mechanism behind this remains unclear. The influence of co-infections on the intestinal epithelium is under investigation, with studies still in their preliminary phases, yet given the number of patients affected, this topic warrants discussion [17]. Travelers returning from tropical destinations are frequently infected by multiple types of *E. coli*, EPEC, EAEC, and others. This trend is particularly common among tourists returning from Indonesia. Co-infections involving Enteroadherent *E. coli*, Enteropathogenic *E. coli*, and norovirus are often observed in patients arriving from Sri Lanka, Madagascar, Tanzania, and the Central African Republic (Tab. 1). The interaction between selected strains of *E. coli* may be a protective feature that facilitates survival in unfavorable environments. It is believed that two strains of *E. coli* can coexist in a form of cross-protection mutualism, protecting each other and surviving in antibiotic concentrations that would inhibit the growth of either type alone [18]. Additionally, the most significant co-infections are suggested to occur between bacteria and viruses. Firstly, direct interactions between pathogens can enhance thermal stability by binding bacterial surface polysaccharides to viral particles [19]. Moreover, the infected intestinal tract becomes more susceptible to infections caused by other pathogens due to disruptions in microbial flora, damage to the intestinal barrier, and increased expression of cell surface receptors [20]. However, there is also potential for unfavorable competition. Certain types of bacteria secrete substances that inhibit the synthesis of important viral proteins. In some cases, the immune response triggered by the first pathogen makes subsequent infections difficult or even impossible [21]. Studies have shown that compared to rotavirus and norovirus infections alone, co-infections with EPEC and EAEC are frequently associated with diarrhea and vomiting [22]. The rate of co-infections linked to norovirus is considered high. Studies showed that the rate of multiple pathogen detection is approximately 30% [23]. Notably, the most common co-infections among patients with norovirus involve *C. difficile* and *E. coli* [24]. This is an important fact because the latest studies focus on the risk of occurrence of diarrhea in patients suffering from multiple pathogens. The main mechanism driving the severity of symptoms is the synergy between pathogens [25]. In patients returning from Nepal, co-infections especially between sapoviruses and noroviruses were observed. Additionally, among patients coming from India, sapovirus was detected alongside other enteric pathogens. This is notable, as previous research has primarily focused on the occurrence of sapoviruses in pediatric populations or elderly individuals (over 60 years old) [26]. Co-infections are common in patients suffering from intestinal infections, and pathogens can influence each other's cell infection processes in certain ways. Viruses that naturally inhabit the intestines may modulate the infection pathways for other pathogens. As a result, the presence of multiple pathogens may herald a more severe course of the disease [27].

Diagnostics

Among the patients described with MII, non-specific symptoms predominated, including fever, abdominal pain, vomiting, nausea, diarrhea with traces of blood, mucus, and water, headaches, and dysuria. Basic laboratory tests revealed an increase in inflammation markers, hyperbilirubinemia, shifts in proteinogram, elevated pancreatic enzyme levels, hypertransaminasemia, and erythrocyturia with leukocyturia. However, to identify specific pathogens and implement patient-tailored therapy, more advanced tests are necessary.

In the cases described above, pathogens were diagnosed using the ELISA method, which tested antibodies in the IgG or IgM classes against *Yersinia enterocolitica* and *Entamoeba histolytica*. The nested PCR method was used to determine the presence of genetic material for Enteroadherent *E. coli*, Enteropathogenic *E. coli*, norovirus, *Salmonella enterica*, *Yersinia enterocolitica*, *Campylobacter jejuni*, Enteroinvasive *E. coli*, Enterotoxigenic *E. coli*, Enterohaemorrhagic *E. coli*, *Shigella* spp., *Clostridioides difficile*, *Giardia intestinalis*, *Entamoeba histolytica*, norovirus GI/GII, rotavirus, and sapovirus. Coproscopic examination was also conducted for *Entamoeba histolytica/dispar*, *Giardia intestinalis*, *Trichomonas hominis*, and *Blastocystis* spp. Assessing risk factors in patients can also aid in diagnosing MII [28]. In this context, one can distinguish between non-modifiable and modifiable risk factors [29]. Recent studies identify age, gender, and country of birth as some of the most significant non-modifiable factors for MII. As for gender, it is suggested that a higher risk may be expected in women [30]. Another study indicates that being born in non-Western regions (Asia, South America, Africa, etc.) may be a protective factor, possibly due to exposure to native gastrointestinal pathogens during childhood, leading to the development of basic immunity [31]. Moreover, it has been postulated that the risk of MII decreases with increasing age in adult patients. This may be related to the increase in living standards and travel patterns, which may occur at different stages of life [32]. As for modifiable risk factors, travel for the purpose of visiting friends (VFT) has recently been considered.

However, due to the complex nature of MII, VFT can be a positive or negative factor depending on the travel destination [33]. In addition, an elevated risk may be associated with the length of travel, with longer travel durations increasing the risk, and with the choice of travel direction, as medium- and low-income countries are linked to an increased risk of disease [34]. Another significant factor that may contribute to the occurrence of MII is the low rate of specialist consultations before traveling to tropical regions. Among the patients observed, only one had consulted a tropical medicine specialist before the planned trip.

Conclusion and future prospect

In light of the growing popularity of trips to tropical regions, the analysis of factors responsible for MIIs seems crucial. A broader understanding of risk factors, alongside a thorough analysis of individual pathogens causing MIIs, could facilitate quicker patient diagnosis and enable more personalized treatment in the future. Currently, in most cases, the initial diagnosis, upon first contact with health services, is based on the assessment of symptoms reported by the patient and the clinical evaluation conducted by the medical facility staff. Travelers unprepared by a specialist in tropical diseases showed a higher incidence of mixed gastrointestinal infections. The situation is worsened by the limited experience in diagnosing and treating MIIs in hospitals and primary healthcare settings, where nonspecific symptoms resulting from a multitude of overlapping pathogenic factors may be improperly managed. To improve the situation, as the number of travelers to regions where exposure to MIIs is prevalent continues to rise, it would be beneficial for patients to have professional preparation for travel, including methods for preventing infections and guidance on actions to take if symptoms arise. To raise awareness, information should be conveyed by qualified medical personnel, travel agencies, and relevant government bodies. Thanks to these actions, it will be possible to significantly reduce the costs borne by hospitals in the future and improve the health outcomes of an increasingly mobile population.

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REVIEW ARTICLE

SHAPING THE PROPERTIES OF THE AEROSOL CLOUD OF NEBULIZED DRUGS. PART II. PRACTICAL ASPECTS

Kształtowanie właściwości chmury aerozolowej leków nebulizacyjnych. Część II. Aspekty praktyczne

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Abstract

In clinical practice, the aerosol cloud of nebulized drugs can be shaped in several ways: by using nebulizers that vary significantly in the characteristics of the aerosol cloud they generate; modifying the nebulization chamber by replacing its internal dispersing elements; adjusting the operating conditions of the nebulizer chamber; adding a holding chamber; and by using different formulations of the same drug in the same nebulizer.

Streszczenie

Możliwości kształtowania chmury aerozolowej leków w praktyce klinicznej obejmują: zastosowanie urządzeń różniących się istotnie charakterystyką wytwarzanej chmury, modyfikację charakterystyki głowicy nebulizacyjnej poprzez zmianę jej wewnętrznych elementów rozpraszających ciecz, przełączenie głowicy na inne warunki wytwarzania aerozolu, dołączenie komory inhalacyjnej, a także zastosowanie różnych formulacji tego samego leku w tym samym nebulizatorze.

Keywords: nebulization; jet nebulizer; ultrasonic mesh nebulizer; aerosol cloud; airways deposition

Słowa kluczowe: nebulizacja; nebulizator pneumatyczny; nebulizator ultradźwiękowy siateczkowy; chmura aerozolowa; depozycja w drogach oddechowych

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How can the parameters of an aerosol cloud generated by a nebulizer be adjusted to meet the patient's needs?

In part I of the paper, we presented the clinical justification and theoretical framework for shaping the properties of aerosols generated by nebulization of drugs [1]. Adjusting aerosol cloud parameters to the patient's current needs is intended to enhance the efficacy and safety of inhalation therapy. The parameters of the aerosol cloud depend primarily on the technical properties of the device, specifically the nebulizer chamber and the compressor in jet nebulizers, or the chamber in mesh nebulizers, and, to a much lesser extent, on the formulation of the drug used. The definitions and abbreviations of the most commonly used aerosol cloud parameters are based on Pirożyński [2].

In practice, shaping the properties of the aerosol cloud is achieved by appropriately selecting the type of nebulizer and its operating parameters [3–5].

In the case of budesonide, it is possible to select a formulation that influences the properties of the aerosol cloud [6]. Our research, along with studies by other authors, has shown that adding a holding chamber to a mesh nebulizer significantly alters the parameters of the inhaled aerosol [7–9].

Currently available nebulization devices allow for adjustment of aerosol cloud parameters in various ways, both in jet and mesh nebulizers (Tab. 1).

Table 1. Methods for modulating aerosol cloud parameters in drug nebulization

	Method	Type of nebulizer	Examples and practical notes
1	The use of nebulizers that produce significantly different aerosol cloud properties from the same drug formulation	JN, MN	The solution is inconvenient, expensive and has little prospects
2a	Modifying the nebulizer chamber by replacing internal components of the liquid dispersion unit	JN	Pari Company System
2b	Changing the parameters of the nebulizer chamber by switching (setting) the nebulizer chamber to a different aerosol generation mode	JN	Many JN s, e.g. Omron, Diagnostic or Flaem Easy and convenient, currently most commonly used
3	Attaching the holding chamber	MN	For example Aerogen Solo + HC Ultra Aerogen or MN Intec Mesh + HC Intec Spiro Kids Only tested sets (MN + HC) should be used
4	Using different formulations of the same drug in the same nebulizer	MN, JN	Data are available only for some drugs, e.g. budesonide
JN – jet nebulizer; MN – mesh nebulizer; HC – holding chamber			

Exemplary solutions for modifying aerosol cloud parameters

Below we present examples of specific solutions currently available on the market.

Solution 1

Over 25 years ago, Finlay et al. compiled data on various types of nebulizers producing different salbutamol aerosol clouds, which gave rise to significant differences in pulmonary deposition [10]. According to this widely cited publication, *in vitro* studies demonstrated that regional pulmonary deposition of salbutamol (expressed as % of the nominal dose) varied significantly (5–8 times) in both jet and classical ultrasonic nebulizers (Tab. 2).

These observations were further expanded nearly 20 years later with regard to mesh nebulizers. Hatley et al., analysing several models of these devices, demonstrated nearly 2.5-fold differences in the volumetric median diameter (VMD) and fine particle fraction (FPF) of salbutamol aerosol clouds [11]. Similar results were reported by Sosnowski et al., who investigated inhaled corticosteroids [12]. These differences clearly translate into clinical outcomes, as demonstrated by the use of salbutamol in asthmatic patients with chronic obstructive pulmonary disease (COPD) [13–15]. The use of nebulizers with varying aerosol cloud characteristics may result in different patterns of drug deposition in the airways, leading to significant variations in clinical efficacy.

Solution 2a

Another method for modifying the aerosol cloud of nebulized drugs involves using nebulizer chambers with different aerosol generation modes for the same drug, within the same jet nebulizer and using the same compressor. This effect is achieved by replacing plastic nozzle inserts inside the nebulizer chamber, which are responsible for aerosol generation. This solution was introduced over 20 years ago by Pari in their LC Sprint jet nebulizers [16, 17]. It involves selecting appropriate inserts that alter the size of the generated droplets, which can be easily evaluated by comparing the mass median aerodynamic diameter (MMAD), mass median diameter (MMD), and fine particle fraction (FPF) of the aerosol cloud. The Pari LC Sprint nebulizer, which is available on the market, includes five nozzle inserts in different colours that enable generation of five distinct aerosol clouds, each designed to target different areas of the airways. The data presented in Table 3, Table 4, and Table 5 refer to studies conducted using a 0.9% NaCl solution (Tab. 3). A similar technology was also employed in Diagnostic Econstellation Plus jet nebulizers [17]. However, this device can generate only three types of aerosol clouds (Tab. 4).

Solution 2b

A similar solution involves a simple, quick adjustment of the nebulizer chamber characteristics in a jet nebulizer, achieved by turning the cover or pressing a button to alter the aerosol generation conditions and the properties of the generated cloud. This approach is becoming increasingly popular. The OMRON A3 nebulizer, which features three different operating positions of the same nebulizer chamber, resulting in varied aerosol cloud parameters and nebulization efficiencies, is a good example (Tab. 5).

The Flaem RF9 4 NEB jet nebulizer operates similarly, offering the user 4 modes of nebulization. Switching the

Table 2. Salbutamol deposition expressed as % of the nominal dose (ND) in different areas of the respiratory tract from different types of nebulizers (Finley, 1998 [10])

Airway region	Expected Salbutamol Deposition Range (%ND)	Maximum differences in deposition between the nebulizers tested
Extrapulmonary	1.8–9.5	5×
Entire lungs	3.1–23.4	7×
Tracheobronchial	1.6–10.6	6×
Alveolar	1.6–12.8	8×

Table 3. Aerosol cloud modulation in Pari LC Sprint NP

Insert colour	MMAD or MMD (µm)	FPF (% ED)	Main deposition site and type of nebulizer
Red	MMAD 2,8	80	Distal (peripheral) airways. Designed for infants and small children with bronchial obstruction and COPD patients. Nebulizers: Pari Boy Junior, Pari Boy Pro, Pari LC Sprint Baby, Pari LC Sprint Star
Yellow	MMAD 3,1	73	Small bronchi in infants and young children. Nebulizer: Pari LC Sprint Junior
Blue	MMAD 3,8	62	Central lungs in older children and adults. Nebulizers: Pari LC Sprint and Pari LC Sprint Tracheo
Transparent	MMD 7,3	65	Optimal deposition in the upper airways (larynx, trachea). Nebulizer: Pari LC Sprint Xlent
Orange	MMD 3,2	71	In combination with the pulsating system – effective deposition in the paranasal sinuses. Nebulizer: Pari LC Sprint Sinus
MMAD – mass median aerodynamic diameter; MMD – mass median diameter; FPF – fine particle fraction; ED – emitted dose; COPD – chronic obstructive pulmonary disease			

Table 4. Possibilities of shaping aerosol cloud parameters in Diagnostic E-Constellation Plus jet nebulizer

Parameters	Position 1	Position 2	Position 3
MMAD (µm)	8.0	5.4	4.0
FPF (% ED)	36	50	64
Efficiency (mL/min)	0.32	0.16	0.14
MMAD – mass median aerodynamic diameter; FPF – fine particle fraction; ED – emitted dose			

position modifies the function of the nebulizer chamber, leading to aerosol clouds with different MMAD values (Tab. 6) [18].

In the latest Flaem nebulizer, the Flaem RF7 Dual Speed Plus Koala, the chamber features a simple switch that allows users to change the mode of generating the aerosol cloud [19]. This device produces an aerosol (data for salbutamol) with likely the most optimal parameters (the lowest MMAD and the highest FPF) required for effective therapy of lower respiratory tract diseases (Tab. 7).

It is worth noting that the changes in MMAD and FPF, as shown in Table 5, Table 6, and Table 7, are accompanied by variations in the aerosol emission efficiency (expressed in mL/min), which impacts nebulization time (shorter for aerosols with larger droplets targeting the upper airways).

All the solutions described above lead to a rapid change in aerosol cloud parameters. In the future, these parameters may be adjusted smoothly and linearly, allowing for even more precise personalization of inhalation therapy to suit individual patient needs. This could be achieved,

Table 5. Possibilities of shaping aerosol cloud parameters in OMRON A3 jet nebulizer

Parameters	Position 1	Position 2	Position 3
MMAD (µm)	about 10.0	about 5.0	about 3.0
Efficiency (mL/min)	0.7	0.5	0.3
MMAD – mass median aerodynamic diameter			

Table 6. Aerosol cloud shaping with NP Flaem RF9 4 NEB

Parameters	Position 0	Position 1	Position 2	Position 3
MMAD (µm)	7.7	5.1	3.7	2.5
Efficiency (mL/min)	0.53	0.36	0.29	0.23
MMAD – mass median aerodynamic diameter				

Table 7. Salbutamol aerosol clouds generated from the Flaem RF7 Dual Speed Plus Koala nebulizer

Parameters	Salbutamol Position 1	Salbutamol Pozycja 2
Efficiency (mL/min)	0.20	0.42
MMAD (µm)	1.64	3.72
FPF (%ED)	95.8	63.5
FPF – fine particle fraction; ED – emitted dose		

among others, by adjusting the airflow rate generated by the compressor [20].

Solution 3

Adding a holding chamber to a mesh nebulizer not only increases aerosol availability by collecting aerosol generated during exhalation, but also modifies the characteristics of the inhaled aerosol cloud by reducing MMAD and increasing FPF due to the chamber's filtering effect. This leads to greater lung deposition, while reducing the oropharyngeal deposition, as well as minimizing aerosol escape into the environment [21–23]. Available data are limited to a small number of in vitro-tested mesh nebulizer and holding chamber combinations. Table 8 presents research findings for the Intec Mesh set used in conjunction with the Spiro Kids holding chamber [8].

The studies conducted using NaCl 0.9% showed (Tab. 8):
- a nearly 73% increase in the mass of the dose available for inhalation compared to a MN used without a holding chamber;
- reduction in Dv50 (median of the volumetric distribution) from 6.2 µm (MN alone) to 4.7 µm (MN + holding chamber);
- an increase in FPF from approximately 35% (MN alone) to about 55% (MN + holding chamber).

Solution 4

As recently demonstrated for nebulized budesonide, generic drug formulations may differ in aspects such as the number of budesonide crystals in suspension, as well as the type and concentration of excipients, which affects the physicochemical properties of the nebulized liquid and, consequently, the quality of the aerosol cloud [6]. Therefore, switching to a generic formulation with different characteristics may lead to variations in clinical efficacy. Previous studies have shown that the size of aerosol droplets can also be modified by changing the physicochemical properties of the liquid, including viscosity (or, more broadly, rheology), surface tension, and, in some cases, ionic strength [24, 25].

In the case of inhaled drugs, this effect can be achieved by incorporating suitable additives, such as biosurfactants or natural viscosity modifiers [26]. These substances offer a potential alternative to the synthetic adjuvants commonly used in inhaled medications, such as polysorbate 80 in nebulized corticosteroids.

In the future, new solutions are likely to emerge that will allow for more precise customization of the properties of aerosol clouds generated by jet nebulizers to better meet individual patient needs. We can anticipate the development of systems that will enable smooth, continuous modulation of aerosol generation rates across multiple operating modes, along with the dynamic adjustment of parameters such as MMAD and FPF. This will be made possible, among others, by adjusting the compressor airflow rate – optimal for the patient and the target deposition site [18].

In a mesh nebulizer, this shaping can be achieved by altering the diameter of the mesh holes and adjusting the mesh vibration frequency [27]. Currently, only models for *in vitro* studies are available, e.g. Micronice®.

Interchangeable nebulization chambers in mesh nebulizers could be another solution. Such attempts have been made by Aerogen/Nektar Therapeutics with Aeroneb Lab Control Module nebulizers. This device features two modules (chambers) that spray solutions, producing aerosol clouds with VMDs of 2.5–4.0 µm and 4.0–6.0 µm, but it has not yet been commercialized as a personal nebulizer [28].

Conclusions

Drug deposition in target airway sites is a key factor determining the efficacy and safety of inhalation therapy with any type of inhaler. The size and mechanisms of nebulized drug deposition are influenced by the patient's condition and inhalation technique, but primarily by the characteristics of the aerosol cloud, which depend on the nebulization method and drug formulation.

Several approaches are available in clinical practice to shape the aerosol cloud, such as selecting the appropriate nebulizer (jet or mesh), choosing the nebulization chamber operating mode (for jet nebulizers), using a holding chamber (with mesh nebulizers), and selecting the suitable drug formulation (for both jet and mesh nebulizers).

In the future, the development of nebulizers (primarily jet nebulizers) is expected to allow smooth modulation

Table 8. Results of measurements and calculations of emission and increased aerosol availability (average of 3 measurements ± standard deviation) for Intec Mesh MN with Spiro Kids type HC

Size	Value
Aerosol emission from a nebulizer: m_E [mg/min]	209.4 ± 31.7
Quantity deposited in IC, m_{KI} [mg/min]	66.6 ± 27.7
Aerosol available for inhalation: m_{INH} [mg/min]	144.5 ± 21.0
Gain [%] compared to the aerosol available without IC, $Z = \left(\frac{m_{INH}}{0{,}4m_E} - 1\right) \times 100\%$	+ 72.5%
HC – holding chamber	

of aerosol particle size (e.g., MMAD, FPF), tailored to the patient's age, type of respiratory pathology, optimal deposition site, drug type, and the functional status of the respiratory tract. This will enable precise calculation of the required therapeutic dose deposited in the target airway region. Such nebulization is expected to be highly clinically effective, safe, and potentially more cost-efficient due to reduced drug loss.

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THE IMPACT OF A LOW-CARBOHYDRATE DIET ON METABOLIC PARAMETERS IN PATIENTS WITH TYPE 1 AND TYPE 2 DIABETES MELLITUS

Wpływ diety niskowęglowodanowej na parametry metaboliczne pacjentów z cukrzycą typu 1 i typu 2

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Abstract

The global prevalence of diabetes mellitus reached 382 million in 2013 and is expected to rise to 592 million by 2035. The consequences of diabetes mellitus, especially if it is poorly controlled, might be dramatic and lead to life-threatening conditions. Therefore, it is crucial to prevent diabetes mellitus, diagnose it as early as possible, and treat it effectively. In addition to medications, lifestyle modification – especially diet and eating habits – seems to be the instrumental factor in the management of diabetes mellitus. This review is focused on the benefits and risks of a low-carbohydrate diet in patients with type 1 and 2 diabetes mellitus. Clinical trials containing data on changes in metabolic parameters, such as fasting glucose, fasting insulin, and HbA_{1c}, resulting from the use of a low-carbohydrate diet by patients with diabetes mellitus were analyzed. Most of the included studies showed improvements in these parameters. Only one study reported an increase in HbA_{1c}, likely due to patients' non-compliance with dietary instructions. Consequently, devoting time to clear explanations of dietary rules, providing help in implementing them, and further monitoring of patients' food intake seem to be crucial. Although the outcomes of this study showed a beneficial effect of a low-carbohydrate diet on metabolic parameters, conducting further studies is still required to clearly and explicitly define all positive and promising outcomes of this review, as well as risks associated with the use of a low-carbohydrate diet by patients with diabetes mellitus.

Streszczenie

W 2013 r. liczba chorych na cukrzycę na świecie wynosiła 382 miliony, a szacuje się, że do 2035 r. wzrośnie do 592 milionów. Konsekwencje tej choroby, szczególnie jeśli nie jest odpowiednio kontrolowana, mogą być dramatyczne i prowadzić do stanów zagrożenia życia. Z tego powodu niezwykle ważne jest zapobieganie cukrzycy, dążenie do szybkiego jej rozpoznania oraz skutecznego leczenia. W walce z tą chorobą oprócz farmakoterapii niewątpliwie kluczowy jest zdrowy styl życia, w szczególności zmiana diety i modyfikacja nawyków żywieniowych. W tym przeglądzie skupiono się na korzyściach i zagrożeniach wynikających ze stosowania diety niskowęglowodanowej u pacjentów z cukrzycą typu 1 i typu 2. Przeanalizowano badania kliniczne zawierające dane na temat zmian w parametrach metabolicznych, takich jak glukoza na czczo, insulina na czczo i HbA_{1c}, które wystąpiły w wyniku stosowania tej diety przez pacjentów z cukrzycą. W większości uwzględnionych badań zaobserwowano poprawę tych parametrów. Tylko w jednym badaniu odnotowano wzrost HbA_{1c} u chorych na cukrzycę typu 1, niemniej był on prawdopodobnie rezultatem nieprzestrzegania zasad diety przez pacjentów. W związku z tym konieczne wydaje się poświęcenie czasu na objaśnienie pacjentom założeń diety niskowęglowodanowej, pomoc w jej wdrożeniu oraz późniejsze monitorowanie spożywanych przez nich pokarmów. Pomimo że wyniki prezentowanego przeglądu wskazują na korzystny wpływ diety niskowęglowodanowej na parametry metaboliczne chorych na cukrzycę, konieczne jest przeprowadzenie dalszych badań w celu jasnego i jednoznacznego określenia wszystkich korzyści i zagrożeń wynikających ze stosowania diety niskowęglowodanowej przez pacjentów z cukrzycą.

Keywords: type 2 diabetes mellitus; type 1 diabetes mellitus; carbohydrate-restricted diet

Słowa kluczowe: cukrzyca typu 2; cukrzyca typu 1; dieta niskowęglowodanowa

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Introduction

The global prevalence of diabetes mellitus (DM) reached 382 million in 2013. By 2035, it is expected to rise to 592 million [1]. This increase is likely driven by factors such as unhealthy and unbalanced diets, lack of physical activity, and the general global rise in obesity rates. The prevalence of type 2 diabetes mellitus (T2DM) increases with age, and because Western societies are consistently aging, the number of new diabetes cases continues to grow steadily. Moreover, longer life expectancy leads to an increase in the prevalence of DM. Similarly, according to some studies, this may apply not only to T2DM but also to T1DM (type 1 diabetes mellitus) [2]. The consequences of DM, especially if it is poorly controlled, might be very severe and lead to life-threatening conditions such as neuropathy, retinopathy, cardiovascular diseases, heart attack, and stroke. Taking these facts into consideration, it is crucial to prevent and effectively treat DM as early as possible [3]. In addition to pharmacological treatment, there are many other recommendations for diabetics. Chief among these are maintaining a proper body weight and balanced glucose levels, which are instrumental in DM management. Secondly, physical activity should be on the daily schedule of every patient with DM. Even low-intensity activities, such as walking, may be immensely beneficial. Smoking cessation is strongly recommended for all individuals, especially those with chronic diseases. When it comes to diet, there are special rules which should be implemented by all diabetics. Firstly, patients are advised to consume low-glycemic, well-balanced meals. It would be additionally beneficial to consume 4–5 meals per day at regular intervals (every 3–4 hours). Monosaccharides should be avoided as much as possible, which may be challenging due to their high prevalence in all kinds of food products such as milk, flour, yoghurts, ketchup, and many others. In cases of excess body weight, a caloric deficit should be introduced. The specific amount of calories will depend among others on the individual's primary body weight and the level of daily activity. Patients are also recommended to exclude products rich in monosaccharides, those with a high content of saturated fats, and ultra-processed foods. In contrast, diabetics should consume more complex carbohydrates and products rich in fiber, which can be found predominantly in products of plant origin. Maintaining a healthy body weight is instrumental in DM management [4]. It is proven that diet is responsible for 80% of weight loss success, whereas physical activity contributes around 20%. Currently, various types of diets and eating habits are gaining popularity, also among individuals who do not suffer from being overweight or any gastrointestinal disruption. Increasingly, they decide to implement restricted diets and exclude whole groups of products without any medical indication. Intermittent fasting, ketogenic diets, low-carbohydrate diets, gluten-free diets, or plant-based diets are the most common choices as some people consider them as the perfect cure for all health conditions [5]. All the above mentioned diets may affect the body in various ways, both positively and negatively. This review focuses on the low-carbohydrate diet, where daily carbohydrate intake should not exceed 30 g or 26% of total caloric intake.

Aim of the review

This review was conducted to estimate whether a low-carbohydrate diet may be beneficial for diabetic patients.

Material and methods

Databases such as Pubmed and Scopus were screened systematically to identify articles published in 2020–2023 that contained information about the influence of a low-carbohydrate diet on metabolic parameters in patients with diabetes mellitus (both type 1 and type 2). This review was conducted according to the PRISMA protocol (Fig. 1) and the PICO method. The search process is shown in the chart below. Titles and abstracts were screened independently by the authors. Only randomized clinical trials published in 2020–2023 were included in the review. An additional inclusion criterion was that the articles had to report on the metabolic parameters in accordance with a low-carbohydrate diet in patients with diabetes mellitus type 1 or type 2. The required parameters included fasting insulin level OR/AND glucose level OR/AND HbA_{1c}. Altogether, 890 articles were found. After the removal of duplicates, 564 articles remained. All titles and abstracts were screened independently. Forty-four were included for further analysis and afterwards read in full. Ultimately, eight studies were included in the review.

Results

Most of the included studies indicate that a low-carbohydrate diet may be beneficial in T2DM patients. Specific changes in fasting glucose levels, HbA_{1c} levels, and fasting insulin level are presented in Table 1, Table 2, and Table 3, respectively. One of the studies enrolled 11 individuals with T2DM and divided them into three groups (low-carbohydrate diet, low-carbohydrate diet + 15-minute walk post-meal, and low-glycemic diet). Those assigned to a low-carbohydrate diet limited their carbohydrate intake to 10% of total energy for four days. The experiment was repeated three times with 9–14 days washout periods between interventions. There was a significant decrease in fasting glucose and the proinsulin-C-peptide ratio in the groups implementing a low-carbohydrate diet. These changes did not occur in individuals on low-glycemic index diet. Thus, it indicates the superiority of a low-carbohydrate diet over a low-glycemic diet in patients with T2DM [6]. Similar outcomes were observed in another study, during which diabetics with poorly controlled T2DM (HbA_{1c} ≥7.5%) had reduced their carbohydrate intake to 90 g/day for 18 months. Outcomes revealed that the HbA_{1c} and two-hour postprandial serum glucose values were significantly lower in the low-carbohydrate diet group than in the traditional diabetic diet [7]. A trial conducted in China, which lasted for three months, indicates that the low-carbohydrate diet is more effective in lowering HbA_{1c} than the low-fat diet [8]. Nevertheless, the low-fat diet seems to be more efficient in lowering triglycerides and cholesterol levels [9]. A low-carbohydrate diet may not only significantly improve the level of metabolic parameters related to DM, but it also help regain healthy body mass

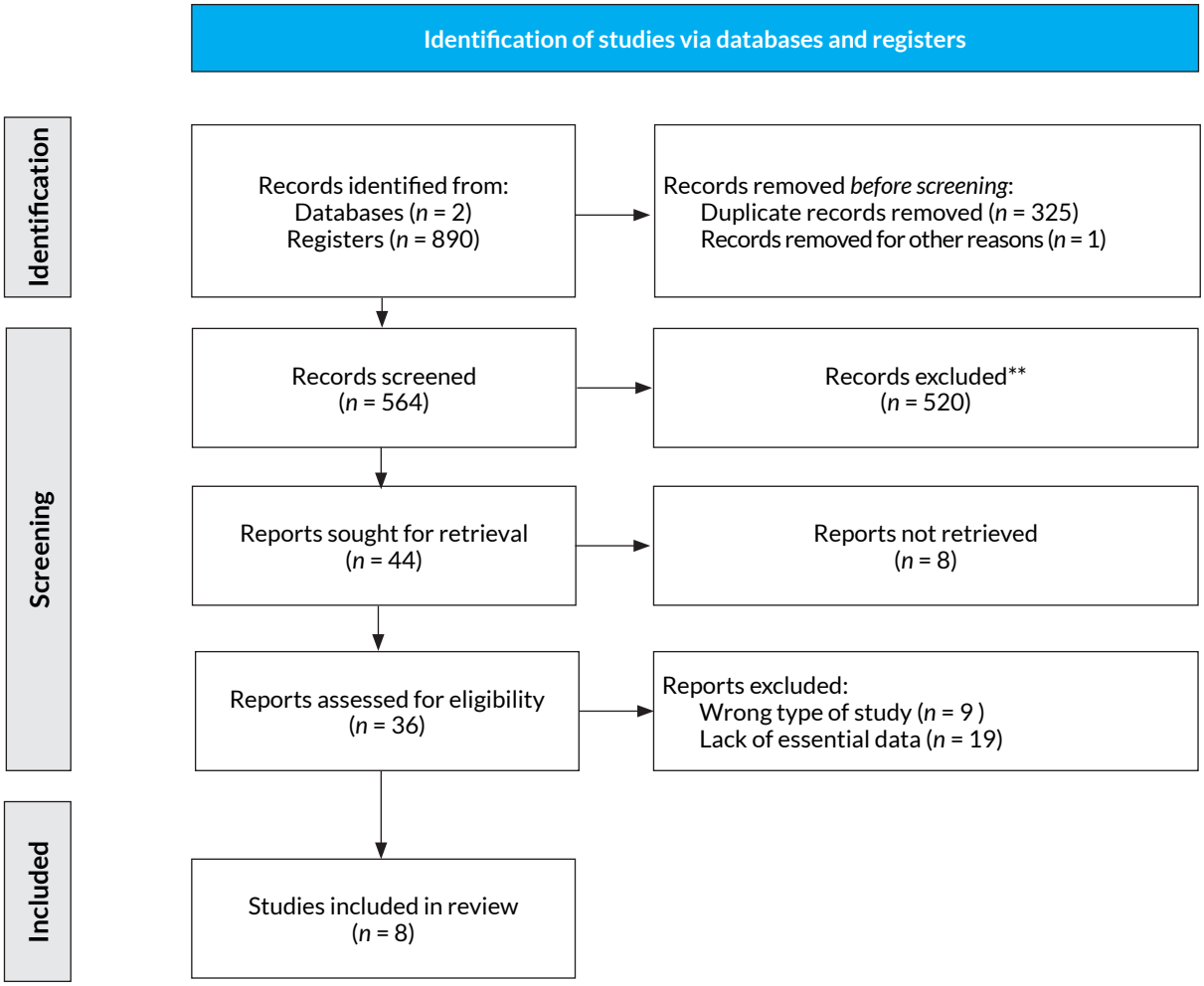

Figure 1. PRISMA flow diagram

in T2DM patients, who do not receive any pharmacological treatment [10]. It is commonly believed that exercises are a crucial factor in weight loss. However, one of the conducted studies shows that a low-carbohydrate diet might be even more effective in obese patients than physical activity – individuals lose 3.56 kg through diet compared to 1.24 through exercise [11]. Reducing carbohydrates while increasing fat and protein intake may seem dangerous – especially in patients with kidney diseases. Nonetheless, the out-

Table 1. Overview of clinical studies on the effects of a low-carbohydrate diet on fasting glucose levels in patients with type 2 diabetes

Authors/ Year published/ Time of study	Number of patients and median age	Duration of diet	Type of diabetes	Fasting glucose pre	Fasting glucose post
Zainordin et al./ 2021/ 2019–2020/ [12]	14 Age: 57	12 weeks	2	8.2 mmol/L = 147.6 mg/dL	6.3 mmol/L = 113.4 mg/dL
Dorans et al./ 2022/ 2018–2021/ [10]	75 Age: 59.3	6 months	2	6 mmol/L = 108.3 mg/dL	5.55 mmol/L = 99.9 mg/dL
Chen et al./ 2022/ 2018–2019/ [7]	36 Age: 63.3	18 months	2	8.9 mmol/L = 160.6 mg/dL	7.4 mmol/L = 133.6 mg/dL
Wang et al./ 2018/ 2015–2016/ [8]	24 Age: 66.79	3 months	2	8.28 mmol/L = 149.04 mg/dL	6.67 mmol/L = 120.06 mg/dL
Han et al./ 2021/ 2019–2020/ [9]	60 Age: 51.45	6 months	2	8.1 mmol/L = 145.8 mg/dL	6.2 mmol/L = 111.6 mg/dL
Cai et al./ 2021/ 2018–2019/ [11]	22 Age: 25.36	3 weeks	-	5.04 mmol/L = 90.72 mg/dL	4.98 mmol/L = 89.64 mg/dL
Myette-Côté et al./ 2018/ 2015–2017/ [6]	11	4 days	2	8.4 mmol/L = 151.35 mg/dL	7.6 mmol/L = 136.94 mg/dL

Table 2. Overview of clinical studies on the effects of a low-carbohydrate diet on HbA_{1c} levels in patients with type 2 diabetes

Authors/ Year published/ Time of study	Number of patients and median age	Duration of diet	Type of diabetes	HbA_{1c} pre	HbA_{1c} post
Zainordin et al./ 2021/ 2019–2020/ [12]	14 Age: 57	12 weeks	2	8.8%	7.3%
Dorans et al./ 2022/ 2018–2021/ [10]	75 Age: 59.3	6 months	2	6.17%	5.91%
Chen et al./ 2022/ 2018–2019/ [7]	36 Age: 63.3	18 months	2	8.4%	6.9%
Wang et al./ 2018/ 2015–2016/ [8]	24 Age: 66.79	3 months	2	7.43%	6.8%
Han et al./ 2021/ 2019–2020/ [9]	60 Age: 51.45	6 months	2	7.7%	6.0%
Cai et al./ 2021/ 2018–2019/ [11]	22 Age: 25.36	3 weeks	-	5.30%	5.28%
Duffus et, al./ 2022/ time frame not specified/ [13]	14 Age: 15.5	12 weeks	1	7.9%	8.4%

Table 3. Overview of clinical studies on the effects of a low-carbohydrate diet on fasting insulin levels in patients with type 2 diabetes

Authors/ Year published/ Time of study	Number of patients and median age	Duration of diet	Type of diabetes	Fasting insulin pre	Fasting insulin post
Dorans et al./ 2022/ 2018–2021/ [10]	75 Age: 59.3	6 months	2	30.9 µIU/L = 205 pmol/L	26.9 µIU/L = 186 pmol/L
Myette-Côté et al./ 2018/ 2015–2017/ [6]	11 Age: 48–72	3 × 4 days with 9–14 days between each intervention	2	9.3 µIU/L = 64.8 pmol/L	8.94 µIU/L = 62.1 pmol/L

comes outlined in one of the studies suggest that a very low-carbohydrate diet in patients with diabetic kidney disease is not only a safe option but may also be associated with significant improvements in glycemic control. This phenomenon was not observed in the group following a standard low-protein diet [12]. In another study, individuals with DM, who had been assigned to a low-carbohydrate diet, were instructed to consume not more than 25% of their total daily caloric intake from carbohydrates. It turned out that during the trial none of these participants adhered to this recommendation – they went from consuming 44.3% to 44.2% of energy from carbohydrates. Not surprisingly, there were no significant differences in glycemic control, lipid profile, or quality of life parameters. This trial aimed to assess the impact of a low-carbohydrate diet on glycemia, lipidemia, and quality of life but instead it outlined the problem of non-compliance with the instructions by participants. These results are immensely helpful with the realization of how poorly some adolescents follow their doctor's orders [13].

In general, as a result of a low-carbohydrate diet the decrease in fasting glucose levels was observed in all included studies, with an average reduction of 1.16 mmol/L = 20.88 mg/dL. A similar phenomenon was observed for another parameter, which was the fasting insulin level – the average decrease was 10.85 pmol/L. In one study, there was an observed increase in HbA_{1c} (7.9%–>8.4%) among patients with type 1 diabetes. There is a distinct possibility that it happened due to the patients' non-compliance with dietary instructions. In the remainder of the included studies, the average decrease in HbA_{1c} was 0.935%.

Discussion

Principal findings

The outlined outcomes indicate that implementation of a low-carbohydrate diet positively affects glycemic management in both the short and long term [7, 6]. Interestingly, a low-carbohydrate diet may have more beneficial effects on glucose management than a diet based on low-glycemic index products [6]. Moreover, reducing carbohydrate intake might help decrease elevated HbA_{1c} levels without the use of medications [10]. There is a strong possibility that it could also have a greater effect on lowering body weight than physical exercise in patients with T2DM [11]. Interestingly, despite its higher fat and protein content, a low-carbohydrate diet may be more effective in reducing HbA_{1c} levels in patients with diabetic kidney disease than a low-protein diet [12]. However, other diets, such as a low-fat diet, result in a significantly better lipid profile, so special attention has to be paid to assessing individual needs and priorities in therapy [8]. It needs to be emphasized that even the best individually designed treatment may prove ineffective due to, as studies show, patients' common tendency to disregard the recommendations, which especially concerns adolescents [13].

Comparison with previous studies

According to the rule "first, do no harm", the potential risks of low-carbohydrate diets and their possible impact on medical conditions are first addressed. To do that, the results of previously conducted studies are referred to and analyzed. Firstly and most importantly, a Japanese study proved that a low-carbohydrate diet does not increase

the risk of developing type 2 diabetes. A strong point of this analysis is the significant number of individuals included, which totaled 19,048 [14]. Moreover, diets characterized by a low carbohydrate intake is inversely associated with the risk of diabetic neuropathy in women [15]. On the contrary, previous use of this diet may result in more detrimental oral glucose tolerance test values in women with gestational diabetes mellitus [16]. In the context of type 1 diabetes, one study conducted in an Australian population showed a significant reduction in HbA_{1c} due to the restriction of carbohydrates [17]. This type of diet is also associated with a lower risk of mortality among adults with T2DM, as shown in a study carried out with 5,677 patients [18]. Evidence also suggests that a low-carbohydrate diet may not only influence the physical state but can also lead to an improvement in psychological health in adults with T2DM according to one of the studies which enrolled 115 individuals [19]. Various forms of low-carbohydrate diets exist; one notable example is the ketogenic diet, which is based on the restriction of the consumed carbohydrates to the maximum level. The findings of a recent study show that individuals with T2DM who followed a ketogenic diet could reduce their intake of insulin and antidiabetic drugs, which is highly beneficial [20]. The lifestyle intervention in individuals at high risk of developing type 2 diabetes, while maintaining a relatively carbohydrate-rich diet, resulted in the long-term prevention of progression to type 2 diabetes and is generally seen as safe [21].

Limitations

The primary limitations of the sources analyzed in this study arise from weaknesses in research design. There is a limited number of longitudinal studies with long-term follow-up periods. Additionally, many studies did not include a large enough number of patients and the duration of the trials varied considerably.

Conclusions

A decrease in fasting insulin, fasting glucose, and HbA_{1c} was observed in all studies included in this review that involved patients with type 2 diabetes mellitus. An increase in HbA_{1c} reported in one of the studies with T1DM patients was likely the result of the patients' non-compliance with dietary instructions. These outcomes indicate that a diet low in carbohydrates might be beneficial for diabetics. However, it is crucial to provide patients with clear dietary guidance and then monitor their adherence. Some individuals may not be sure about the allowed products and due to the lower variety of products they may also struggle with cooking ideas. Thus, it seems to be a good idea to recommend dietary consultation in this group. Moreover, calculating macronutrient content for every single meal is a formidable challenge which patients have to face. However, there are specific smartphone applications designed to help monitor calories and nutritious intake from products, which may immensely simplify the process and consequently lead to better dietary compliance. Nevertheless, despite the positive and promising outcomes of this review, further studies, especially with long follow- up periods and a representative number of participants, are required to clearly and explicitly determine all benefits and risks associated with the use of low-carbohydrate diets among patients with diabetes mellitus.

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THE INFLUENCE OF CHRONIC STRESS ON ORAL HEALTH: A LITERATURE REVIEW

Wpływ przewlekłego stresu na zdrowie jamy ustnej: przegląd literatury

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Abstract

Chronic stress, particularly in the context of post-traumatic stress disorder, has significant implications for oral health due to its multifaceted physiological, psychological, and behavioral effects. This review outlines the key mechanisms and clinical consequences of chronic stress on oral health outcomes, drawing on findings from a systematic review of 16 studies. Post-traumatic stress disorder has been strongly associated with an increased prevalence of periodontitis, bruxism, xerostomia, and temporomandibular disorders. Chronic activation of the stress response disrupts autonomic regulation and systemic immune function, exacerbating oral health conditions. Behavioral factors such as poor oral hygiene and increased tobacco use further contribute to periodontal disease, while psychological stress amplifies pain perception in conditions like temporomandibular disorders and chronic orofacial pain. Pharmacological treatments for post-traumatic stress disorder, including selective serotonin reuptake inhibitors, while effective in managing psychological symptoms, frequently cause hyposalivation, leading to xerostomia and increased risk of dental caries and periodontal disease. Bruxism, prevalent among individuals with post-traumatic stress disorder, is strongly linked to elevated stress levels, resulting in significant wear and damage to teeth, as well as contributing to orofacial pain and temporomandibular disorders. Insomnia and sleep disturbances, common among post-traumatic stress disorder sufferers, impair immune function and tissue regeneration, further heightening susceptibility to oral infections and delaying wound healing. The bidirectional relationship between post-traumatic stress disorder and chronic orofacial pain underscores the need for integrated care that addresses both physical and psychological health. Multidisciplinary approaches incorporating trauma-informed care and tailored oral health interventions are critical for mitigating the oral health challenges faced by individuals with post-traumatic stress disorder. These strategies not only improve oral health outcomes but also enhance overall well-being by addressing systemic inflammation and psychological distress. Future research should focus on optimizing treatment protocols and fostering collaboration between dental and mental health professionals.

Streszczenie

Przewlekły stres, szczególnie w kontekście zespołu stresu pourazowego, ma istotny wpływ na zdrowie jamy ustnej ze względu na swoje złożone skutki fizjologiczne, psychologiczne i behawioralne. W niniejszym przeglądzie przedstawiono kluczowe mechanizmy oraz implikacje kliniczne przewlekłego stresu dla zdrowia jamy ustnej, opierając się na wynikach systematycznego przeglądu literatury obejmującego 16 badań. Zespół stresu pourazowego jest silnie powiązany z wyższą częstością występowania periodontopatii, bruksizmu, kserostomii oraz zaburzeń stawu skroniowo-żuchwowego. Przewlekła aktywacja odpowiedzi na stres zaburza regulację autonomiczną i funkcje układu immunologicznego, pogłębiając problemy zdrowotne jamy ustnej. Czynniki behawioralne, takie jak zaniedbywanie higieny jamy ustnej czy zwiększone spożycie tytoniu, dodatkowo przyczyniają się do rozwoju chorób przyzębia, podczas gdy stres psychologiczny nasila percepcję bólu w schorzeniach takich jak zaburzenia stawu skroniowo-żuchwowego i przewlekły ból twarzy. Farmakoterapia zespołu stresu pourazowego, w tym stosowanie selektywnych inhibitorów wychwytu zwrotnego serotoniny, choć skuteczna w leczeniu objawów psychologicznych, często prowadzi do hiposaliwacji, powodując kserostomię oraz zwiększone ryzyko próchnicy i chorób przyzębia. Bruksizm, częsty u pacjentów z zespołem stresu pourazowego, jest silnie związany z podwyższonym poziomem stresu, co skutkuje znacznym zużyciem i uszkodzeniem zębów oraz przyczynia się do bólu twarzy i zaburzeń stawu skroniowo-żuchwowego. Bezsenność i zaburzenia snu, powszechne wśród osób z zespołem stresu pourazowego, osłabiają funkcje układu odpornościowego i regenerację

tkanek, co zwiększa podatność na infekcje jamy ustnej oraz opóźnione gojenie się ran. Dwukierunkowa relacja między zespołem stresu pourazowego a przewlekłym bólem twarzy podkreśla potrzebę zintegrowanej opieki, uwzględniającej zarówno aspekty fizyczne, jak i psychiczne. Podejście wielodyscyplinarne, obejmujące opiekę dostosowaną do traumatycznych doświadczeń oraz ukierunkowane interwencje stomatologiczne, jest kluczowe dla łagodzenia problemów zdrowotnych jamy ustnej u pacjentów z zespołem stresu pourazowego. Takie strategie poprawiają nie tylko zdrowie jamy ustnej, ale także ogólne samopoczucie, redukując stan zapalny i stres psychologiczny. Przyszłe badania powinny koncentrować się na optymalizacji protokołów leczenia oraz współpracy między specjalistami z zakresu zdrowia psychicznego i stomatologii.

Keywords: PTSD; post-traumatic stress disorder; oral health; chronic stress

Słowa kluczowe: PTSD; zespół stresu pourazowego; zdrowie jamy ustnej; przewlekły stres

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Introduction

The intricate relationship between mental and physical health plays a significant role in oral health outcomes. Psychological conditions, such as depression and anxiety, often lead to the neglect of oral hygiene practices, resulting in a higher prevalence of dental caries, periodontal disease, and other oral pathologies. For instance, individuals with severe mental illness may exhibit reduced self-care abilities, contributing to poor oral health outcomes and increased risk of oral infections [1, 2]. Moreover, systemic conditions like diabetes mellitus or cardiovascular disease are strongly linked to oral health deterioration, emphasizing the bidirectional connection between systemic health and oral well-being [3].

Post-traumatic stress disorder (PTSD) is a psychological condition that can result from exposure to traumatic events, such as warfare, accidents, physical violence, or other extreme stressors. PTSD affects overall health, including oral health, and can lead to both physiological and psychological consequences for the oral cavity and teeth. PTSD is characterized by persistent re-experiencing of the traumatic event, avoidance behaviors, and negative alterations in cognition and mood. While PTSD is the most widely recognized disorder following trauma exposure, other stress-related conditions, such as acute stress disorder and generalized anxiety disorder, share overlapping symptoms, including intrusive thoughts and hypervigilance.

However, PTSD is distinct in its prolonged duration and intensity, often leading to significant functional impairment [4]. PTSD poses significant challenges to the mental health of military personnel, often exacerbated by their exposure to combat and operational stressors. Studies reveal that military service is inherently associated with elevated rates of PTSD, depression, and anxiety disorders [5].

Emerging evidence suggests that PTSD has a direct and multifaceted impact on oral health. Individuals with PTSD are more prone to bruxism (teeth grinding). This behavior may occur as a result of chronic stress, a common symptom of PTSD. Stress leads to increased muscle tension, and teeth grinding is one of the physiological mechanisms through which the body responds to this tension, especially during sleep.

PTSD is also frequently associated with poor oral hygiene, which can lead to oral mucositis and periodontal diseases. Chronic stress and depression, both common among PTSD sufferers, contribute to decreased motivation to maintain proper oral care, which in turn increases the risk of caries and gum disease [6].

Pharmacological treatments, particularly antidepressant medications such as selective serotonin reuptake inhibitors (SSRIs), are a cornerstone in managing PTSD and other mood disorders. Despite their efficacy, these medications frequently produce adverse effects on oral health, including hyposalivation (reduced salivary flow) [7]. Hyposalivation can lead to xerostomia (dry mouth), which in turn promotes the development of dental caries, periodontal disease, and oral discomfort [8]. Additionally, the use of certain antidepressants has been linked to changes in oral microbiota and impaired wound healing, further complicating oral health outcomes [9].

Insomnia and other sleep disturbances, common in PTSD, may also contribute to the deterioration of oral health. Poor sleep reduces the body's ability to regenerate, which can weaken immune function and make individuals more susceptible to infections, including those affecting the oral cavity [10].

These behaviors, combined with psychological stressors, contribute to a cycle of worsening oral and systemic health. The aim of this review is to synthesize the available literature on the impact of PTSD and stress on oral health, highlighting the challenges faced in clinical dentistry and outlining the need for further research to improve treatment protocols in this area.

Material and methods

The literature review was conducted utilizing the PubMed database to ensure comprehensive coverage of relevant studies. The inclusion criteria for article selection were as follows: availability in either Polish or English, and

thematic focus on the relationship between stress – specifically PTSD – and oral health. Particular emphasis was placed on studies exploring the physiological, psychological, and behavioral pathways through which PTSD affects oral health outcomes. After applying these criteria, 14 articles were deemed eligible and included in the final review, providing a robust foundation for analyzing the interplay between PTSD and oral health.

Discussion

PTSD and periodontal health

PTSD is strongly associated with a higher prevalence of periodontitis, primarily due to both behavioral and physiological factors. Tagger-Green et al. reported that individuals with PTSD exhibit a significantly higher prevalence of severe periodontal disease (66.2%), which was attributed to neglected oral hygiene, increased tobacco use, and systemic immune system alterations caused by chronic stress [11]. Similarly, Muhvić-Urek et al. demonstrated that Croatian war veterans with PTSD displayed markedly worse oral health outcomes, including advanced periodontal disease and tooth loss, when compared to individuals without PTSD [12].

In addition to these clinical findings, De Oliveira Solis et al. highlighted that PTSD alters pain perception during periodontal probing. Patients with PTSD reported significantly higher pain scores (VAS >40 mm) compared to controls, despite no significant differences in periodontal clinical parameters. This underscores the role of psychological factors in modulating the experience of oral pain [13].

PTSD and bruxism

Bruxism, both during wakefulness and sleep, is commonly reported among individuals with PTSD. Tagger-Green et al. observed a notably high prevalence of bruxism (90.1%) among PTSD patients, which they linked to elevated stress levels and parafunctional behaviors [11]. Similarly, De Oliveira Solis et al. reported that PTSD patients are over three times more likely to exhibit awake bruxism, a condition frequently accompanied by orofacial pain [14].

Knibbe et al. further confirmed that PTSD severity correlates with higher rates of both awake (48.3%) and sleep bruxism (40.1%), with significantly greater prevalence compared to the general population (p <0.001) [15]. Importantly, therapeutic interventions targeting both physical and psychological symptoms have shown promise. Wörner et al. demonstrated that combined therapies, including splint therapy, massage, and jaw exercises, significantly reduced bruxism-related symptoms and improved quality of life in PTSD patients [16]. Furthermore, PTSD-focused treatments have been shown to reduce bruxism prevalence over time, highlighting the importance of trauma-informed care approaches [17].

PTSD and temporomandibular disorders

Temporomandibular disorders (TMD) represent another critical issue among patients with PTSD. Al-Khudhairy et al. found that PTSD exacerbates TMD symptoms, resulting in chronic pain, a lowered pain threshold, and diminished treatment efficacy [18]. Minervini et al. demonstrated that more than half (56.2%) of war veterans with PTSD exhibited signs of TMD, including pain on muscle palpation and disc displacement, compared to only 20.18% in non-exposed controls [19].

The association of chronic orofacial pain and TMD in PTSD patients is further supported by De Leeuw et al., who reported that 15% of individuals with chronic orofacial pain also exhibited PTSD symptoms. These patients experienced more severe pain and greater psychological distress compared to those without PTSD [20]. Yap et al. emphasized the significant role of psychological factors in amplifying TMD-related pain, noting high rates of depression (39%) and somatization (55%) among TMD patients [21]. The negative impact of TMD on oral health-related quality of life (OHRQoL) has also been well documented. Almoznino et al. observed that TMD patients frequently reported severe physical pain and psychological discomfort, which impaired daily functioning [22]. Similarly, Miettinen et al. found that women with TMD exhibited significantly worse OHRQoL, with depression and somatization being major contributing factors [17].

PTSD and poor oral hygiene

PTSD is closely linked to poor oral hygiene practices, significantly contributing to oral health deterioration. Tagger-Green et al. attributed the elevated prevalence of periodontitis among PTSD patients to neglected daily oral hygiene and increased tobacco use, which are often associated with chronic stress and psychological distress [11]. Similarly, Muhvić-Urek et al. reported that war veterans with PTSD exhibited poorer overall oral health, including more severe periodontal conditions and greater tooth loss, compared to the general population [12].

Conclusions

The reviewed evidence underscores a strong association between PTSD and various oral health issues, particularly periodontal disease, bruxism, xerostomia, and temporomandibular disorders (TMD). PTSD significantly exacerbates these conditions, as seen in higher rates of severe periodontal disease, TMD, and bruxism among PTSD patients compared to controls. Psychological comorbidities – such as depression and somatization – further amplify pain perception and impair oral health, particularly in TMD patients.

The bidirectional relationship between PTSD and chronic orofacial pain suggests that these conditions mutually exacerbate one another, underscoring the need for integrated care that addresses both physical and psychological health. Interventions focusing on trauma-specific treatments have shown promise, with evidence of reduced severity of TMD and bruxism, improved pain management, and enhanced quality of life.

Both xerostomia, temporomandibular joint pain, and periodontal disease are common health issues among individuals with PTSD, associated with both the direct effects of post-traumatic stress and its indirect consequences, such as dysregulation of the autonomic

nervous system, medication use, and neglect of oral hygiene.

Addressing these interrelated health issues requires a multidisciplinary approach that includes both psychological and dental aspects. It is important for individuals with PTSD to be aware of these potential health problems and to regularly consult with a dentist and mental health professionals to effectively manage both the emotional and physical aspects of their health.

Tailored oral health care strategies, incorporating mental health evaluations and interventions, are essential for managing PTSD-related oral health disturbances. Such approaches not only improve oral health outcomes but may also mitigate systemic inflammation and enhance overall well-being. These findings highlight the critical need for a multidisciplinary approach in the treatment of PTSD patients with oral health challenges.

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MUSHROOM POISONING – IS IT BECOMING AN INCREASINGLY SERIOUS PROBLEM?

Zatrucie grzybami – czy to coraz poważniejszy problem?

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Abstract

Introduction and objective: Mushrooms have remained popular for years. The positive effects they have on the human body are increasingly emphasized. Despite the increase in knowledge among mushroom pickers, Polish hospitals still admit patients with symptoms of poisoning. This study analyzes poisoning caused by the consumption of mushrooms in adults, based on hospitalization records in the Clinical Department of Toxicology and Cardiology of the Cardinal Stefan Wyszyński Regional Specialist Hospital in Lublin. The aim of the study is to assess whether the problem of mushroom poisoning is increasing. **Material and methods:** This study had a retrospective character. Medical records of 1,539 adult patients hospitalized because of intoxication were analyzed. Of these, a group of 14 patients with mushroom poisoning was identified. **Results:** Of the patients hospitalized in 2021–2022, 14 were diagnosed with mushroom poisoning. Among them, 9 were male (64.29%) and 5 were female (35.71%). The age range of the study subjects was 25–92 years. The patients lived mainly in rural areas (9 individuals). The majority (64.29%) had collected the mushrooms on their own, and in two cases there was collective poisoning. The highest number of cases was recorded in the summer-autumn months, with most incidents occurring in September. Symptoms usually appeared between 7 and 12 hours after ingestion. The average length of hospital stay was 7.1 days. No deaths were reported in the study group. **Conclusions:** A decrease in the number of poisonings was observed. It is necessary to raise awareness about the consequences of consuming poisonous mushrooms and how to identify them. It is important to highlight the safety of eating cultivated mushrooms.

Streszczenie

Wprowadzenie i cel: Grzyby od lat cieszą się niesłabnącą popularnością. O ich pozytywnym wpływie na organizm człowieka słyszy się coraz częściej. Mimo wzrostu wiedzy wśród grzybiarzy na ich temat, do polskich szpitali wciąż trafiają pacjenci z objawami zatrucia. W niniejszej pracy dokonano analizy zatruć spowodowanych spożyciem grzybów przez osoby dorosłe na podstawie dokumentacji hospitalizacji w Klinicznym Oddziale Toksykologiczno-Kardiologicznym Wojewódzkiego Szpitala Specjalistycznego im. Stefana Kardynała Wyszyńskiego w Lublinie. Celem badania jest ocena, czy problem zatruć grzybami narasta. **Materiał i metody:** Badanie miało charakter retrospektywny. Wykorzystano analizę dokumentacji medycznej 1539 dorosłych pacjentów hospitalizowanych w latach 2021–2022 z powodu zatruć. Spośród nich wybrano grupę 14 osób zatrutych grzybami. **Wyniki:** Spośród pacjentów hospitalizowanych w latach 2021–2022 u 14 zdiagnozowano zatrucie grzybami. W badanej grupie było 9 mężczyzn (64,29%)

i 5 kobiet (35,71%). Przedział wiekowy badanych wynosił 25–92 lata. Pacjenci mieszkali głównie na obszarach wiejskich (9 osób). Większość (64,29%) zbierała grzyby samodzielnie, a w dwóch przypadkach doszło do zatrucia zbiorowego. Największą liczbę zatruć zaobserwowano w miesiącach letnio-jesiennych, najwięcej we wrześniu. Objawy pojawiały się zwykle między 7. a 12. godziną po spożyciu. Średnia długość pobytu na oddziale wynosiła 7,1 dnia. W badanej grupie nie zaobserwowano zgonów. **Wnioski:** Zaobserwowano spadek liczby zatruć grzybami. Konieczne jest rozpowszechnianie informacji o konsekwencjach spożywania grzybów trujących i sposobach ich identyfikacji. Ważne jest podkreślanie bezpieczeństwa spożywania grzybów uprawnych.

Keywords: adults; mushrooms; poisoning; amanitin

Słowa kluczowe: dorośli; grzyby; zatrucie; amanityna

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Introduction and purpose

Mushrooms are a group of eukaryotic organisms classified in their own kingdom, with approximately 100,000 known species. Around 50–100 of these are considered poisonous [1].

Mushrooms have a long history of use in both medicinal and culinary contexts, dating back thousands of years. As early as 400 BC, Hippocrates noted their medicinal properties. The ancient Greeks also recognized their potential dangers; for instance, Euripides mourned the tragic death of a mother and her three children after consuming mushrooms – one of the earliest references to their toxicity in ancient Greek literature [2]. In the modern era, significant discoveries have been made in the field of mycology. Penicillin, the first antibiotic, was isolated from molds in 1938 by Alexander Fleming, Howard Florey, and Ernst Chain. Molds also play a role in the development of certain cheeses, while yeast is essential in the production of wine and baked goods. Despite these positive uses, mushrooms also have a darker side – hallucinogenic and poisonous species pose significant risks to health.

Mushrooms have long held cultural significance in various societies, including Polish tradition. For many generations, they have been integral to the diet, as well as a source of recreational activity. In late summer and autumn, families often gather in forests to forage for mushrooms – an activity that strengthens community bonds. In Polish folk culture, mushrooms were even believed to have prophetic powers. Their fertility and sudden abundance were seen as signs of impending major events, such as war or pestilence [3]. This belief in the symbolic power of mushrooms reflects their deep cultural importance.

While mushrooms were historically collected from the wild, their artificial cultivation can be traced back to Asia, with France being the pioneer in Europe, cultivating double-spore mushrooms in the 18th century [4]. Today, cultivated mushrooms are widely consumed and have become a staple in many diets. However, the traditional practice of mushroom foraging has not disappeared, and many still enjoy collecting, preparing, and preserving mushrooms on their own. Mushrooms are now recognized not just for their flavor and aroma, but also for their nutritional and health benefits. Over time, they have evolved from being viewed as an occasional treat or hard-to-digest food to being valued for their medicinal properties and contribution to a balanced diet [5].

While mushrooms offer many benefits, they also pose potential dangers. Some varieties are toxic, and consuming them can lead to serious health issues or even death. The historical reference to mushroom poisoning in ancient Greece highlights the long-standing awareness of these risks. On the other hand, the positive aspects of mushrooms – including their roles in medicine, cuisine, and nutrition – underscore their multifaceted nature. The continued interest in both foraging and cultivating mushrooms reflects both their cultural and culinary importance, as well as their potential health advantages when consumed responsibly.

Mushroom poisoning remains a recurring issue during the summer and autumn seasons. Every year there are several hundred reported cases, some of which end in death. The majority of affected individuals are adults, approximately 70%, and the remainder are pediatric patients under the age of 14 [2, 6, 7]. One of the factors influencing annual poisoning rates is the abundance of mushroom growth in a given year. In practice, this means a reduction in poisonings during poor harvests and climate crisis [6, 8].

It is also worth noting that both poisonous mushrooms and those commonly considered edible can be responsible for poisoning [5]. One of the primary causes is incorrect identification of mushrooms, particularly mistaking toxic species for edible ones. The widespread belief that poisonous mushrooms cause blackening of onions and silverware lacks scientific basis, and even the most experienced mushroom hunters can occasionally misidentify a species.

The most commonly confused edible and poisonous species include:

- *Russula virescens* (green-cracking russula), *Tricholoma equestre* (yellow knight), *Macrolepiota procera* (parasol mushroom) – with *Amanita phalloides* (death cap);
- *Agaricus campestris* (field mushroom) – with *Amanita verna* (destroying angel) and *Amanita virosa*;

- *Morchella esculenta* (morel mushroom) – with *Gyromitra esculenta* (false morel).

An additional concern is the growing interest in mushrooms with hallucinogenic properties, particularly among young people. Easy access to the Internet facilitates obtaining information about the appearance of mushrooms with psychoactive properties, which can lead to misidentification by inexperienced mushroom pickers, potentially resulting in fatal outcomes [9].

The clinical presentation of mushroom poisoning varies depending on the species and the specific toxin consumed, but the most common symptoms include gastrointestinal issues such as nausea, vomiting, abdominal pain, and diarrhea, as well as liver and kidney damage, neurological complications, and respiratory and cardiovascular distress [10].

Initial treatment aims to eliminate any remaining traces of mushrooms from the gastrointestinal tract before toxins are absorbed into the bloodstream. This is commonly achieved through gastric lavage, which is most effective during the early (asymptomatic) phase of poisoning [11]. Unfortunately, patients often seek medical assistance after a significantly longer period. Inducing vomiting is not recommended due to its low effectiveness, potential complications such as aspiration, and potential delays in administering the targeted antidote [12, 13]. The next step in treatment involves reducing the absorption of toxins from the gastrointestinal tract and interrupting the enterohepatic circulation of toxins by administering activated charcoal. Between successive doses of charcoal, suctioning of gastric contents is recommended [2, 6, 11]. To reduce the accumulation of amatoxins in the liver, specific therapy can be applied, which involves administering antidotes within the first 24 hours after poisoning. These antidotes rely primarily on silybilin. Penicillin G, once considered an antidote, is no longer routinely used nowadays; it is administered exceptionally in extremely rare clinical situations [11]. Within the first 24 hours of poisoning, extracorporeal elimination such as hemodialysis may also be employed.

Symptomatic treatment, fluid therapy, and close monitoring of the patient's clinical condition through laboratory tests such as ALT, AST, and INR are standard therapeutic approaches [2, 11].

This study aims to analyze cases of mushroom poisonings in individuals aged 18 and over, hospitalized in the Clinical Department of Toxicology and Cardiology of the Cardinal Stefan Wyszyński Regional Specialist Hospital in Lublin during the years 2021–2022.

Material and methods

The present study was retrospective in nature and based on the analysis of medical records of patients hospitalized in the Clinical Department of Toxicology and Cardiology of the Cardinal Stefan Wyszyński Regional Specialist Hospital in Lublin during the years 2021–2022.

Among 1,539 poisoning-related hospitalizations (ICD-10 codes T36-T65) that occurred during the specified period, a target group of 14 individuals was identified with a primary or concomitant diagnosis of T62.0 (toxic effect of ingested mushrooms).

During the analysis, factors such as age, gender, place of residence, whether the poisoning was intentional or part of a collective incident, the type of mushroom consumed, and whether the subject collected the mushroom themselves, were taken into account. The length of hospitalization, patient condition at admission, and the time from mushroom ingestion to symptom onset were also considered. Additionally, the study examined parameters related to liver and kidney damage and the presence of amanitin in blood serum.

Results

The study group consisted of 14 individuals, with 35.71% (5 individuals) being female and 64.29% (9 individuals) being male. There were no recorded cases of mushroom poisoning in children in the study group. The age of the patients ranged from 25 to 92 years, with a median age of 61 years (Fig. 1).

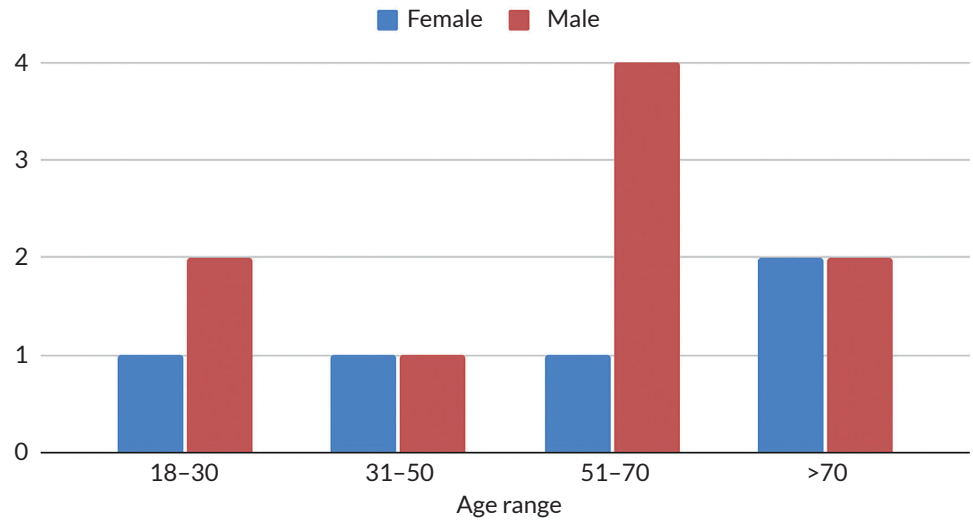

Figure 1. Distribution of the study population by age group and gender

Among the participants, there was a prevalence of individuals residing in rural areas (9 cases, 64.29%) compared to urban settings.

The majority of intoxications (85.71%) were unintentional. Two cases (14.29%) involved collective poisoning (Tab. 1).

Of the affected individuals, 64.29% (9 cases) had personally collected the mushrooms that caused the symptoms. Among those who gathered the mushrooms on their own, two-thirds (6 subjects) lived in rural areas, while the remaining three were urban residents. Alcohol (ethanol) was detected in one patient.

Among the surveyed cases, 9 patients reported consuming mushrooms with a lamellar hymenophore (hymenophore being the part of the mushroom's fruiting body on which the hymenial layer, producing spores, is located) [14].

Analysis of the collected data revealed that the highest number of mushroom poisoning cases occurred in the second half of the year, particularly in late summer and early autumn. In September and October, a total of 9 patients were admitted to the Department, accounting for 64.29% of the study group. The highest number of poisonings was recorded in September (Fig. 2).

The length of patient hospitalization ranged from 3 days (the shortest stay) to 12 days (the longest hospitalization). In 8 cases (57.14%), the hospital stay exceeded 5 days. The average length of stay was 7.1 days, with a median of 7 days (Fig. 3).

The time from mushroom consumption to the onset of symptoms ranged from 4 to 72 hours, with an average of 15.6 hours and a median of 12 hours. In 3 cases (21.43%), the time from ingestion to symptom onset did not exceed 6 hours. Among the surveyed individuals, 3 patients were admitted in severe condition, with the time from mushroom consumption to symptom onset being >6 hours (9, 12, and 16 hours, respectively) (Tab. 2).

After analyzing the medical records, the following information was obtained regarding the tests performed upon patient admission, including liver function parameters (ALT, AST, INR) and the presence of amanitin in the patients' blood serum. Half of the subjects had elevated transaminase values, and 7 individuals also had abnormal INR values. At the time of admission, 2 patients had normal liver function parameters (Tab. 3).

In the examined group, 8 patients (57.14%) had coexisting somatic diseases. Among the participants, 3 individuals developed organ complications, with 2 experiencing liver and kidney dysfunction, and 1 suffering from pulmonary embolism.

Each hospitalized individual underwent the determination of amanitin levels in the blood serum, with 50%

Table 1. List of mushrooms that patients believed they were collecting/eating

Mushroom species	Number of cases	Percentage share
Macrolepiota procera	3	21.43
Russula	3	21.43
Tricholoma equestre	2	14.29
Suillus luteus	2	14.29
Agaricus campestris	1	7.14
Imleria badia	1	7.14
Lactifluus volemus	1	7.14

Table 2. Time elapsed from mushroom consumption to the onset of initial symptoms in individual patients

Time from ingestion to symptom onset	Number of patients	Percentage distribution
<6 hours	3	21.43
7–12 hours	6	42.86
13–18 hours	3	21.43
19–24 hours	0	0.00
25–48 hours	1	7.14
49–72 hours	1	7.14

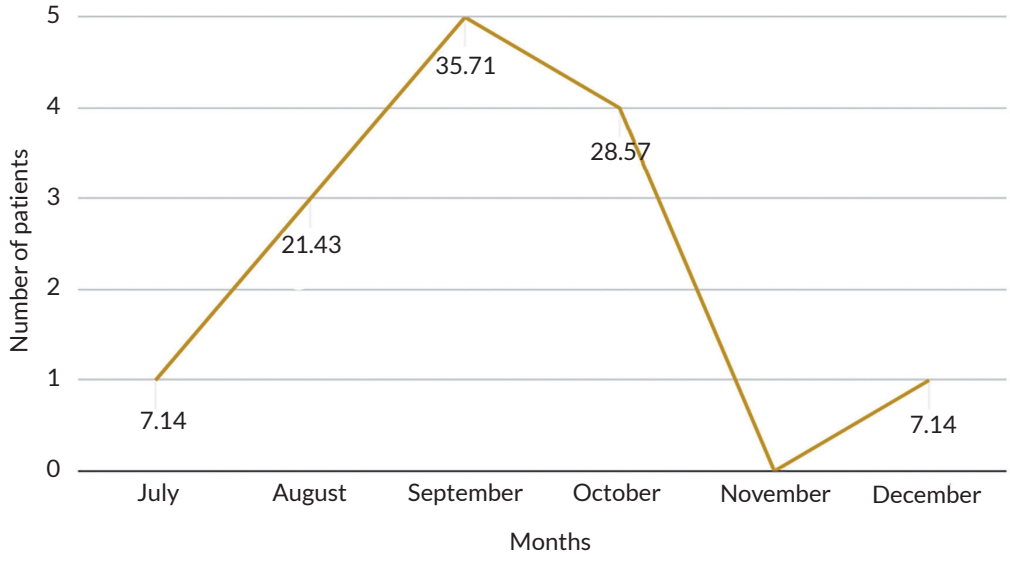

Figure 2. Distribution of mushroom poisoning-related hospitalizations across individual months

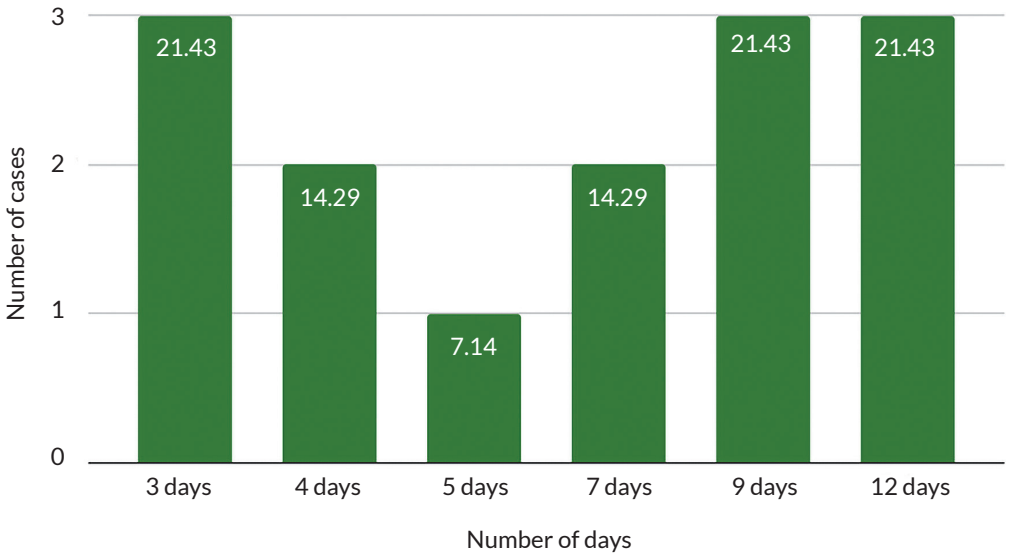

Figure 3. Distribution of the duration of individual hospitalization

Table 3. Biochemical parameter values indicating liver dysfunction measured at admission to the Clinical Department

Parameter	Average value	Value range (min–max)	Scope of standard
Alanine aminotransferase (ALT)	332.86	7–3244	5–41 U/L
Aspartate aminotransferase (AST)	236.57	13–2491	5–38 U/L
International normalized ratio (INR)	2.09	1–12.4	0.80–1.15

yielding a positive result. Among those with a positive amanitin finding, 5 patients (71.43%) had elevated liver enzyme levels, and 3 patients (42.86%) had abnormally high INR values. One person presented with an elevated INR without biochemical evidence of liver damage.

Among patients with a positive amanitin result, the time from mushroom consumption to symptom onset ranged from 5 to 16 hours, with an average of 11.4 hours. The length of hospitalization for these patients varied from 3 to 12 days, with an average of 9.5 days.

Regarding the types of mushrooms consumed by patients with a positive amanitin result, 3 individuals reported eating lamellar mushrooms, 1 person had ingested mushrooms with a tubular hymenophore, and 3 individuals were unsure of the type of mushrooms they had eaten.

In addition, data were collected regarding patients hospitalized in the Clinical Department of Toxicology and Cardiology of the Cardinal Stefan Wyszyński Regional Specialist Hospital in Lublin in 2017–2018 due to mushroom poisoning (Fig. 4).

The medical records of patients with a positive amanitin result were analyzed with regard to three aspects: length of hospitalization, liver damage parameters, and the types of mushrooms consumed by the patients. The results obtained were as follows: out of 36 patients hospitalized during that period, 14 individuals (38.89%) had a positive amanitin result. At admission, 71.4% of the study participants (10 individuals) had elevated liver function parameters (ALT and/or AST), of which 8 individuals also had abnormally high INR values, indicating kidney impairment. Four patients (28.6%) exhibited no signs of liver or kidney damage at admission. The length of hospitalization ranged from 1 to 27 days, with a mean of 10.2 days. It should be noted that the one-day hospitalization in the department was due to the need for patient qualification for liver transplantation and subsequent transfer to another hospital.

Discussion

Although mushroom poisoning is not among the most common causes of hospitalization, several dozen cases are reported each year, some of which result in severe organ complications or even death.

Based on the findings presented in this study, it can be determined that mushroom poisonings accounted for 0.92% of all hospitalizations in the Clinical Department of Toxicology and Cardiology of the Cardinal Stefan Wyszyński Regional Specialist Hospital in Lublin between 2021–2022. It is important to note that this analysis does not fully reflect the scope of the problem of mushroom poisoning, as it only includes patients from the mentioned department. The analysis excludes cases of intoxication among children, a group of patients more commonly admitted to Intensive Care Units. According to data published by the National Institute of Public Health NIH – National Research Institute Department of Epidemiology and Surveillance of Infectious Diseases in 2014–2023, a total of 192 cases of mushroom poisoning were registered in Poland. Of these, 24 cases were re-

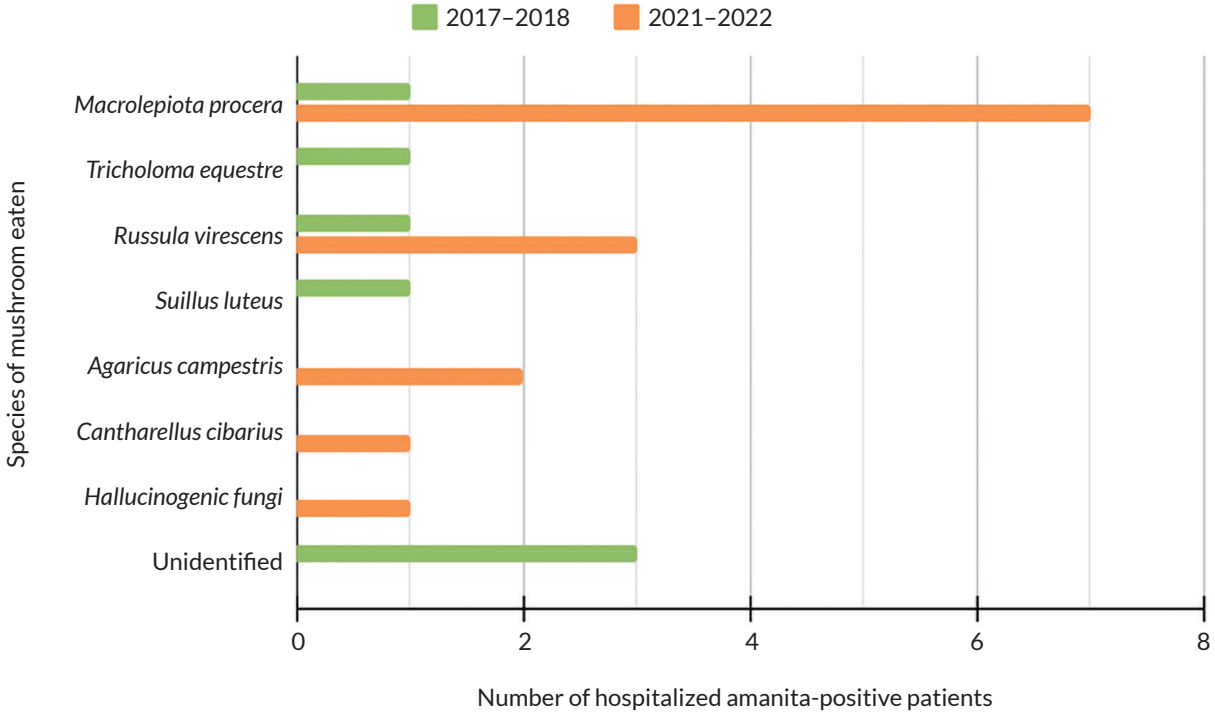

Figure 4. Comparison of mushroom species consumed by patients with a positive amanitin result in 2017–2018 and 2021–2022

ported in 2021–2022. In these 10 years, 59 poisonings were registered in the Lublin Province [15–19].

According to the collected data, 85.7% of mushroom poisoning cases were accidental. The main reasons for intoxication was improper identification of edible and poisonous mushrooms. Other mentioned causes (primarily responsible for gastrointestinal symptoms) included the following [5, 20, 21]:

- large quantity of consumed mushrooms, especially due to the presence of compounds that are difficult to digest, such as chitin, trehalose, and mannitol;
- absence of the enzyme trehalase in the patient's body, which is responsible for breaking down trehalose, as its excess in the intestinal lumen leads to osmotic diarrhea;
- consumption of aged fruiting bodies, improper preparation of dishes from edible mushrooms, and inadequate storage conditions (e.g., using plastic bags for collecting, consuming mushrooms along with alcohol or milk);
- contamination of mushrooms with bacteria, microorganisms, or environmental pollutants in which the fungus grows – including pesticides, heavy metals, and radioactive compounds (e.g., in industrial areas);
- consumption of edible mushrooms by individuals in high-risk groups (e.g., persons with gastrointestinal diseases, children, elderly individuals, pregnant women).

In rare cases, suicide attempts by consuming mushrooms were observed. Another concerning phenomenon was the experimentation with mushrooms exhibiting psychoactive properties, especially among young individuals [9].

Mushroom poisonings can be classified into six categories based on the effects they induce:

I. Cytotoxic poisonings – caused by mushrooms containing cytotoxins (*Amanita*, *Lepiota*, and *Galerina* – each of these may contain amanitin);
II. Neurotoxic poisonings;
III. Myotoxic poisonings;
IV. Poisonings involving metabolic and endocrine disorders;
V. Gastroenterotoxic poisonings;
VI. Various adverse reactions.

This article focuses on two types of poisonings – gastroenterotoxic and cytotoxic – due to their higher frequency of occurrence.

The discussion begins with the fifth group of poisonings, involving fungi with gastroenterotoxic effects, which include the vomiting russula (*Russula emetica*), brown rollrim mushroom (*Paxillus involutus*), woolly milkcap (*Lactarius torminosus*), common earthball (*Scleroderma citrinum*), and livid entoloma (*Entoloma sinuatum*), among others. The precise structure of the toxins in this group remains unidentified in many cases. After ingestion, symptoms of gastrointestinal poisoning typically appear within 6 hours and usually resolve spontaneously. Common symptoms include acute gastroenteritis, manifesting as abdominal pain, nausea, diarrhea, and vomiting. Importantly, no organ damage is usually observed. Deadly poisonous mushrooms contribute to the first type of poisoning, which will be discussed hereinafter. In Poland, the most commonly implicated species are the death cap (*Amanita phalloides*), the destroying angel (*Amanita verna*), and venomous toadstools (*Amanita virosa*) [8, 9]. Their toxins usually have a peptide structure, such as α-amanitin, which is a member of the amatoxin group characterized by its cyclic octapeptide configuration. Amatoxins are among the most potent poisons produced by fungi of the toadstool family, and do not degrade even when subjected to high tempera-

tures. In addition, their toxicity increases when bound to albumin. Their main action occurs at the DNA level by inhibiting protein synthesis in the cells of internal organs, causing their death. Amatoxins have the greatest affinity for the liver; however, they can also damage cells of other organs including the kidneys, pancreas, myocardium, as well as circulating neutrophils and erythrocytes [2, 22]. In this case, the latency period before symptom onset is longer than 6 hours, usually 10–12 hours [7, 20, 23]. This type of poisoning can lead to acute toxic organ damage, primarily affecting the liver and kidneys, which may result in death [24–26].

The treatment of mushroom poisoning can be divided into several stages. The early phase involves gastrointestinal decontamination, primarily through gastric lavage. This intervention is most effective within the first hour after intoxication. However, due to the potential presence of fungal spores in the gastric folds for an extended period, gastric lavage remains justified even beyond 4 hours post-ingestion. Subsequent gastric lavage is also performed for mycological identification purposes [11, 27]. The next stage involves the administration of high doses of activated charcoal (1.0 g/kg body weight), either orally or via gastric lavage probe, in repeated doses every 4–6 hours, at a dose of around 25 g over a 24-hour period [26].

This approach aims to prevent the reabsorption of amatoxins by inhibiting their enterohepatic circulation [6]. During the intervals between successive doses of activated charcoal (prior to administering each dose), the gastric and duodenal contents should be aspirated [11].

The third stage involves the administration of specific treatment. Amatoxins persist in the bloodstream for approximately 12–24 hours before binding to nuclear RNA polymerase II in hepatocytes. Therefore, the window for administering specific antidotes is limited to less than 24 hours. The primary agent used is silybin, which blocks the transport protein, thereby inhibiting the hepatic uptake of amatoxins. Alternatively, benzylpenicillin and cefazolin may be administered. Additionally, N-acetylcysteine is employed independently, following the standard protocol used in acetaminophen poisoning. For secondary detoxification, forced diuresis using mannitol and sodium bicarbonate is employed. However, this intervention should be applied cautiously due to the potential risk of patient dehydration [6, 27].

During the first 24 hours, hemodialysis is also effective, but its clinical utility is limited as patients rarely present to the hospital with symptoms within such a short timeframe [27]. Extracorporeal elimination is more commonly employed in children due to the faster onset of symptoms and more severe course of poisoning, leading to earlier hospitalization in this patient group.

Pediatric patients are particularly vulnerable to severe mushroom poisoning. In the general statistics, mushroom intoxications account for approximately 4–6% of all poisoning cases reported to the Toxicological Information Bureau in Warsaw [28]. This type of poisoning is most common in children under 5 years of age [29]. It seems reasonable, therefore, to completely avoid serving mushroom-based dishes to young children.

The main prognostic factors in cases of mushroom intoxication, apart from the species of mushroom consumed, include the presence of amanitin in blood serum and/or urine, an increase in liver and kidney function markers (ALT, AST, INR), timely implementation of targeted treatment, and coexisting diseases and concurrent medications, especially drugs responsible for inducing cytochrome P450 or depleting glutathione reserves [7, 22, 23].

In cases of mushroom poisoning, the risk of toxic damage to the liver and kidneys is always present. It is often difficult to determine the exact dose of mushrooms ingested by the patient. Furthermore, it is frequently unknown whether the patient was concurrently exposed to other hepatotoxic or nephrotoxic agents [6, 23, 30].

The demographic structure of mushroom poisoning indicates a higher proportion of residents from small towns and rural areas compared to urban populations. This is likely due to easier access to forested areas in these regions.

Conclusions

Mushrooms have long held an important place in both culinary tradition and the pharmaceutical industry. However, mushroom foraging can be risky due to misidentification, leading to poisoning. While the number of hospitalizations related to mushroom poisoning has decreased in recent years, the risk remains, particularly for those unfamiliar with safe foraging practices.

To prevent poisoning, it is crucial to collect only well-known mushroom species, thoroughly inspect gathered mushrooms (especially those collected by children), and avoid collecting gilled mushrooms or immature specimens. Public awareness campaigns have contributed to fewer people collecting unknown mushroom species. Additionally, proper mushroom storage and professional packaging with clearly marked expiration dates further reduce the risk of consuming spoiled or poisonous mushrooms.

The growing popularity of hallucinogenic mushrooms poses a new risk, especially among young people. Therefore, comprehensive education on the dangers of these mushrooms is essential for adolescents, parents, and educators.

While the sale of fresh, dried, and packaged mushrooms is carefully monitored by the State Sanitary Inspection, fostering a preference for cultivated mushrooms from trusted sources can further reduce poisoning incidents [31]. Ultimately, the goal is to emphasize the importance of caution during mushroom foraging and to promote the consumption of safe, cultivated mushrooms with similar culinary qualities.

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AURICULAR RECONSTRUCTION AFTER A HORSE BITE INJURY

Rekonstrukcja małżowiny usznej po urazie powstałym w wyniku ugryzienia przez konia

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Abstract

The paper presents a case of a 71-year-old female patient admitted to the Department due to severe damage to the right ear lobe as a result of a horse bite. The patient was qualified for ear reconstruction using an autologous cartilage graft and an adipocutaneous flap, which resulted in a satisfactory aesthetic and functional outcome. The intervention consisted of two stages of reconstruction, separated by a three-month interval. The described case demonstrates the positive outcomes of this technique and its effectiveness in reconstructing various types of ear injuries.

Streszczenie

W pracy przedstawiono przypadek 71-letniej pacjentki, która została przyjęta na oddział z powodu zaawansowanego uszkodzenia prawej małżowiny usznej w wyniku ugryzienia przez konia. Pacjentkę zakwalifikowano do rekonstrukcji małżowiny z zastosowaniem przeszczepu autologicznej chrząstki oraz płata skórno-tłuszczowego, co pozwoliło na uzyskanie zadowalającego wyniku estetycznego i funkcjonalnego. Zabieg obejmował dwa etapy rekonstrukcji, oddzielone trzymiesięczną przerwą. Przedstawiony przypadek potwierdza korzystne efekty zastosowanej techniki i utwierdza w przekonaniu, że tego typu metody mogą być skuteczne w rekonstrukcji różnego rodzaju urazów małżowiny usznej.

Keywords: ear reconstruction; plastic surgery; autologous ear cartilage graft; bite wounds; ear wounds

Słowa kluczowe: rekonstrukcja małżowiny usznej; chirurgia plastyczna; przeszczep autologicznej chrząstki ucha; rany kąsane; rany małżowiny usznej

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Introduction

Injuries inflicted by animals are a serious public health problem worldwide, but auricular bites by a horse are rarely reported. The annual incidence of horse and donkey bites is estimated at 7.8/100,000 [1]. Approximately half of Americans will experience bites in their lifetime, with the annual cost of treatment estimated to exceed $100 million. Potential complications include disfigurement, amputation, and infection. Effective treatment requires prompt medical evaluation and may involve surgical intervention as well as prophylactic antibiotic therapy [2].

The auricle, composed of skin and cartilage, plays an important role in facial aesthetics. As the external part of the ear, the auricle is particularly vulnerable to trauma and deformities due to its prominent and exposed position. Auricular deformity poses a significant challenge to the surgeon.

Selecting a surgical strategy for traumatic ear defects is challenging due to significant variability in defect size, shape, and the condition of the surrounding skin. The choice of reconstructive technique depends on the patient's individual characteristics, the extent of soft tissue loss, and the location of the auricular defect [3].

This paper presents a case of a 71-year-old female patient who sustained right auricle injury following a horse bite.

Many auricular reconstruction techniques are employed in plastic surgery. The choice of method should be individualized based on the defect's size and location, the condition of surrounding skin tissues, patient expectations, and the surgeon's experience.

Case report

A 71-year-old patient presented to the Hospital's Emergency Department (ED) and was subsequently referred to the Department of Plastic Surgery, Reconstructive Surgery, and Burn Treatment due to a horse bite injury. She was urgently qualified for the first stage of auricular reconstruction. Examination revealed a defect involving the auricular skin and cartilaginous structures, including the helix, antihelix, and antitragus (Fig. 1).

The first step involved reconstruction of the skin defect using an adipocutaneous flap mobilized from the postauricular area to cover the exposed cartilage and ensure vascularization in the reconstructed area. The procedure was performed under general anaesthesia. The surgery proceeded as follows: a fragment of the auricle and the top part of the cartilage were infiltrated with lignocaine. An incision line was made on the skin behind the ear to lift and move the adipocutaneous flap forward. The tissues were then dissected along the designated lines. The damaged part of the auricle, including the exposed cartilage, was positioned onto the surface of the skull behind the ear and temporarily fixed with an absorbable suture. The tissue defect was covered using the elevated flap, which was trimmed to match the shape of the defect. Full coverage of the defect was achieved. During the procedure, the ear flap showed no signs of ischaemia. Both the flap and the surrounding skin were secured with sutures, and haemostasis was satisfactorily maintained (Fig. 2, Fig. 3).

The second stage of reconstruction was performed three months after the initial procedure. Its goal was to repair the auricular cartilage defect and reposition the auricle away from the head to achieve symmetry with the opposite ear. A cartilage graft was harvested from the other auricle, along with a free split-thickness skin graft (FTSG) taken from the thigh. The procedure was performed under general anaesthesia and began with an incision along the planned flap line, intended for the reconstruction of the posterior surface of the right auricle. The tissues were dissected to the edge of the ear helix, haemostasis was achieved, and the cartilage defect was identified and measured. A cartilage fragment measuring approximately 4 cm in length and 7 mm in thickness was harvested from the left ear (Fig. 4).

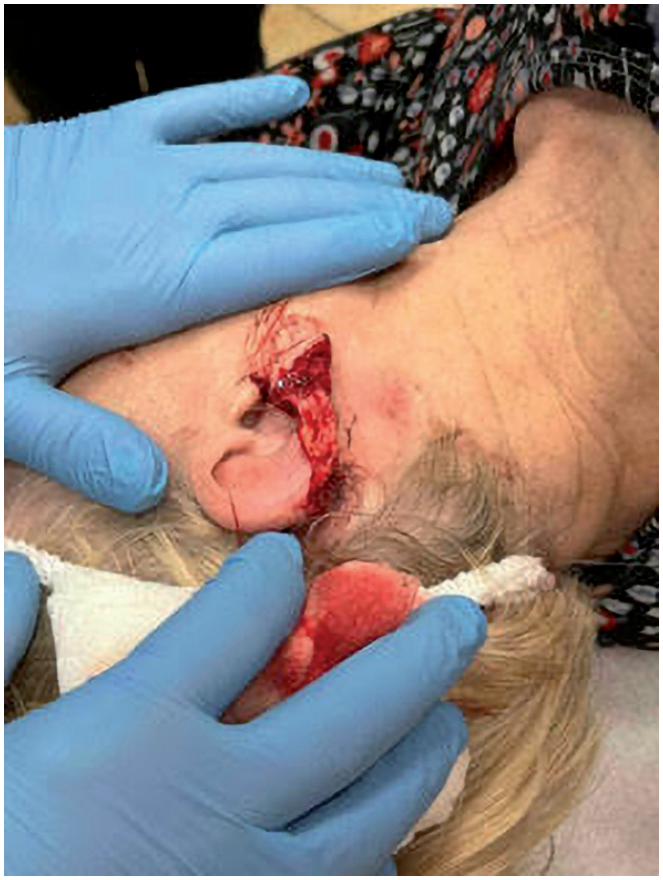

Figure 1. The ear defect on admission

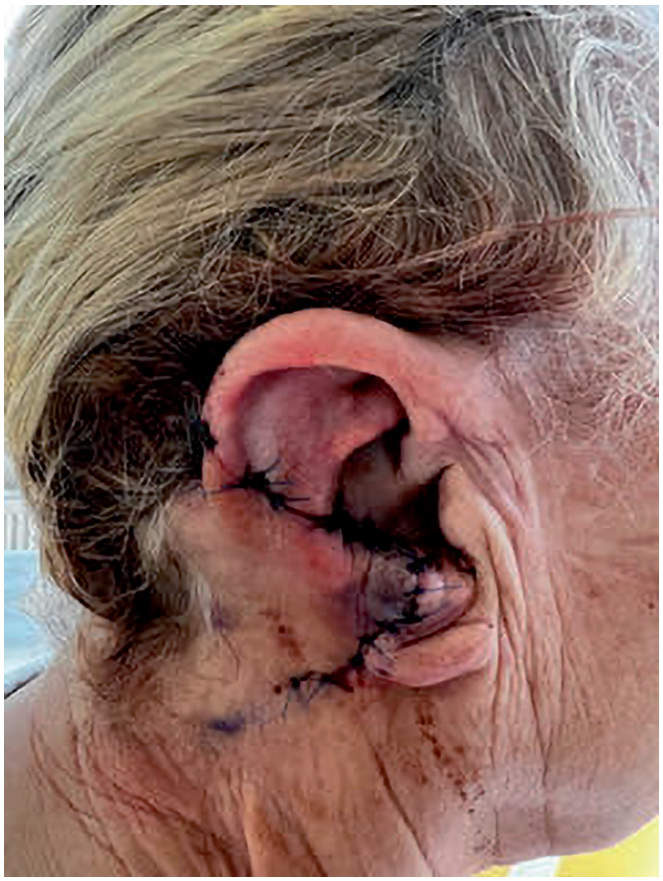

Figure 2. The outcomes after the first stage of ear reconstruction, two days post-surgery

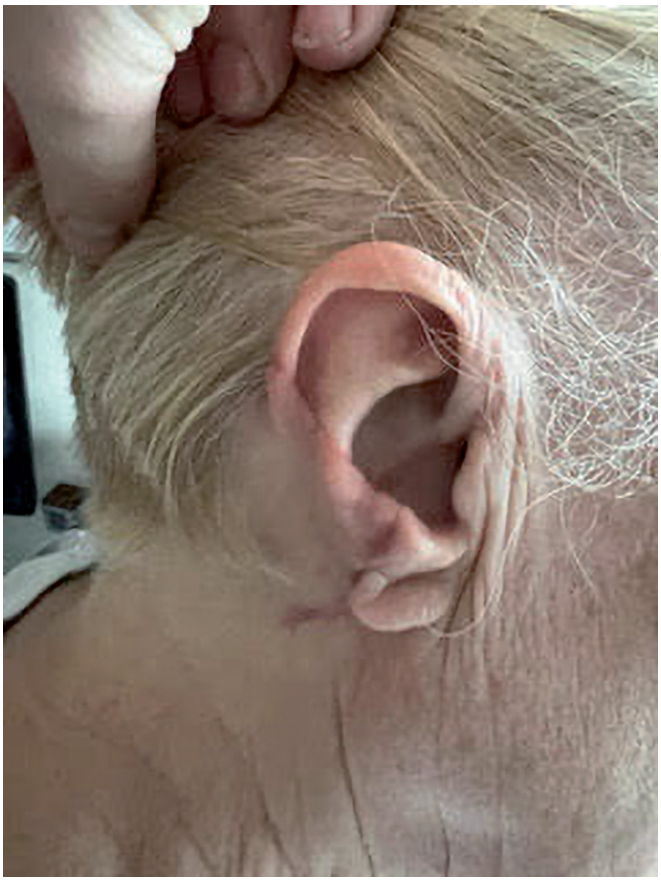

Figure 3. The outcomes after the first stage of ear reconstruction, three weeks post-surgery

The wound was closed using a continuous suture. The harvested cartilage graft was carefully prepared, adjusted, and sutured into the auricular defect (Fig. 5).

The tissues were covered with the previously created adipocutaneous flap and sutured. A free split-thickness skin graft, harvested from the right thigh, was placed over the skin defect behind the right ear (Fig. 6). Haemostasis was adequate, and a dressing was applied.

The patient was discharged on day 3 postoperatively in good general condition, with appropriate postoperative recommendations.

Two weeks after the surgery, the patient attended a follow-up visit, during which the skin sutures were removed (Fig. 7).

Discussion

Our patient underwent auricular reconstruction using autologous cartilage transplantation, which is reported in the literature as an effective approach. In cases of traumatic auricular damage, reconstructive techniques vary depending on the extent of the defect, the location of the injury, and the availability of tissue resources.

In 2018, Habiba et al. described treatment options for partial auricular reconstruction, highlighting their benefits for patients' quality of life. The prospective study involved individuals with traumatic partial auricular defects. Reconstructions were done using various techniques, including simple local skin flaps, tubular flaps, and cartilage scaffolds from auricular or rib cartilage, covered with a local skin flap.

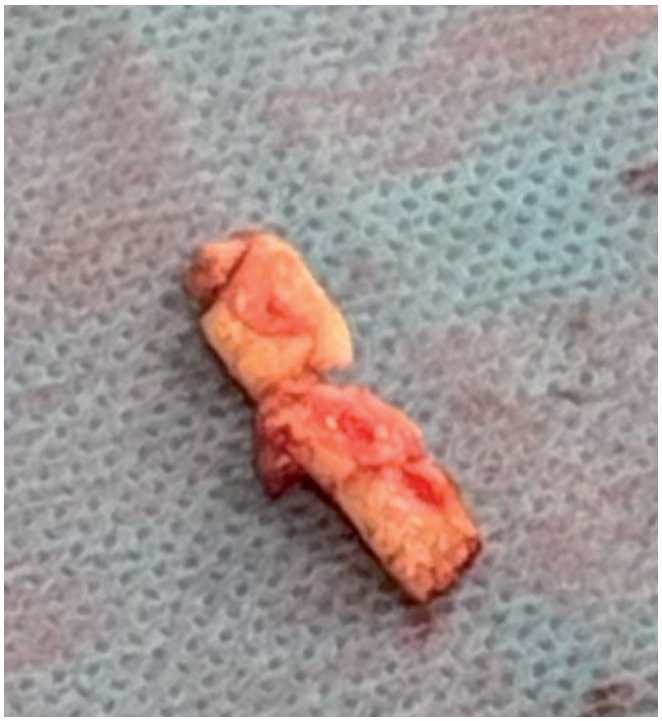

Figure 4. Cartilage graft harvested from the left ear

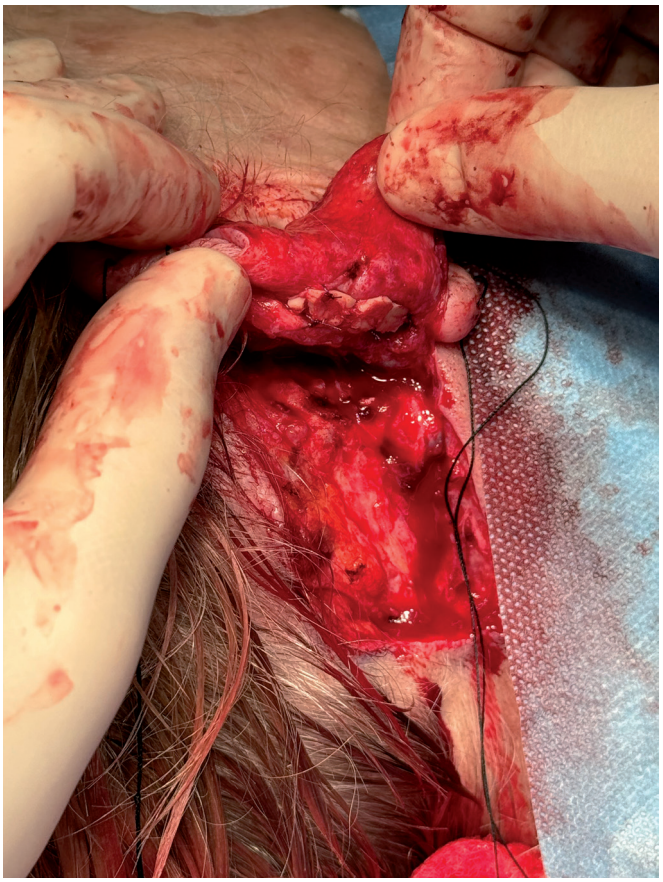

Figure 5. Grafted cartilage placed in the right ear defect

Figure 6. Final outcome after the second stage of ear reconstruction

The study demonstrated that retroauricular and mastoid skin flaps, with or without a cartilage scaffold, produced favourable aesthetic and functional outcomes. These ear reconstruction techniques resulted in fully satisfactory functional outcomes and contributed to enhanced patient confidence [4].

In 2023, Hajebian et al. reported a case of complete auricular avulsion in a child as a result of a dog bite. The ear was reconstructed using prelaminated native auricular cartilage. Based on their study, the authors concluded that in cases of traumatic auricular avulsion with preserved native cartilage, successful reconstruction can be achieved using a two-stage technique involving prelaminated native ear cartilage. This modality involves creating a posterior ear pocket and placing a skin graft over the cartilage [5].

Autologous auricular cartilage transplantation for traumatic defects allows for a satisfactory outcome, restoring an acceptable appearance of the reconstructed auricle.

In their study in 2024, Singh et al. utilised rib cartilage grafts to reconstruct larger auricular defects. They demonstrated that this approach offers structural stability and satisfactory aesthetic outcomes, though it requires additional surgical steps [6].

In 2006, Sclafani et al. described various reconstructive techniques, including retroauricular skin flaps. The study compared the aesthetic and functional outcomes of various modalities, highlighting the effectiveness of combining cartilage grafts with local flap coverage [5].

A 2022 study evaluated the effectiveness of complex microscopic techniques for auricular reconstruction

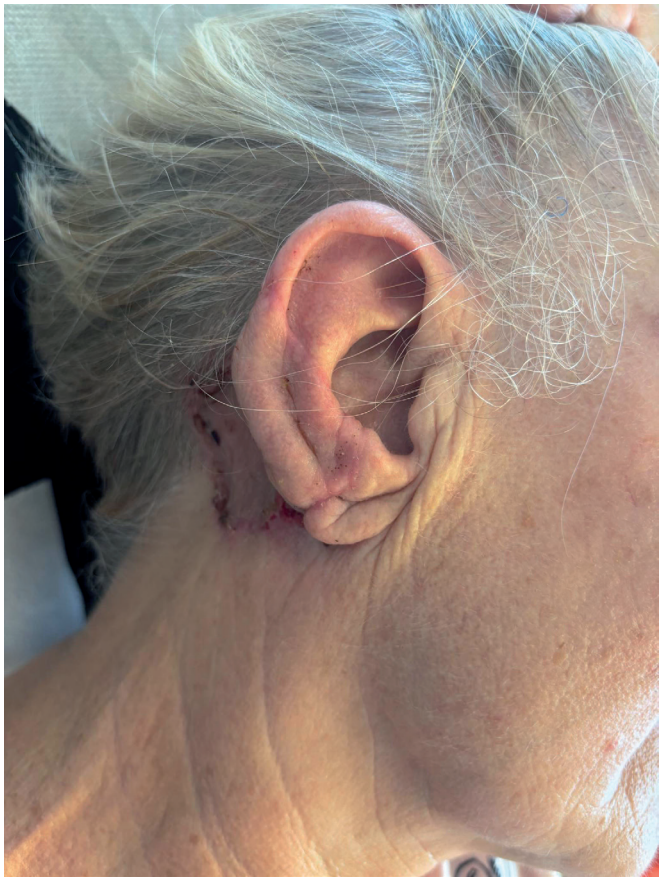

Figure 7. Final outcome three weeks after the second stage of ear reconstruction

following trauma. Tissue transfer and reconstruction techniques using microsurgery enabled precise restoration of the ear's anatomical structures. The study demonstrated high patient satisfaction and effective graft integration with surrounding tissues. This approach is particularly recommended for more complex defects [4].

In 2021, a study was conducted using modern biopolymer scaffolds for auricular reconstruction. The scaffolds were shaped to match the anatomical structure of the damaged cartilage and covered with skin grafts. Positive outcomes were particularly observed in cases with limited availability of autologous tissue. Biopolymer scaffolds demonstrated both satisfactory aesthetic and functional outcomes, with good biocompatibility and integration into surrounding tissues [7].

Conclusions

Reconstruction of the auricle following injuries such as a horse bite is a complex process requiring an individualized approach. In the described case, the use of autologous cartilage transplantation combined with an adipocutaneous flap achieved satisfactory aesthetical and functional outcomes. Literature data confirm the effectiveness of these techniques in reconstructing various types of auricular injuries, with the choice of method depending on the size and location of the defect, as well as the condition of the surrounding tissues.

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OCCLUSIVE RETINAL VASCULITIS FOLLOWING INTRAVITREAL BROLUCIZUMAB FOR WET AGE-RELATED MACULAR DEGENERATION

Okluzyjne zapalenie naczyń siatkówki po doszklistkowym podaniu brolucizumabu w terapii wysiękowego zwyrodnienia plamki związanego z wiekiem

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Abstract

Brolucizumab is a humanized single-chain fragment of a monoclonal antibody that blocks vascular endothelial growth factors. The aim of this paper is to present a case of occlusive retinal vasculitis with intraocular inflammation following intravitreal administration of brolucizumab in a patient with wet age-related macular degeneration. An 84-year-old woman complained of decreased visual acuity in the right eye and floaters in the visual field. These symptoms occurred 54 days after the first intravitreal injection of 6 mg brolucizumab. Snellen visual acuity decreased from the pre-injection level of 0.6 to 0.05. An intraocular inflammatory reaction was detected. Ophthalmoscopy of the right eye revealed oedema of the optic nerve disc, pale foci of ischemia in the form of "cotton wool spots", retinal haemorrhages, and perivascular sheathing of retinal arteries with their multifocal complete or partial occlusion. Based on the clinical picture and diagnostic tests, the patient was diagnosed with occlusive retinal vasculitis with intraocular inflammation as a complication of intravitreal brolucizumab. Treatment included local and systemic steroid therapy. Right eye visual acuity improved reaching 0.4. A secondary sectoral reduction in the thickness of the nerve fibre layer of the right eye was found, with visual field defect. Conclusions. Early diagnosis and initiation of appropriate treatment as soon as possible can prevent severe vision loss in most cases of rare vascular inflammatory complication after intravitreal brolucizumab. However, ischemia associated with vasculitis may cause permanent changes in the morphology of retinal nerve fibres and lead to visual field deficits.

Streszczenie

Brolucizumab jest humanizowanym jednołańcuchowym fragmentem przeciwciała monoklonalnego, blokującym czynnik wzrostu śródbłonka naczyń. W pracy przedstawiono przypadek okluzyjnego zapalenia naczyń siatkówki z zapaleniem wewnątrzgałkowym, które wystąpiło po doszklistkowym podaniu brolucizumabu u pacjentki z wysiękowym zwyrodnieniem plamki związanym z wiekiem. 84-letnia kobieta zgłosiła się z powodu osłabienia ostrości wzroku w prawym oku oraz mętów w polu widzenia. Objawy te pojawiły się 54 dni po pierwszej iniekcji doszklistkowej 6 mg brolucizumabu. Ostrość wzroku pogorszyła się z przediniekcyjnej wartości 0,6 według tablicy Snellena do 0,05. Stwierdzono obecność wewnątrzgałkowego odczynu zapalnego. W badaniu oftalmoskopowym prawego oka uwidoczniono obrzęk tarczy nerwu wzrokowego, blade ogniska niedokrwienia (tzw. kłębki waty), drobne krwotoki siatkówkowe, pochewki zapalne przy naczyniach tętniczych siatkówki z ich wieloogniskową okluzją – całkowitą lub częściową. Na podstawie obrazu klinicznego i wyników badań diagnostycznych rozpoznano okluzyjne zapalenie naczyń siatkówki z towarzyszącym zapaleniem wewnątrzgałkowym jako powikłanie po podaniu brolucizumabu. W leczeniu zastosowano steroidoterapię miejscową i ogólną. Odnotowano poprawę ostrości wzroku w prawym oku do 0,4 wg Snellena. Zaobserwowano wtórne sektorowe zmniejszenie grubości warstwy włókien nerwowych tego oka, z ubytkiem w polu widzenia. Wnioski: U pacjentów z rzadkim naczyniowym powikłaniem zapalnym po doszklistkowym podaniu brolucizumabu, wczesne rozpoznanie i jak najszybsze wdrożenie odpowiedniego leczenia w większości przypadków może zapobiec ciężkiej utracie widzenia. Jednak niedokrwienie towarzyszące zapaleniu naczyń może trwale zmienić morfologię włókien nerwowych siatkówki i ograniczyć pole widzenia.

Keywords: wet age-related macular degeneration; intraocular inflammation; brolucizumab; occlusive vasculitis

Słowa kluczowe: wysiękowe zwyrodnienie plamki związane z wiekiem; zapalenie wewnątrzgałkowe; brolucizumab; okluzyjne zapalenie naczyń

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Introduction

Brolucizumab is an intravitreal vascular endothelial growth factor (VEGF) blocker. It was approved by the U.S. Food and Drug Administration (FDA) for the treatment of wet age-related macular degeneration (wAMD) in 2019. The European Medicines Agency (EMA) followed with its approval in 2020. Brolucizumab is a humanised single-chain Fv (scFv) antibody fragment produced by recombinant DNA technology in *Escherichia coli*. It is the smallest molecule among the currently available anti-VEGF drugs. Its molecular weight is 26 kDa and is significantly smaller compared to aflibercept (114 kDa) and ranibizumab (48 kDa) [1–3].

Brolucizumab is administered intravitreally at a dose of 6 mg. It delivers a 12-fold higher molar dose as compared to 2 mg aflibercept and 22-fold higher molar dose as compared to 0.5 mg ranibizumab [1]. The drug has a strong inhibitory effect and high affinity for all VEGF-A isoforms. Inhibition of the VEGF pathway has been shown to slow the progression of neovascular lesions, suppress endothelial cell proliferation, and reduce vascular permeability.

The molecular structure of brolucizumab contributes to significantly improved morphological outcomes of wAMD therapy, including reduced central retinal thickness and decreased fluid accumulation (intraretinal, subretinal, and beneath the retinal pigment epithelium), which are indicators of disease activity [2–4]. In clinical practice, brolucizumab is used to treat wAMD in both treatment-naïve patients and those who have become unresponsive to other anti-VEGF agents [5].

Despite the unquestionably good outcomes of intravitreal wAMD therapy, both inflammatory and non-inflammatory adverse events (AEs) associated with anti-VEGF treatments, including brolucizumab, have been reported. Intraocular inflammation (IOI), either sterile or infectious, is the most serious complication. Retinal vasculitis is a newly identified AE of brolucizumab [6, 7].

In this paper, we present a clinical case of occlusive retinal vasculitis (ORV) with intraocular inflammation (IOI) following intravitreal administration of brolucizumab in a patient diagnosed with wAMD.

Case report

An 84-year-old woman reported to the Department of Ophthalmology of the Military Institute of Medicine – National Research Institute due to blurred vision with accompanying decreased visual acuity (VA) in the right eye and floaters in the field of vision. Although these symptoms occurred 54 days after the first intravitreal injection of 6 mg brolucizumab into the right eye for wAMD, the patient presented four days after symptom onset. The woman had previously been treated under a drug programme and had been receiving an intravitreal anti-VEGF drug, aflibercept, in her right eye. Despite repeated injections, the neovascular membrane activity persisted with the presence of fluid collections. Therefore, a decision was made to switch to brolucizumab. Her left eye did not show any significant abnormalities. The woman received chronic treatment for systemic diseases such as hypertension, type 2 diabetes mellitus and gout.

Ophthalmological examination showed reduced right VA from the pre-injection Snellen acuity of 0.6 to 0.05. Visual function in the left eye was normal. The intraocular pressure (IOP) was normal in both eyes. Slit-lamp examination of the anterior segment of the right eye revealed minimal deep injection (redness), fine corneal endothelial deposits, and grade +1 inflammatory cells in the anterior chamber (AC), without hypopyon. The posterior segment of the right eye showed grade +1 inflammation in the vitreous chamber. In addition to degenerative macular changes, ophthalmoscopy and true colour ultra-widefield fundus imaging of the right eye found a pale optic disc with blurred oedematous borders, pale peripapillary cotton wool ischemic spots, peripheral retinal and vascular haemorrhages, as well as perivascular sheathing along the retinal arteries, with their complete (greyish inflammatory material inside the vessels) or partial multifocal occlusion, with interruption of the blood column in the vessel (Fig. 1A). The anterior and posterior segments of the left eye were normal.

Fluorescein angiography (FA) (Fig. 2A) showed delayed filling of the retinal vascular bed with retrograde flow of the dye into the right ocular vessels, extensive peripapillary and peripheral nonperfusion zones in the posterior pole (temporal quadrants), partially preserved perfusion in the macula lutea, complete or partial arterial occlusion with segmentally disrupted dye flow, dye leakage through the vessel walls in the late phases of the examination in a few retinal arteries, and dye leakage on the optic disc.

Spectral domain optical coherence tomography (SD-OCT) of the right macula revealed elevation of the retinal pigment epithelium without intraretinal or subretinal fluid. Increased reflectivity of the inner retinal layers was observed in the perifoveal zone with blurring of the retinal lamellar structure, suggesting ischemia (Fig. 3B).

Due to the symptoms of right IOI, laboratory workup was done, including erythrocyte sedimentation rate

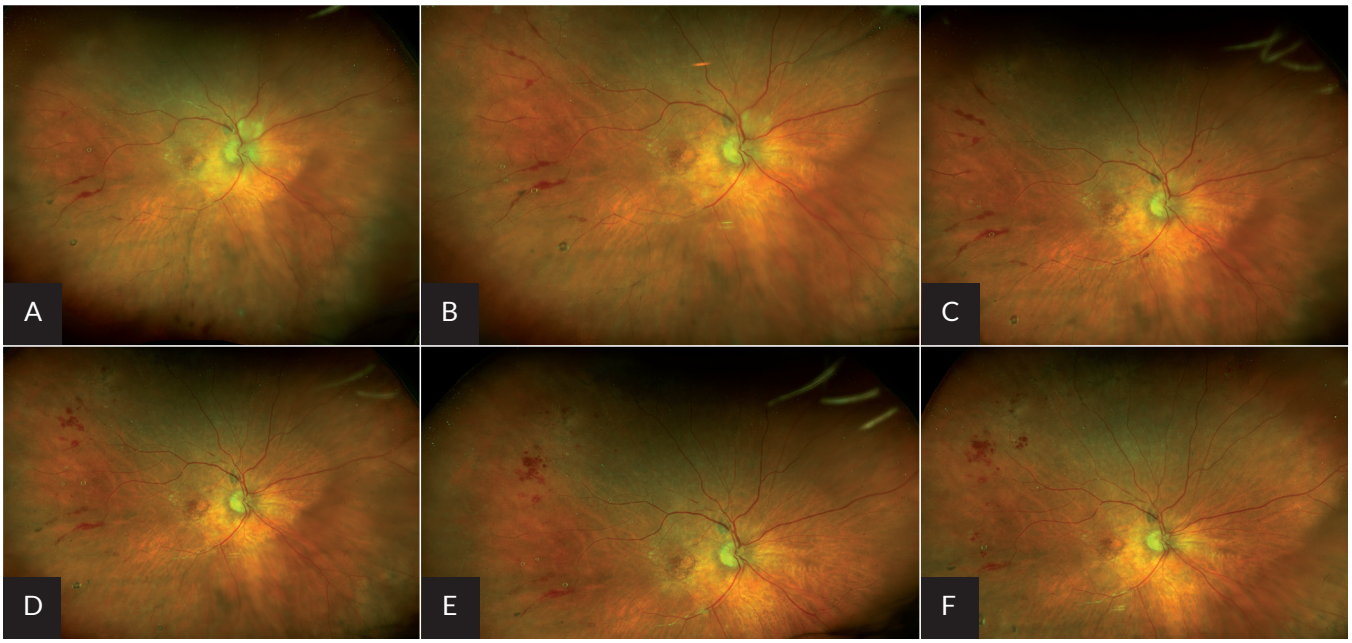

Figure 1. Colour images of the fundus of the right eye. **A.** On admission. **B.** One week after treatment onset. **C.** At 2 weeks. **D.** At 6 weeks. **E.** At 8 weeks. **F.** At 10 weeks

(ESR), C-reactive protein and peripheral blood count with differential. No abnormalities were found, which allowed, among other things, to exclude giant cell arteritis.

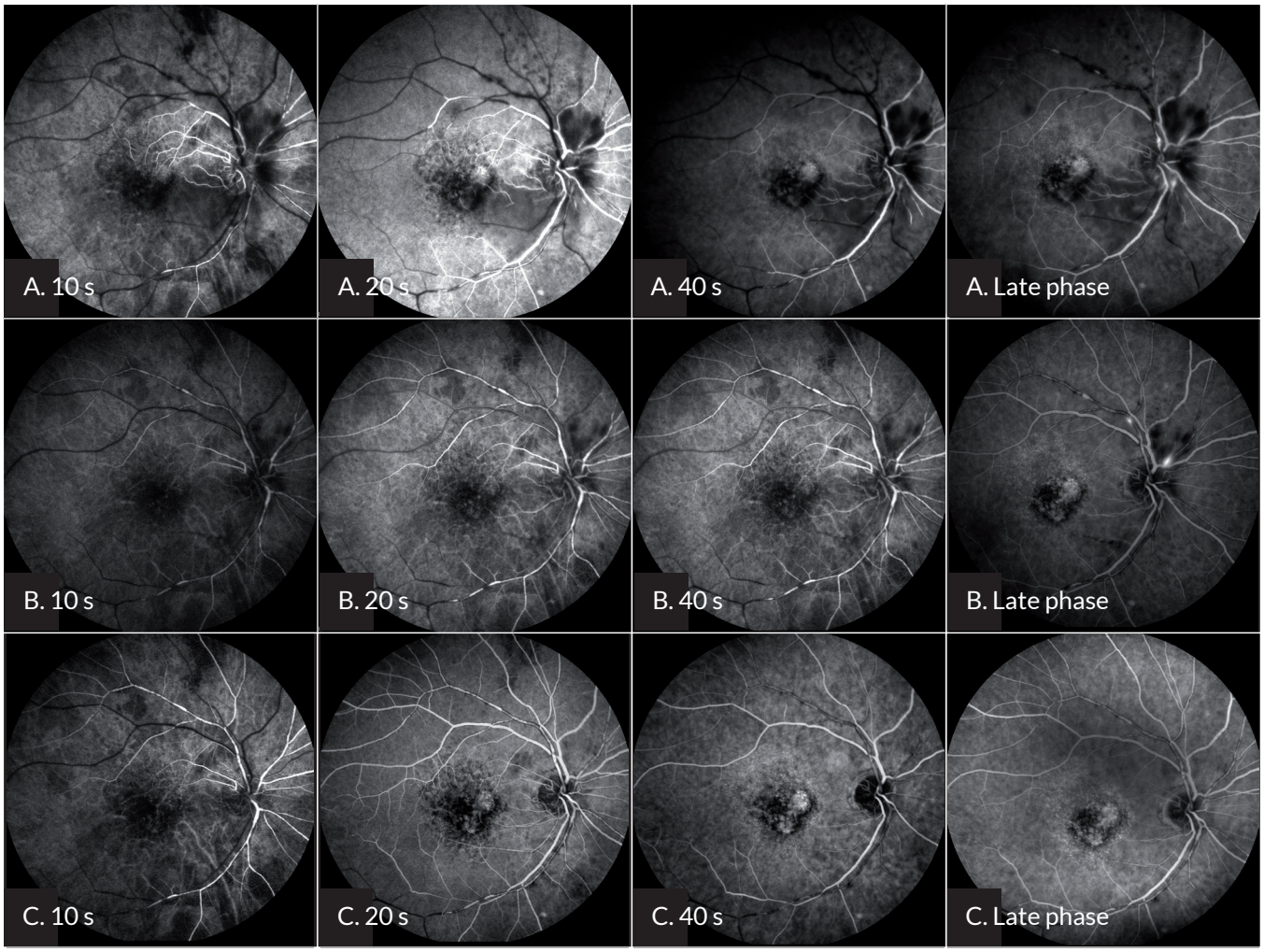

Figure 2. Fluorescein angiography (FA) of the right eye. **A.** On admission and ORV diagnosis. **B.** One week after treatment onset. **C.** One month after treatment onset

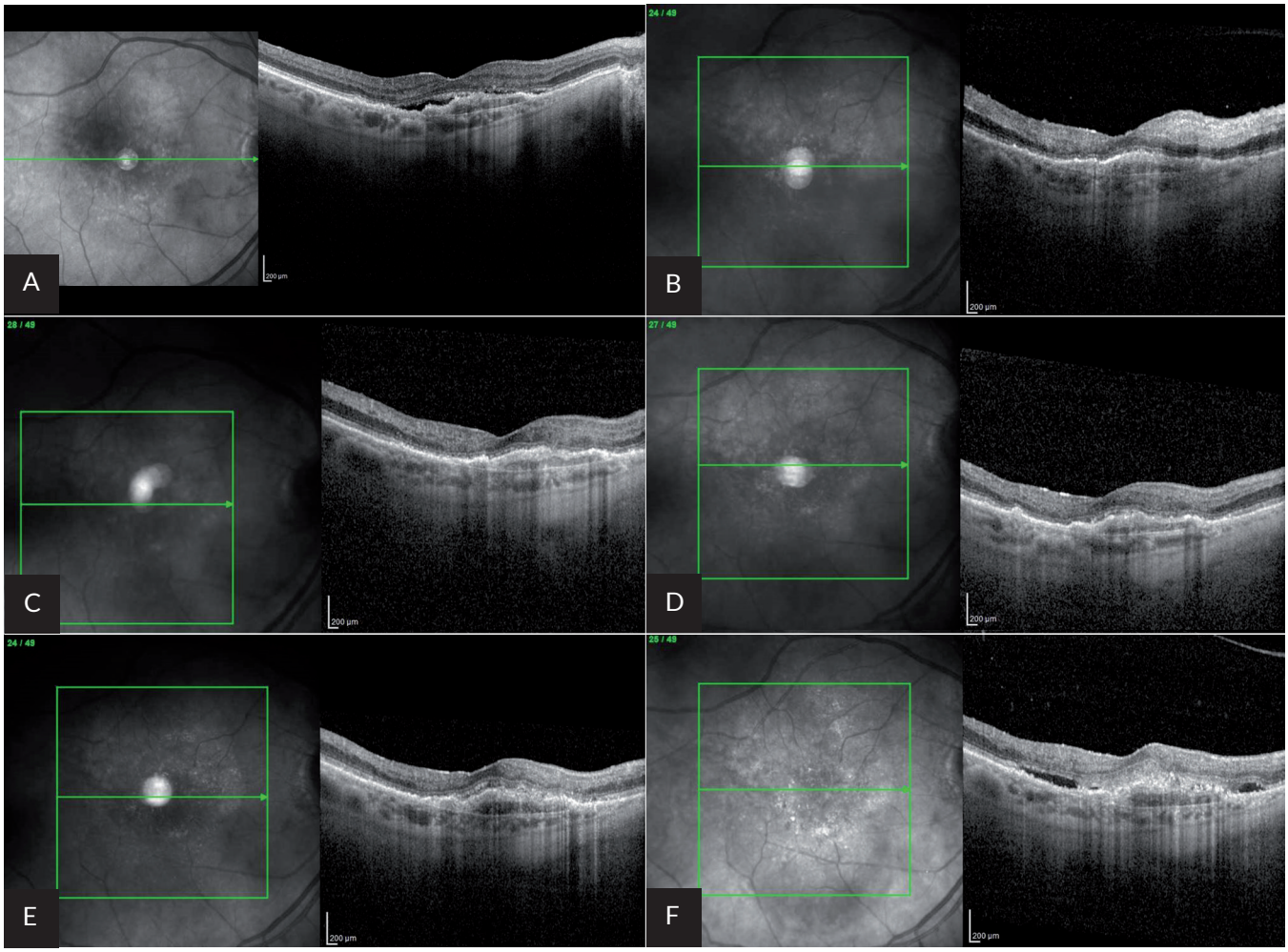

Figure 3. Optical coherence tomography (OCT) of the right eye. **A.** Before brolucizumab injection; subretinal fluid present. **B.** At 2 months of brolucizumab injection, on the day of presentation to the Clinic with ORV symptoms. **C.** At one week of steroid therapy onset. **D.** At 3 weeks of steroid therapy onset. No signs of neovascularization, significant resolution of perifoveal hyperreflectivity. **E.** At one month of steroid therapy onset and 3 months after brolucizumab administration. Visible subretinal fluid (gradual relapse of disease activity) and progression of retinal pigment epithelial detachment (PED) parameters. **F.** At 4 months of brolucizumab administration; clearly visible subretinal fluid

Based on the clinical picture, imaging findings, and similar clinical cases reported by the American Society of Retinal Specialists (ASRS), the patient was diagnosed with a complication of intravitreal brolucizumab, i.e. brolucizumab-associated retinal vasculitis (BARV) with IOI. Local and systemic steroid therapy was started. Periocular prednisolone acetate, topical dexamethasone 0.1% (eye drops, initially at 1-hour intervals, then five times daily), along with a non-steroidal anti-inflammatory drug and mydriatics were included. Intravenous steroid therapy with methylprednisolone 2 × 500 mg per day was initiated, reaching a total dose of 3 g. Then, oral steroid therapy with prednisone was continued at an initial dose of 40 mg per day, which was gradually reduced by 5 mg in the weeks that followed.

One week after the diagnosis of BARV, right VA improved to Snellen 0.3. Slit-lamp examination revealed no inflammatory cells in the AC of the right eye, with reduced inflammatory exudate in the vitreous chamber. Ophthalmoscopy and colour fundus photography of the right eye showed gradual regression of perivascular sheathing (Fig. 1). Fluorescein angiography (FA) showed reduced vascular leakage with segmental perivascular pigment stasis, delayed arteriolar filling with partial improvement of retinal perfusion compared to baseline (Fig. 2), and no pigment leakage on the optic disc. SD-OCT showed no signs of active wAMD (Fig. 3).

Six weeks after BARV diagnosis, right visual acuity stabilized at 0.4 Snellen. Right eye FA showed no vascular leakage, delayed and partial filling of the temporal branches of the central retinal artery, nonperfusion zones in the temporal quadrants, and a dark, ischemic optic disc (Fig. 2). Ophthalmoscopy and colour fundus photography at subsequent follow-ups showed resolution of inflammatory opacities in the vitreous body, optic disc oedema, and cotton wool spots, partial arterial revascularization with segmental blood column restoration in the affected vessels, as well as persistent intraretinal haemorrhages (Fig. 1). Analysis of the thickness of the right retinal nerve fibres showed their secondary, sectoral thinning within the optic disc (Fig. 4). A scotoma was detected in the right eye, covering the upper half of the visual field (Fig. 5).

After BARV diagnosis, right eye intravitreal therapy was discontinued. Subsequent follow-up examinations, con-

ducted 3 and 4 months after brolucizumab administration, showed a decrease in right VA to Snellen 0.16. Right macular SD-OCT revealed recurrence of wAMD activity, with the presence of subretinal fluid and increased pigment epithelial detachment (PED) parameters (Fig. 3). The patient was qualified to resume anti-VEGF therapy with a medication other than brolucizumab.

Discussion

Sterile intraocular inflammation (SII) following anti-VEGF treatment is characterized by acute onset and intraocular involvement in the absence of an infectious agent. Reported incidence rates vary across studies, ranging from 0.02% to 0.37% [8, 9]. Symptoms of SII typically appear within 24 hours to seven days following intravitreal injection [10–12]. The most common manifestations include blurred vision, floaters, and mild to moderate ocular pain, with photophobia occurring less frequently [12, 13]. Although visual acuity typically recovers to an average of 20/55 after resolution of SII following treatment, which may involve topical and systemic steroids, mydriatics, antibiotics, and, in severe cases, pars plana vitrectomy (PPV), approximately 15% of cases result in permanent vision loss of two lines or more, often associated with advanced inflammation with fibrin deposits and older age [12, 14].

Brolucizumab-associated SII does not significantly differ in terms of symptoms, treatment, or therapeutic outcomes from inflammations observed after other anti-VEGF agents [14]. However, data from clinical practice indicate that it has a more delayed course. In cases without vascular involvement, symptoms typically appear an average of 24 days post injection [15]. Brolucizumab has a higher rate of SII (>4%) compared to other anti-VEGF therapies. This may be due to higher serum levels of anti-brolucizumab antibodies in patients undergoing therapy compared to other anti-VEGF medications [2, 15]. The HAWK and HARRIER trials found that these antibodies were present in 36 to 52% of patients even before initiation of brolucizumab therapy, increasing to 53–67% once the treatment was started [2, 15]. Higher rates of SII were observed among individuals with these antibodies (6%) compared to those without (2%) [15].

In February 2020, i.e. a few months after FDA approval of brolucizumab, the ASRS announced receiving over a dozen BARV case reports. More than two-thirds of these were considered ORVs, which were associated with significant VA loss [16, 17]. These reports, along with case studies from routine clinical practice, prompted Novartis Pharma AG to establish a committee to monitor brolucizumab safety data. A post hoc analysis of HARRIER and HAWK [18] found that among 1,088 eyes treated with brolucizumab, 36 cases (3.3%) developed 'probable or definite' retinal vasculitis. Vasculitis coexisted with IOI in 24 of these 36 cases (67%). The rates of BARV (3.3% and 2.1%, respectively, for the individual studies) and vascular occlusion were significantly higher than those reported in the original HARRIER and HAWK trials. However, despite the actual risk of vision loss associated with these events, the overall rate of moderate to severe visual acuity loss (≥15 ETDRS letters) was comparable between brolucizumab (7.4%) and aflibercept (7.7%) treatment groups [2, 4, 18].

The aetiology of brolucizumab-related retinal vasculitis remains unknown. It is unlikely that the molecule itself directly causes inflammation, particularly since it lacks an Fc region and does not activate the complement system or antibody-mediated cytotoxicity mechanisms [19].

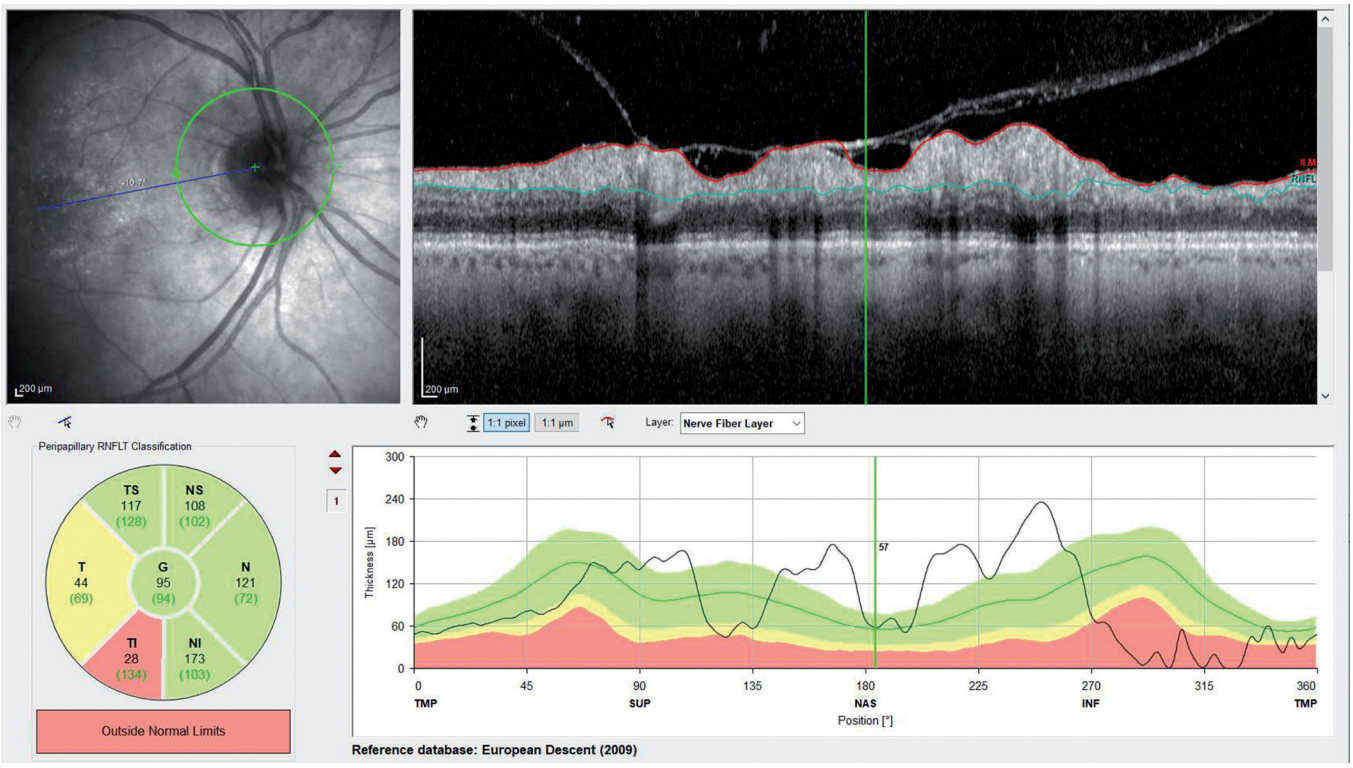

Figure 4. OCT of the right optic nerve. Evident sectoral loss of nerve fibres in the lower part

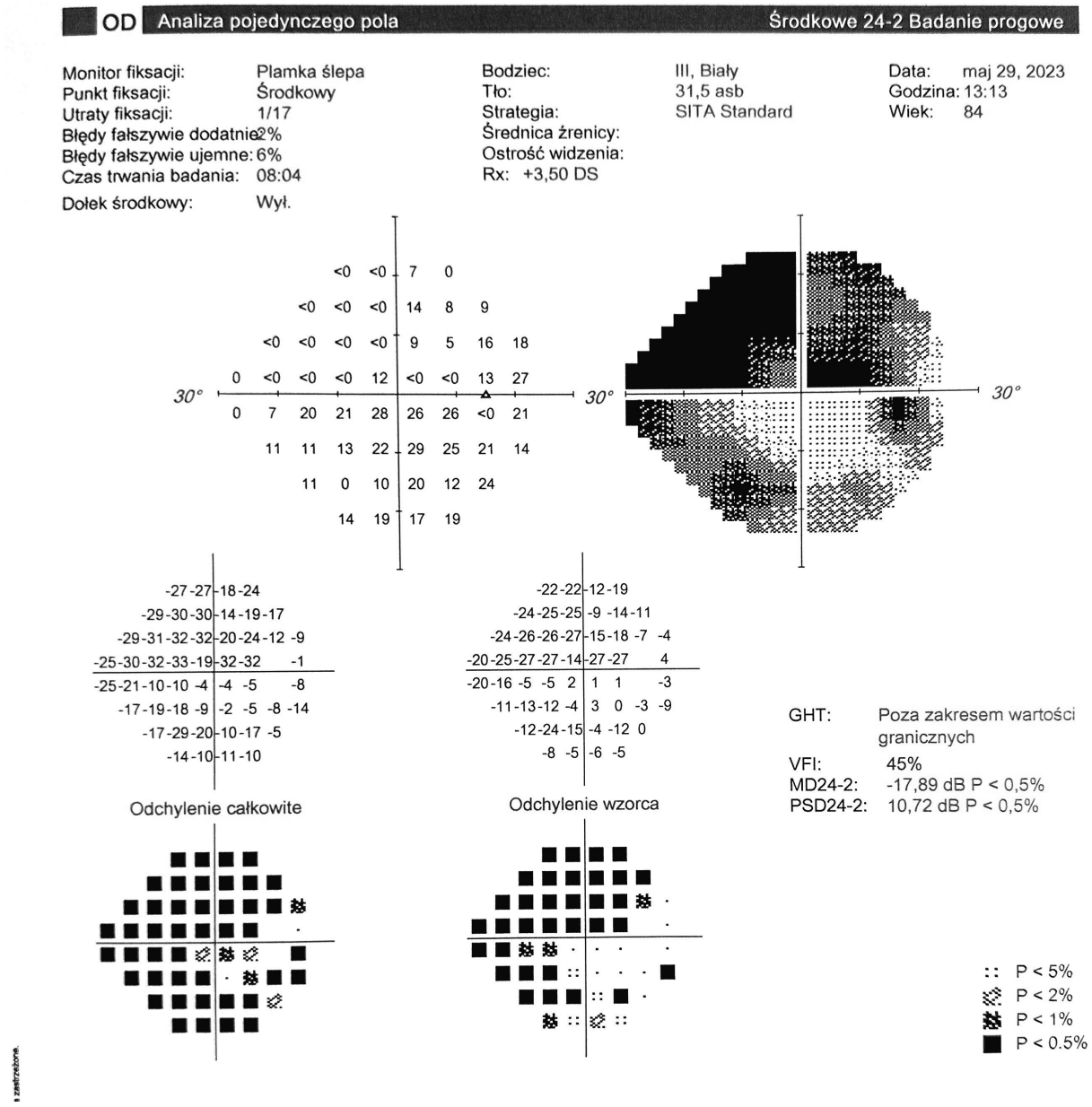

Figure 5. Visual field test for the right eye. Evident limitation of the visual field, mainly in the upper quadrants

Although impurities related to drug manufacturing, storage, or delivery are known to contribute to SII, this is unlikely to account for the majority of BARV cases given that symptom onset is often delayed and most cases are very rare. One hypothesis suggests that brolucizumab's smaller molecular weight may allow for deeper retinal penetration and increased VEGF inhibition. In the presence of concomitant inflammation, this could additionally diminish vascular perfusion and increase ischaemia, especially in eyes with reduced retinal blood flow at baseline [6, 17]. Alternatively, BARV may arise from the already mentioned anti-brolucizumab antibodies [2, 15]. In the presence of anti-drug antibodies, systemic monoclonal antibody therapy, including anti-VEGF agents, e.g. in the treatment of cancer, induces type III hypersensitivity reaction leading to vasculitis [20]. BARV may represent a similar reaction wherein intravascular deposition of IgG/IgM complexes causes vasculitis and vascular occlusion. This mechanism would be similar to the pathogenesis of haemorrhagic occlusive retinal vasculitis (HORV), which is seen in some patients who receive intraocular vancomycin and have been exposed to vancomycin previously [21].

Currently, histopathological studies related to HORV also suggest possible involvement of a type IV hypersensitivity reaction primarily involving T cells [22]. A case report with an analysis of a vitreous sample collected during vitrectomy in a patient with BARV showed the presence of CD3, CD4, CD8 and CD68 proteins. These findings indicate the presence of T cells and histiocytes, suggesting a type IV hypersensitivity reaction [23]. The observed coincidence of the presence of B and T cells may indicate a mixed type III and IV response [23, 24]. The time of BARV symptom onset also suggests a delayed hypersensitivity reaction, in which repeated exposure to the drug may result in a more rapid immune response. In the reported BARV case series, symptoms appeared on average between 30 and 53 days after injection [6, 15]. However,

Baumal et al. found that retinal vasculitis occurred earlier in patients who received more than one brolucizumab injection [6]. Additional factors, such as HLA subtype, immune status, comorbidities, or previous exposure to compounds structurally similar to brolucizumab, may also play a role in the pathogenesis of BARV [6].

Previous studies suggest that BARV is more common in women (88–100%), with an average age of 77 to 79 years. Most cases (92–96%) occur in Caucasians [6, 15]. Cardiovascular diseases (CVDs), such as hypertension, cardiac arrhythmias, as well as diabetes mellitus, and previous pneumonia may be risk factors for BARV. All ORV patients included in the HARRIER and HAWK trials had a medical history of CVD [18]. Similar findings have been reported in retrospective case series [4, 6]. Cancer or autoimmune disorders (e.g. multiple sclerosis, Graves disease or Raynaud's syndrome) were rarely reported [4, 6]. Symptoms of inflammation appear within 7 to 56 days after the last administration of brolucizumab [4, 6, 16, 17]. Blurred vision (58–62%), floaters (46–67%), redness (19%), pain (17–31%), and scotoma (12–25%) are the hallmark symptoms [4, 6, 16–17]. Visual acuity usually deteriorates, from an average of 20/53 at the time of brolucizumab administration to a mean of 20/191 at diagnosis [6]. IOI is usually present (92–100% of cases). Inflammation may be localized to the AC (0–31%), vitreous body (27%), or both (35–73%) [4, 16, 17]. Additionally, fine keratic precipitates, conjunctival injection, and Descemet folds have also been observed. No cases of hypopyon have been reported. Clinical signs of vasculitis are typically, though not always, present at the time of diagnosis. A minority of patients may present with recurrent IOI with vascular involvement, even if corticosteroids were started and the intraocular inflammation has decreased [25]. Vasculitis can involve arteries, veins, and capillaries. Both large- and small-calibre retinal arteries can be affected, showing narrowing, occlusion, and perivascular sheathing. Symptoms of retinal ischemia include retinal whitening, cotton wool spots, intraretinal haemorrhage, and pericentral acute middle maculopathy. Vascular occlusion accompanies inflammation in 67–85% of cases [6, 15].

The presented clinical case of BARV with IOI aligns with the known risk factors for this complication, as reported in the literature and mentioned above. Typical symptoms also emerged within a characteristic delayed time frame following brolucizumab injection. Both the anterior segment and the vitreous body of the eye were involved. The inflammation was sterile; however, infectious causes (infection-related symptoms typically arise within 3–4 days of drug administration, whereas aseptic reactions to brolucizumab usually manifest after several weeks) and systemic diseases that can cause vasculitis should always be considered in the differential diagnosis of IOI. Diagnostic tools, including FA, SD-OCT and wide- field imaging, allowed for the detection of ORV hallmarks, as well as for a precise assessment of the distal retinal periphery. Wide-field imaging is crucial in this complication, as signs of vasculitis may be subtle, scattered, and located just beyond the central posterior pole. In the presented case, the inflammatory changes were accompanied by a significant decline in visual acuity. The most prognostically concerning findings were ischemic changes in critical visual areas of the posterior pole, specifically the peripapillary region and macula, characterized by limited perfusion and secondary blurring of the papillary retinal lamellar structure.

Treatment of IOI, whether or not accompanied by vasculitis, should be prompt and aggressive. In cases of inflammation limited to the anterior chamber with preserved visual function, intensive topical corticosteroids (with sub-Tenons steroid injections) may be sufficient. Simultaneous monitoring of the posterior segment is essential. Inflammatory reaction involving the vitreous body is an indication for systemic steroids, initially at high intravenous doses, followed by oral maintenance therapy for a period of usually 6–12 weeks [6, 15, 16, 26–29]. In cases with significant vitreous involvement, PPV may be considered [28]. Case studies of BARV have shown that visual function may improve in some patients following steroid therapy [6, 15–17, 21–29], although not always to the pre-brolucizumab level. Wykoff et al. (2023) reviewed a total of 19 publications (70 eyes) on BARV. Of the eyes assessed for pre- and post-event VA, 22/42 eyes (52.4%) showed unchanged (±0.08 logMAR) or improved VA compared with the last recorded pre-event assessment, whereas 15/42 eyes (35.7%) showed ≥0.30 logMAR VA reduction (≥15 letters). Patients showing no VA loss were on average slightly younger and had higher rates of nonocclusive events [30].

In the presented case with vitritis, intensive local and systemic steroid therapy was initiated immediately upon the patient's presentation. During the first week of treatment, marked functional improvement and reduction of inflammation were achieved. After six weeks of therapy, Snellen VA of 0.4 was noted, which is two lines lower compared to the pre-brolucizumab values. Despite resolution of active inflammation and partial retinal revascularization, long-term follow-up revealed persistent consequences of prior ischemia in the form of optic nerve atrophy and visual field defect. In our view, ischemia secondary to BARV should be regarded as one of the most significant risk factors for permanent functional impairment following this complication.

Given the risk of adverse events such as BARV, the question arises as to how the associated risk of vision loss can be minimized. Patients should be educated about the potential symptoms of IOI following brolucizumab administration and advised to report to the clinic immediately upon experiencing any concerning symptoms [26, 27]. In the presented case, the patient reported a few days after symptom onset, delaying the initiation of appropriate treatment. Available data indicate that IOI symptoms following brolucizumab injection may occur over a broad time interval. Additional monitoring follow-ups between brolucizumab injections are not recommended; however, special emphasis should be placed on patient education. Before each subsequent brolucizumab injection, a thorough ophthalmological examination should be performed using a slit lamp (following pupil dilation) and vitreous assessment to detect inflammatory cells and subtle peripheral vascular occlusions. Most IOI cases (74%) in HAWK and HARRIER trials were detected within the first 6 months of treatment, with only 14% occurring between

6 and 12 months and another 12% after 12 months [4]. Therefore, ophthalmologists should remain vigilant for signs of inflammation, even beyond the first six months of therapy.

In the presented case, several months after BARV onset and following the resolution of inflammation, further significant decline in right eye VA was observed. Thorough diagnosis using wide-field imaging ruled out the recurrence of inflammation. VA deterioration was due to activation of wAMD, as confirmed by SD-OCT. The patient was qualified to resume anti-VEGF therapy, but with a different agent. This is one of the elements of prophylaxis. Furthermore, simultaneous administration of brolucizumab to both eyes should be avoided [31]. Ongoing treatment of wAMD in our patient is being closely monitored.

Conclusions

Brolucizumab is widely used worldwide for wAMD and diabetic macular oedema. Its efficacy and adverse events are continuously monitored through current literature [30, 32–34]. When qualifying patients for intravitreal brolucizumab injections and during treatment monitoring, it is important to remain aware of a rare yet vision-threatening complication in the form of retinal vasculitis, which often coexists with intraocular inflammation. Patient education, early diagnosis and prompt initiation of appropriate treatment can prevent severe vision loss in most cases. However, ischemia accompanying vasculitis may lead to permanent morphological changes in the retinal nerve fibres and, consequently, reduced field of vision.

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CHALLENGES IN THE DIAGNOSIS AND TREATMENT OF NEPHROTIC SYNDROME IN AN ELDERLY PATIENT

Trudności diagnostyczne i terapeutyczne zespołu nerczycowego u pacjenta w wieku podeszłym

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Abstract

Nephrotic syndrome is a set of symptoms primarily characterized by daily protein loss in the urine exceeding 3.5 grams, which can be caused by a range of underlying conditions. The presented case of an 88-year-old patient with nephrotic syndrome illustrates the challenges associated with the diagnostic process and treatment of this disorder in the presence of multiple comorbidities and advanced age. Despite contraindications for biopsy and, consequently, the lack of histological findings, treatment was initiated, resulting in significant partial remission, marked by a substantial reduction in proteinuria, decreased creatinine levels, and a satisfactory eGFR. This case highlights the importance of treating nephrotic syndrome in elderly patients and demonstrates the possibility of effective therapy despite diagnostic difficulties arising from contraindications for renal biopsy.

Streszczenie

Zespół nerczycowy to zespół objawów, charakteryzujący się przede wszystkim dobową utratą białka z moczem powyżej 3,5 grama, który może być wywołany przez szereg jednostek chorobowych. Przedstawiony przypadek 88-letniego pacjenta z zespołem nerczycowym obrazuje wyzwania związane z procesem diagnostycznym oraz leczeniem tego zespołu przy licznych obciążeniach i zaawansowanym wieku pacjenta. Mimo przeciwwskazań do wykonania biopsji nerki i braku jej wyniku, wdrożono leczenie, które pozwoliło na uzyskanie niepełnej, lecz znaczącej remisji w postaci istotnego zmniejszenia białkomoczu, obniżenia stężenia kreatyniny i uzyskania wartości przesączania kłębuszkowego na satysfakcjonującym poziomie. Opisany przypadek podkreśla konieczność leczenia zespołu nerczycowego u pacjentów w bardzo zaawansowanym wieku oraz pokazuje, że skuteczna terapia jest możliwa pomimo trudności diagnostycznych wynikających z przeciwwskazań do wykonania biopsji nerki.

Keywords: elderly patient; diagnostic challenges; nephrotic syndrome

Słowa kluczowe: pacjent geriatryczny; trudności diagnostyczne; zespół nerczycowy

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Introduction

Nephrotic syndrome (NS) is a clinical condition characterized by proteinuria >3.5 grams/day, hypoalbuminaemia, lipiduria, hyperlipidaemia, severe oedema, and transudation into body cavities [1]. It may be primary, arising from glomerulopathies, or it may develop secondary to systemic conditions such as diabetes mellitus, amyloidosis, or lupus erythematosus. Nephrotic proteinuria arises from damage to the glomerular filtration membrane caused by the disease process, specifically affecting the basement membrane and podocytes, particularly their foot processes. As a result, in addition to mechanical damage, the electrostatic barrier is lost, leading to increased permeability to proteins, primarily albumin [2].

Oedema is often the first clinical manifestation noticed by the patient. Other symptoms may include generalised

asthenia, abdominal pain, headache, nausea, vomiting, loss of appetite, malnutrition, and transudation of fluids into body cavities.

The diagnosis of NS patients has three main objectives: to identify the underlying disease, to assess complications, and to determine the histological type of glomerular changes [3]. Diagnostic workup should consider the most common causes of NS within the patient's age group, as well as individual factors such as medication history and prior infections. Importantly, elderly patients should be screened for neoplastic aetiology.

The third diagnostic goal, i.e. determining the exact aetiology, often requires percutaneous renal biopsy. The obtained biopsy is then analysed using light, fluorescence, and electron microscopy – the gold standard for diagnosing renal parenchymal diseases [4].

Treatment of NS is challenging due to the lack of clear guidelines supported by scientific evidence [3]. Current recommendations, based on expert consensus, offer only a few general guidelines [5]. Once the aetiology is established, causal treatment should be initiated. The therapy additionally incorporates dietary recommendations (sodium and fluid restriction), oedema reduction, proteinuria control, as well as prevention and management of complications.

Acute kidney injury (AKI), chronic kidney disease (CKD), infections, and venous thrombosis are the most common complications of NS. Systematic reviews do not support routine antithrombotic or anti-infective prophylaxis; however, it is important to monitor serum albumin and, if it drops below 2.5 g/dL, low-molecular-weight heparins should be administered [6, 7].

As with many other diseases, the patient's advanced age is an additional factor complicating the diagnosis and treatment of NS. Elderly individuals often present with multiple comorbidities, which can obscure symptoms and reduce vigilance, especially in the patient. Elderly patients require special consideration, as invasive or aggressive procedures are not always applicable in this group, further complicating the therapeutic process.

Case report

An 88-year-old man was admitted to the Department of Internal Medicine, Nephrology, and Dialysis at the Military Institute of Medicine – National Research Institute after being brought to the Emergency Department following a fainting episode. The patient had been hospitalized four times in various departments over the past six months. The current admission was a continuation of the diagnostic process initiated during two previous stays at the Department of Nephrology, Transplantology and Internal Diseases at the University Clinical Center of the Medical University of Gdańsk.

Nephrotic syndrome in the course of CKD, stage G3aA3, was the primary diagnosis and the reason for hospital stay on admission. Additionally, the patient presented with multiple chronic diseases, including hypertension, chronic coronary syndrome treated with coronary angioplasty with drug-eluting stent implantation in the circumflex branch of the left coronary artery (15 years ago), sick sinus syndrome with bradycardia, axonopathic sensorimotor polyneuropathy, multilevel degenerative and discopathic changes involving the lumbar-sacral spine, a history of L1 body compression fracture, benign prostatic hyperplasia, post-inflammatory cystic changes in the pancreas and one intraductal papillary mucinous neoplasm (IPMN), peptic ulcer disease of the stomach and duodenum, gastric atrophy, depression, bilateral hearing loss, a history of stroke with left-sided facial-brachial paresis, vascular changes of the white matter and generalized cortical-subcortical atrophy.

Due to the above-mentioned comorbidities, the patient received combination therapy. Until admission, CKD was managed with glucocorticoids (GCs), initially administered intravenously and then orally. Additionally, prednisone, omeprazole, acetylsalicylic acid, valsartan, amlodipine, sertraline, rosuvastatin, tamsulosin, finasteride, allopurinol, and pregabalin were used for other comorbidities.

On admission, the patient was in relatively good general condition, alert, and oriented. Physical examination revealed lower leg oedema and signs of stasis at the base of the lungs. Laboratory workup showed impaired renal function: creatinine 1.5 mg/dL, estimated glomerular filtration rate (eGFR) 47 mL/min/1.73 m², and urea 76 mg/dL. Urinalysis showed decreased specific gravity, significant proteinuria (>3 g/L), and haematuria of 17.1/µL (normal: up to 13.6/µL).

Renal biopsy was not performed due to contraindications. Further diagnosis focused on less invasive investigations, with an emphasis on symptom management. Secondary glomerulopathies were excluded in the first place. Normal blood glucose and glycated haemoglobin (HbA_{1c}) ruled out diabetic nephropathy. Additionally, low serum amyloid A and absence of echocardiographic features of amyloid deposition excluded amyloidosis.

Due to significantly increased serum gamma globulin fraction, plasma-cell dyscrasia was initially suspected. However, it was ruled out based on normal free light chain index and the absence of monoclonal protein in serum and urine immunofixation. Given the patient's age, paraneoplastic syndrome was also considered; however, extensive imaging, including gastroscopy, ultrasonography, computed tomography, and magnetic resonance imaging of the abdomen and pelvis, revealed no suspicious findings, except for a stable IPMN in the pancreas.

An immunological panel was also performed, including the assessment of ANCA, c-ANCA, ANA, anti-dsDNA, and anti-PLA2R antibodies, as well as C3 and C4 complement components. The results obtained allowed for the exclusion of several autoimmune diseases, including membranous nephropathy, the only primary glomerulopathy that can be diagnosed without renal biopsy. The presence of haematuria, which is not typical of this condition, further excluded the diagnosis.

Ultimately, primary glomerulopathy was considered the most likely aetiology, although a more specific diagno-

sis could not be reached. It was decided to intensify the treatment, adding oral tacrolimus to GCs. The patient was placed under further observation, waiting for the expected clinical response.

Partial, yet clinically meaningful, remission was achieved during the six-month follow-up. Urine protein, which had peaked at 6.59 g/L, dropped to 0.58 g/L, corresponding to a daily protein loss of up to 1.5 g. Creatinine decreased from >1.5 mg/dL to 1.1 mg/dL, while eGFR improved from 47 mL/min/1.73 m² to 64 mL/min/1.73 m². Once partial remission was achieved, GCs were discontinued, and the patient was maintained on tacrolimus monotherapy. Clinical and laboratory parameters remained stable over one-year follow-up at the Nephrology Clinic.

Discussion

The presented case highlights the therapeutic challenges associated with managing multiple comorbidities in an elderly patient. Determining the aetiology of NS without a kidney biopsy was the primary challenge. Histological verification provides the most reliable basis for diagnosis and, consequently, the implementation of effective treatment. In the case discussed, the diagnostic approach relied on a series of less invasive investigations and a stepwise exclusion of the most epidemiologically likely conditions.

After excluding autoimmune-related glomerulopathies, as well as plasma-cell dyscrasias or paraneoplastic syndrome, it was considered that the disease most likely belongs to the group of primary glomerulopathies. Primary causes are the most common aetiology of NS in the adult population, whereas secondary factors, often related to long-term chronic diseases, tend to predominate among the elderly [8]. Hence the importance of broad differential diagnosis, which should include screening for signs of new disorders, e.g. by performing echocardiography for amyloid deposition, as well as assessment of chronic disease control, e.g. by measuring HbA_{1c}.

As already mentioned, an accurate diagnosis requires histological evaluation; however, biopsy should be carefully considered even in the absence of contraindications as the patient's age also influences the expected treatment outcomes. Renal biopsy would probably be performed without hesitation in a younger patient's case to enable prompt initiation of aggressive and effective treatment to ensure long-term survival. In the case described, the patient was 88 years old and, although in relatively good condition for this age, his life expectancy was limited. This permits a slightly greater tolerance for residual symptoms, the long-term effects of which may not become clinically significant within his remaining lifespan. Furthermore, while the expected eGFR exceeds 90 mL/min/1.73 m² in young individuals, it begins to decline by approximately 1 mL/min/1.73 m² per year beginning from the third decade of life [9]. For this reason, eGFR of 64 mL/min/1.73 m² obtained after six months was entirely satisfactory in the described patient. It is also worth noting that the patient, initially classified as having CKD stage G3aA3, was reclassified as G2A3, further reflecting the success of the implemented therapy.

The patient's treatment initially involved high-dose GC pulses, followed by continued oral administration. In the six months that followed, an oral calcineurin inhibitor, tacrolimus, was introduced. Once partial remission was achieved, therapy was de-escalated and GCs were discontinued due to their widespread systemic effects and the risk of multiple complications associated with prolonged use. Satisfactory outcomes were maintained after one year of follow-up on tacrolimus monotherapy. If the patient's condition deteriorates, careful assessment of the potential benefits and risks of further treatment, including the possible reintroduction of GCs, should be conducted. At the same time, the focus should remain on providing the most effective therapy possible.

The partial remission achieved underscores the key conclusion of this case: nephrotic syndrome requires active treatment regardless of advanced age. Since proteinuria is the primary prognostic factor for the progression of CKD, its effective control reduces the risk of advancing to more severe disease stages [10, 11]. This is particularly important considering the number of medications taken by the patient, many of which may required dose adjustments or discontinuation. Such changes carry the risk of disrupting the fragile homeostatic balance in this 88-year-old patient [12].

Conclusions

Immunosuppressive treatment of nephrotic syndrome is crucial and can be effective even in elderly patients. Diagnostic challenges posed by the lack of possibility to perform a kidney biopsy should prompt a thorough differential diagnosis. This approach often allows for selecting effective therapy.

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Introduction

DIFFERENTIAL DIAGNOSIS OF CHRONIC KIDNEY DISEASE PROGRESSION IN A PATIENT WITH PSORIASIS AND XANTHOGRANULOMATOUS PYELONEPHRITIS

Diagnostyka różnicowa progresji przewlekłej choroby nerek u pacjentki z łuszczycą i żółtakoziarniniakowym odmiedniczkowym zapaleniem nerki

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Abstract

Chronic kidney disease refers to a group of disorders characterised by lasting abnormalities in kidney structure or function – persisting for over three months – and associated with conditions of various aetiologies. The classification of chronic kidney disease is based on two fundamental categories. The first one, marked as G, refers to the glomerular filtration rate, usually estimated using the CKD-EPI formula. The second, marked as A, relates to the amount of albumin excreted in the urine. Identifying the underlying causes of the disorders is essential, as targeted treatment can slow the natural progression of the disease and postpone the onset of the final, fifth stage – end-stage kidney disease – which necessitates the initiation of renal replacement therapy. The paper presents a case of a 50-year-old female patient with chronic kidney disease at stage G5 A3, with multiple comorbidities including suboptimally treated psoriasis, gout, recurrent urinary tract infections, and changes characteristic of xanthogranulomatous pyelonephritis of the right kidney, along with a history of chronic hydronephrosis.

Streszczenie

Przewlekła choroba nerek to zespół nieprawidłowości w zakresie czynności lub budowy nerek, utrzymujących się powyżej 3 miesięcy, występujących w jednostkach chorobowych o różnej etiologii. Klasyfikacja przewlekłej choroby nerek opiera się na dwóch podstawowych kategoriach. Pierwsza z nich – G – odnosi się do wartości przesączania kłębuszkowego, przy czym zwykle posługuje się jego szacowaną wartością, wyliczoną za pomocą wzoru CKD-EPI. Druga wartość –A – dotyczy ilości albuminy wydalanej z moczem. Ustalenie etiologii zaburzeń jest ważne, ponieważ ukierunkowane leczenie może spowolnić naturalny postęp choroby i opóźnić wejście w ostatnie, piąte stadium, zwane schyłkową niewydolnością nerek, które wiąże się z koniecznością wdrożenia leczenia nerkozastępczego. W pracy przedstawiono przypadek 50-letniej pacjentki z przewlekłą chorobą nerek w stadium G5 A3, z licznymi obciążeniami, między innymi nieoptymalnie leczoną łuszczycą, dną moczanową, nawracającymi zakażeniami układu moczowego oraz zmianami o charakterze żółtakoziarniniakowego odmiedniczkowego zapalenia prawej nerki i przewlekłym wodonerczem w wywiadzie.

Keywords: psoriasis; end-stage renal failure; xanthogranulomatous pyelonephritis

Słowa kluczowe: łuszczyca; schyłkowa niewydolność nerek; żółtakoziarniniakowe odmiedniczkowe zapalenie nerek

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Introduction

Chronic kidney disease (CKD) is a condition affecting many patients, very often coexisting with other disorders and contributing to multimorbidity [1]. Despite being relatively easy to diagnose, CKD is an insidious disease because it may not cause noticeable symptoms until advanced stages, and thus go undetected. The aetiology of CKD is highly diverse – ranging from primary and genetic causes to infectious factors and secondary complications of other systemic diseases, as well as more complex origins. The progression of the disease is gradual, and its severity is classified based on two main parameters. The first is a 5-stage classification denoted by the letter G. It defines the glomerular filtration rate (GFR) – though, for practical reasons, an estimated GFR (eGFR) is almost always used, calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. The second is a 3-stage classification described by the letter A, referring to albuminuria. This is assessed using either a 24-hour urine collection or the albumin-creatinine ratio in a spot urine sample. In patients with stage G5 CKD, kidney failure is diagnosed, which, due to the irreversibility of changes, is also referred to as end-stage kidney disease (ESKD). At this point, renal replacement therapy is required, which may take the form of haemodialysis, peritoneal dialysis, or kidney transplantation [2].

The following case involves a patient with multimorbidity, including several conditions that predispose to progressive kidney damage, thereby complicating differential diagnosis.

Case report

A fifty-year-old woman of Ukrainian nationality was admitted to the Department of Internal Medicine, Nephrology and Dialysis, Military Institute of Medicine – National Research Institute in Warsaw, due to progression of CKD. Her medical history included nephrolithiasis, chronic right-sided hydronephrosis, recurrent urinary tract infections, psoriasis, well-controlled type 2 diabetes mellitus previously treated with metformin, hypertension, normocytic anaemia, gout, and hypothyroidism managed with hormone replacement therapy. The patient also reported long-term tobacco use. Approximately 10 years earlier, the patient had undergone right-sided nephrolithotomy for staghorn calculi, with a past history of appendectomy. The woman presented to the Emergency Department in early January 2024 due to an elevated serum creatinine level (4.7 mg/dL), detected during outpatient tests performed as part of the preparatory work-up for a computed tomography (CT) scan. The examination was ordered by a urologist for the diagnosis of a hypoechoic lesion in the right kidney, previously visualised on ultrasound. In the previous measurement, performed more than three years earlier, the creatinine level was 1.2 mg/dl.

On admission, the patient reported dysuric symptoms, for which she had received antibiotic treatment three times in the past two months. Worsened blood pressure control and blurred vision were also observed. In addition, the patient reported an exacerbation of long-standing nausea over the past three months, now accompanied by vomiting occurring two to three times per week. In recent years, psoriasis treatment had primarily relied on topical therapies; however, their effectiveness had been modest. Previous narrowband UVB phototherapy had yielded good clinical response.

On physical examination, numerous confluent psoriatic lesions were observed on the skin of the back, abdomen, thighs, elbows, and the scalp, with sparing of the face and upper half of the trunk. The findings were consistent with a severe course of the disease. Additionally, mild oedema was observed.

Laboratory tests performed upon admission revealed the following: serum creatinine: 4.1 mg/dl (reference range: 0.5–0.9), eGFR CKD-EPI: 13 ml/min/1.73 m², blood urea nitrogen: 194 mg/dl (reference range: 15–43), uric acid: 14.8 mg/dl (reference range: 2.4–5.7). The patient also presented with metabolic acidosis: pH 7.182, with HCO_3^- concentration 15.1 mmol/l, hyperphosphataemia: 6.3 mg/dl (reference range: 2.6–4.5), mildly elevated parathyroid hormone (PTH): 79.4 pg/ml (reference range: 10–60) and erythrocyte sedimentation rate (ESR): 111–109 mm/h. Additional laboratory tests revealed elevated levels of serum amyloid A: 14.3 mg/dl (reference range: <0.64) and beta-2-microglobulin: 13.4 ug/ml (reference range: 1.09–2.53), accompanied by severe mixed dyslipidaemia (total cholesterol 298 mg/dl [<190], LDL 147 mg/dl [<116], triglycerides 456 mg/dl [<150], HDL 38 mg/dl [reference range: >45] and normocytic anaemia: haemoglobin 11 g/dl (reference range: 12–15). C-reactive protein (CRP) and procalcitonin levels remained within the normal range. On admission, urinalysis revealed proteinuria (100 mg/dL), leukocyturia, and haematuria. The urine cultures showed mixed flora. A subsequent culture was negative; however, follow-up testing demonstrated persistent leukocyturia without bacteriuria, along with haematuria. The 24-hour urine collections revealed proteinuria at the level of 2.6–3.2 g/24 h. The glycated haemoglobin level was 5.5%. Total calcium and albumin concentrations were within normal limits. The proteinogram revealed no evidence of monoclonal protein. Infection with HIV, active or past hepatitis B and C, as well as tuberculosis, was excluded. Complement components C3 and C4 were within the normal range. The reticulocyte count was also normal, with no evidence of haemolysis, iron deficiency, or vitamin B_{12} or folic acid deficiency. Antibody tests for ANA, anti-dsDNA, p- and c-ANCA, and rheumatoid factor (RF) were negative.

Echocardiographic examination revealed left ventricular hypertrophy, with no segmental wall motion abnormalities or significant valvular defects; the ejection fraction was 65%.

During hospitalisation, antihypertensive treatment was optimised, metformin was discontinued, and linagliptin was initiated. Metabolic acidosis was corrected through oral administration of bicarbonates, which led to the resolution of nausea and vomiting. In addition, an attempt was made to treat renal failure conservatively by introducing allopurinol and atorvastatin.

During hospitalisation, the patient experienced two episodes of sudden pain, swelling, and redness of the second toe on the right foot, suggestive of a gout flare. A comparative radiological and ultrasound examination of the feet revealed no signs of active inflammation. A good response to colchicine treatment was achieved, which supported the diagnosis of a gout attack. During her stay in the Department, the patient was consulted by a dermatologist, who recommended urgent initiation of UVB phototherapy. Topical psoriasis treatment was also intensified. Ophthalmological consultation revealed no signs of diabetic or hypertensive retinopathy.

In the follow-up ultrasound of the urinary tract, the right kidney showed hypertrophy of the middle renal column, measuring approximately 34×36 mm, with no possibility of excluding an isoechoic focal lesion. In the parenchyma of the right kidney, three hypoechoic lesions were visualised in the vicinity of the pyramids, without detectable vascularity, measuring: 5×15 mm in the upper pole, 12×21 mm in the middle column region, and 15×27 mm in the lower pole. The findings could be consistent with abscesses accompanied by papillary necrosis or neoplastic growth. The parenchyma of both kidneys demonstrated heterogeneous echostructure, increased echogenicity, and hyperechoic areas in the peripyramidal regions. The pelvicalyceal systems appeared slightly dilated bilaterally, with no evidence of calculi. Based on these findings, antibiotic therapy with ceftriaxone and ciprofloxacin was initiated, alongside antifungal treatment with fluconazole.

To verify the nature of the urinary tract abnormalities, after intravenous administration of fluids and acetylcysteine, a CT scan of the abdomen and pelvis was performed before and after the administration of intravenous contrast agent, including the urographic phase. The right kidney showed approximately a dozen hypodense lesions with hair-thin septations, which exhibited irregular contrast filling during the urographic phase and displayed pathological enhancement of both walls and septa in the venous phase. The pelvis and ureter of the right kidney had irregularly thickened walls. Additionally, on the right side, there were areas of increased density in the perirenal and pararenal fat tissue, as well as several enlarged paraaortic lymph nodes. The overall imaging findings raised a suspicion of xanthogranulomatous pyelonephritis of the right kidney. Selected CT scan images with annotated structures described in the text are presented in Figure 1 and Figure 2.

In subsequent phases of the study, normal contrast enhancement of both kidneys was observed, with delayed excretion of contrasted urine into the pelvicalyceal systems of both kidneys. Further passage through the undilated ureters to the urinary bladder, which had uniformly thickened walls, was undisturbed. Additionally, small fat hernias were described in the periumbilical region, with defect diameters up to 10 mm, as well as an oblique inguinal hernia on the left side with a defect diameter of 20 mm, containing normal visceral adipose tissue within the hernia sac. The patient underwent a urological consultation and was initially considered for diagnostic ureterorenoscopy or right-sided nephrectomy; however, after reassessment, outpatient observation was recommended.

Despite preserved diuresis, no significant improvement in kidney function was achieved (creatinine level was 4.3 mg/dl, eGFR CKD-EPI 12 ml/min/1.73 m², urea level 148 mg/dl). Consequently, possible kidney replacement therapy methods were discussed with the patient. She initially preferred peritoneal dialysis; however, due to the presence of hernias, uncertainty regarding the condition of the right kidney, and communication difficulties related to the language barrier, referral was issued for the creation of an arteriovenous fistula for haemodialysis. The patient was placed under

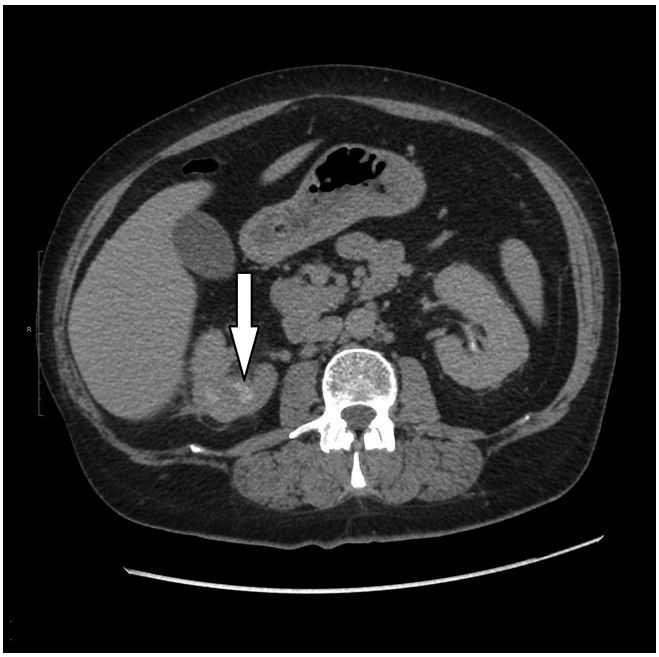

Figure 1. CT scan revealing one of the hypodense lesions in the right kidney

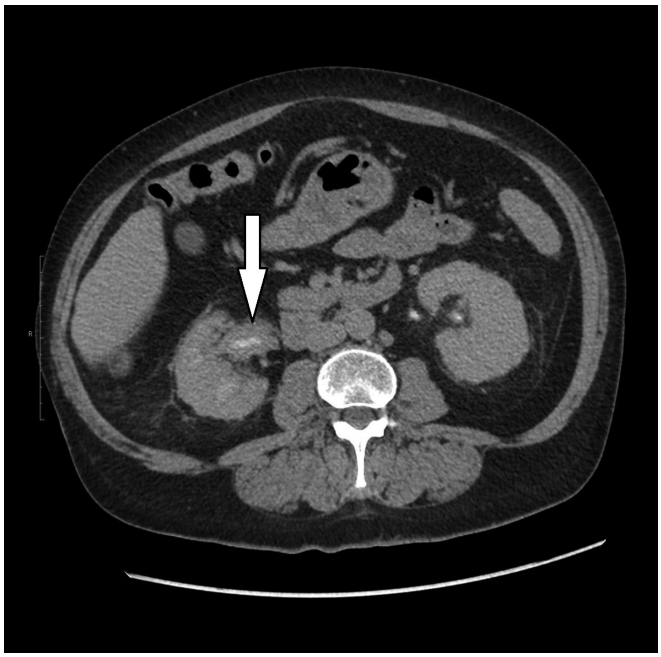

Figure 2. CT scan revealing thickened walls of the right renal pelvis

predialysis care at the Nephrology Outpatient Clinic, where she received darbepoetin alfa for the treatment of renal anaemia.

Discussion

In the described case, CKD was diagnosed at an advanced stage (G5 A3). Due to contraindications to kidney biopsy, it was not possible to determine the exact aetiology of nephron damage. Meanwhile, biopsy – enabling immunopathological evaluation of the collected material – currently constitutes the cornerstone of diagnostic assessment both in Poland and globally [3, 4].

The patient presented with multiple comorbidities, each of which could independently contribute to the development of chronic kidney disease. The most probable leading cause was determined to be glomerulonephritis in its most common form, IgA nephropathy, which may be associated with long-term, suboptimally treated psoriasis, as also indicated by the present haematuria [5, 6]. Other factors that may have contributed to the deterioration of kidney function include chronic tubulointerstitial nephritis secondary to gouty nephropathy, as well as radiologically diagnosed xanthogranulomatous pyelonephritis [7, 8]. An additional comorbidity was arterial hypertension, which, however, was well controlled, and ophthalmological examination did not reveal features of hypertensive retinopathy [9].

Another condition that could have contributed to the patient's poor condition was diabetes mellitus and diabetic nephropathy. However, the lack of retinopathy and a normal glycated haemoglobin level suggested that this aetiology could be excluded [10]. Amyloidosis was considered unlikely because, despite an elevated serum amyloid A (SAA) protein concentration, no amyloid deposits were visualised in the gingival biopsy [11].

Regardless of the aetiology, the advanced stage of kidney disease in this patient may necessitate the initiation of kidney replacement therapy in the near future. The patient initially opted for peritoneal dialysis – a method that is rarely chosen in Poland. According to 2023 data, only 766 patients used this form of treatment, accounting for approximately 4% of the just over 21,000 individuals undergoing dialysis in Poland at that time. This number decreased by nearly 50 patients compared to the previous year [12, 13].

Every form of kidney replacement therapy comes with its own specific inconveniences. For this reason, it is crucial for patients to be able to choose the therapy that best suits their expectations and lifestyle. However, contraindications to specific dialysis methods are also crucial. In the described case, the patient's umbilical and oblique inguinal hernias would complicate peritoneal dialysis. Therefore, and also due to communication difficulties related to the patient's background, a decision was made to prepare her for the initiation of haemodialysis. Based on the nephrologist's assessment, disseminated or advanced xanthogranulomatous pyelonephritis is an indication for nephrectomy [8]. However, while this procedure might expedite the initiation of haemodialysis, it would concurrently eliminate one of the sources of chronic inflammation. Moreover, histopathological examination of the removed kidney would enable assessment of the nature of the changes, including the exclusion of a tumour. This is a prerequisite for considering kidney transplantation; therefore, at present, this treatment option is unavailable to the patient. The optimal approach would be a preemptive transplant from a living related donor. This entails performing the transplantation during the predialysis stage, utilising a kidney graft from a living donor who voluntarily elects to donate one of their healthy kidneys. Most kidney transplants come from deceased donors and are implanted in individuals already undergoing dialysis while awaiting an organ. Nevertheless, such a transplant offers a more favourable prognosis than dialysis therapy [14, 15].

It should be noted that the patient has multiple comorbid conditions. Multimorbidity worsens the prognosis, which is why effective diagnosis and treatment of comorbidities, as well as the prevention of further complications, are so important [16, 17]. Predialysis nephrological care and optimisation of pharmacotherapy, including treatment of anaemia, may delay the need to initiate dialysis therapy. At the same time, coordinated care involving multiple medical specialties is essential for the effective management of the patient.

Summary

This case highlights the diagnostic complexity involved in determining the aetiology of kidney failure, which is likely multifactorial. The patient was diagnosed with glomerulonephritis – one of the most common causes of chronic kidney disease. However, the rapid progression to end-stage kidney disease was most likely driven by a combination of contributing factors including diabetes, hypertension, and gout. In patients with a history of conditions that predispose to nephron damage, it is essential to perform regular laboratory monitoring of renal function, including serum creatinine measurement with glomerular filtration rate estimation, and urinalysis with evaluation for proteinuria and urinary sediment. These tests may facilitate early detection and indicate the need for further diagnostic evaluation and more intensive management of underlying comorbidities contributing to CKD. Early disease identification and implementation of appropriate therapeutic measures may delay the need for renal replacement therapy, thereby improving both prognosis and quality of life.

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REPORT FROM THE 6TH CONGRESS OF THE POLISH SOCIETY OF MEDICAL BIOLOGY

Sprawozdanie z VI Zjazdu Polskiego Towarzystwa Biologii Medycznej

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Abstract

The 6th Scientific Congress of the Polish Society of Medical Biology (2024) was held in Warsaw from 19 to 21 September 2024. The meeting took place at the Airport Hotel Okęcie in Warsaw. This traditional gathering brought together scientists and clinicians to explore the broad spectrum of medical biology. Participants had the opportunity to attend lectures delivered by leading experts and share their own experiences in the field. There was also an opportunity to present scientific findings and forge new professional and personal connections. The Management Board of the Polish Society of Medical Biology entrusted the organisation of the Congress to the Military Institute of Medicine – National Research Institute and the University of Warsaw.

Streszczenie

VI Zjazd Naukowy Polskiego Towarzystwa Biologii Medycznej odbył się w Warszawie w dniach 19–21 września 2024 roku. Obrady miały miejsce w Airport Hotel Okęcie. Było to tradycyjne spotkanie naukowców i klinicystów zajmujących się szeroko pojętymi zagadnieniami biologii medycznej. Uczestnicy mieli okazję wysłuchać wykładów wybitnych przedstawicieli tej dyscypliny naukowej oraz wymienić z nimi poglądy. Była to także okazja do przedstawienia własnych prac i nawiązania nowych kontaktów zawodowych i osobistych. Organizację Zjazdu Zarząd Polskiego Towarzystwa Biologii Medycznej tym razem powierzył Wojskowemu Instytutowi Medycznemu – Państwowemu Instytutowi Badawczemu oraz Uniwersytetowi Warszawskiemu.

Keywords: medical biology; scientific congress

Słowa kluczowe: biologia medyczna; zjazd naukowy

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The 6th Scientific Congress of the Polish Society of Medical Biology took place in Warsaw from 19 to 21 September 2024, and was organised by the Military Institute of Medicine – National Research Institute and the University of Warsaw. The inauguration was attended by Lieutenant General Dariusz Łukowski, Deputy Head of the National Security Bureau, accompanied by the Head's adviser Lucjan Bełza; Deputy Minister of Science Maciej Gdula; Deputy Governor of the Mazowieckie Voivodeship Patryk Fajdek; Deputy Marshal of the Mazowieckie Voivodeship Anna Katarzyna Brzezińska; President of the National Chamber of Laboratory Diagnosticians Monika Pintal-Ślimak; Rector of the University of Warsaw Alojzy Z. Nowak; and Director of the Military Institute of Medicine – National Research Institute, Major General Grzegorz Gielerak.

Traditionally, the meeting brought together scientists and clinicians focused on the broad field of medical biology. Participants had the opportunity to attend lectures delivered by leading representatives of this scientific field, exchange views with them, and discuss their own research findings. The Congress also provided a platform for presenting individual work and establishing new interdisciplinary scientific collaborations. This year's edition was the largest to date and exceptional in many respects. In addition to a record-breaking turnout of over 250 participants, this year's Congress welcomed an unprecedented number of young scientists – including students and doctoral candidates. The event truly embodied the mission of the Polish Society of Medical Biology, promoting both interdisciplinary collaboration and intergenerational exchange.

Figure 1. Opening of the Congress. From left to right: Patryk Fajdek, Deputy Governor of the Mazowieckie Voivodeship; Prof. Zbigniew Izdebski, Coordinator of the Medical Faculty, University of Warsaw; Prof. Grzegorz Gielerak, Director of the Military Institute of Medicine – National Research Institute; Prof. Alojzy Z. Nowak, Rector of the University of Warsaw (*Photo by Krystian Szczęsny*)

Figure 2. Networking discussions. From left to right: Prof. Jacek Kubiak, Prof. Maria Anna Ciemerych-Litwinienko, Prof. Bolesław Kalicki, Deputy Marshal of the Mazowieckie Voivodeship – Anna Katarzyna Brzezińska (*Photo by Krystian Szczęsny*)

The Congress opened with an inaugural lecture delivered by a world-renowned expert in gene therapy, Professor Ian Alexander from the Children's Medical Research Institute and the Sydney Children's Hospitals Network, University of Sydney, Australia. Professor Alexander presented his team's research on innovative therapies for liver cell modifications. These therapies utilise various engineered forms of AAV (adeno-associated viruses) to achieve stable genome editing of hepatocytes in both paediatric and adult patients.

The Congress featured a series of outstanding lectures delivered by leading Polish and international scientists. The scientific proceedings were organised into 17 thematic sessions – including cell biology, immunology, oncology, paediatrics, molecular medicine, regenerative medicine, epidemiology, diagnostics, and medical chemistry – during which 58 presentations were given. Additionally, two poster sessions showcased a total of 60 poster presentations. Two sessions for young scientists were also organised – one oral and one poster session – during which young students of biology, biotechnology and medicine had the opportunity to present their work and discuss their research findings with leading experts in their fields.

The significance of the event was highlighted by the presence of a distinguished group of plenary speakers. Among those who accepted the invitation were: Prof. Maria Siemionow (Microsurgery Research, Department of Orthopaedics, University of Illinois at Chicago, Chicago, Illinois, USA), Prof. Małgorzata Kloc (Houston Methodist Research Institute, Transplant Immunology, Houston, TX, USA), Prof. Wiktor Jędrzejczak (University Clinical Centre, Medical University of Warsaw, Poland), Prof. Andrzej Dziembowski (International Institute of Molecular and Cell Biology in Warsaw / University of Warsaw, Poland), Prof. Piotr Siciński (Department of Genetics, Harvard Medical School / Department of Cancer Biology, Dana-Farber Cancer Institute, USA), Prof. Jacek Jemielity (Centre of New Technologies, University of Warsaw, Poland), Prof. Michael Stear (Department of Animal, Plant and Soil Sciences, AgriBio, La Trobe University, Australia), Dr Marcin Pękalski (University of Oxford, UK / Laboratory of Molecular Oncology and Innovative Therapies, Military Institute of Medicine – National Research Insti-

Figure 3. Congress inauguration, Deputy Minister of Science and Higher Education – Prof. Maciej Gdula (*Photo by Krystian Szczęsny*)

Figure 4. Congress inauguration, Chair of the Scientific Committee Prof. Ewa Bulska and Prof. Bolesław Kalicki (*Photo by Krystian Szczęsny*)

Figure 5. Ceremonial awarding of the title of Honorary Member of the Polish Society of Medical Biology to Prof. Jacek Malejczyk from the Medical University of Warsaw (*Photo by Krystian Szczęsny*)

Figure 6. Inaugural lecture by prof. Ian Alexander from Children's Medical Research Institute and Sydney Children's Hospitals Network, University of Sydney, Australia (*Photo by Krystian Szczęsny*)

tute, Poland), Dr Tino Schenk (Clinic of Internal Medicine II, University Hospital Jena, Department of Haematology and Medical Oncology, and Institute of Molecular Cell Biology, Centre for Molecular Biomedicine, Jena, Germany).

The thematic sessions also upheld exceptionally high scientific standards in both lectures and presentations. Numerous distinguished Polish experts shared their research results and clinical achievements.

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