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Informacje dla autorów

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   Books:
   Rudzki E. Alergia na leki: z uwzględnieniem odczynów anafilaktycznych i idiosynkrazji. Lublin, Wydawnictwo Czelej, 2002: 338–340
   Chapter of a book:
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   7) ensure confidentiality and security of personal data processing in accordance with applicable regulations (including GDPR).

Letter from the Editor-in-Chief

Welcome!

This is the 4th issue of Military Physician in 2023, during an intensive time in academic life: another year at the universities has begun, classes with students are in progress, while conventions and scientific conferences are being organised. We hope that we receive many interesting reports resulting from your activities and academic work.

We have selected a number of interesting papers to be published in the final issue of this year. Please pay special attention to the papers devoted to the surgical treatment of distal humeral fractures and hyperbaric oxygen therapy, which presents the principles of operation of the hyperbaric chamber, along with indications and contraindications for this method. The work devoted to the treatment of brain aneurysms is also of great practical and educational importance.

In recent months, the influx of many patients from a country with a different health care system has become a challenge for doctors. Therefore, in publishing these papers we have a focus on the problems associated with a vaccination plan that is different from the Polish one. I would also like to draw your attention to an article discussing the differences in the criminal liability of a military doctor and a civilian doctor. This issue concludes with a report on the XXVII International Congress of the Polish Cardiac Society.

I hope you have an inspiring read! May the New Year of 2024 bring us all further scientific development and great satisfaction in our professional and private lives.

I would like to thank all the authors and reviewers, as well as the entire editorial board. If it were not for their efforts, our journal would not be able to develop.

Bolesław Kalicki MD, PhD

The Editorial Board of "Military Physician" would like to thank the following reviewers for their work, commitment, reliability, conscientiousness and effort during the evaluation of the submitted papers in 2023:
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REPORTS

PHYSIOTHERAPY AFTER A DISTAL HUMERAL FRACTURE SURGERY

FIZJOTERAPIA PO OPERACYJNYM LECZENIU ZŁAMAŃ DALSZEGO KOŃCA KOŚCI RAMIENNEJ

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Abstract: The treatment of distal humeral fractures is a considerable challenge. The stabilisation method depends on a number of factors, including the complexity of the damage to both the bone and soft tissue, the number of bone fragments produced and their arrangement. At the same time, general scientific literature lacks information on the rehabilitation of these patients. The article sets out a rehabilitation programme and guidelines for physiotherapists treating patients after distal humeral fracture surgery.

Streszczenie: Leczenie złamań dalszego końca kości ramiennej stanowi niemałe wyzwanie. W zależności od skomplikowania uszkodzenia kości i tkanek miękkich, liczby powstałych odłamów kostnych i ich ułożenia, dobierana jest odpowiednia metoda stabilizacji. Jednocześnie, w ogólnodostępnej literaturze naukowej istnieje niewiele informacji dotyczących rehabilitacji tej grupy pacjentów. W artykule prezentowany jest program usprawniania i wskazówki dla fizjoterapeutów w leczeniu pacjenta po operacyjnym leczeniu złamania dalszego końca kości ramiennej.

Keywords: bone fracture, rehabilitation, traumatology, distal humeral fracture

Słowa kluczowe: złamanie kości, rehabilitacja, traumatologia, złamanie dalszego końca kości ramiennej

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Distal humeral fractures pose a particularly difficult problem for orthopaedists and physiotherapists. They occur rarely, with statistical studies in the US reporting a rate of 43 cases per 100,000 individuals [1]. By comparison, proximal humeral fractures show an incidence rate of 60 cases per 100,000 individuals. In the upper limb, distal radius is the most common site of fracture, with 162 cases per 100,000 individuals [2].

This paper presents our own method of physiotherapy after surgical treatment of distal humeral fractures.

The elbow joint is a complex, biaxial, hinge and pivot joint with three interconnected bones: humerus, radius and ulna. It performs two functions, namely flexion-extension and pronation-supination. The elbow flexion-extension range of motion lies between 140° and 150°. The physiological value of an elbow pronation is up to 10°. The total supination-pronation range of motion is about 180°. We should note that the functional range of motion for the elbow joint, used for most daily activities, is flexion from 30° to 130° and pronation and supination of 50°.

There are two groups of people who are most likely to suffer a distal humeral fracture. The first one is young men who sustain a high-energy injury as a result of traffic accidents, falls from great heights or during sports [4]. High-energy trauma fractures are characterized by the formation of a large number of bony fragments and soft tissue injuries, which can cause vascular and nerve damage [5]. The second group includes elderly patients with osteoporosis, who suffer from a low-energy injuries most often associated with a fall from the patient's height. High-energy injuries happen increasingly often to elderly patients who engage in risky physical activity that puts them at risk of musculoskeletal injuries. Due to osteoporotic changes in the bone structure, fractures in this group of patients are difficult to reconstruct surgically [6]. The most common local complications of fractures in this area include damage to the radial, ulnar and median nerves.

Radiological classification of fractures is based on the AO/ASIF (*Association for Osteosynthesis/Association for Study of Internal Fixation*) system. According to this commonly used classification, fractures are divided into extraarticular, partial articular and complete articular types, taking into consideration the location and the possible

presence of comminuted fractures. Each fracture type or subtype is accompanied by a description of the method of surgical stabilisation, adapted to the patient's overall condition [7]. Fixation in a comminuted distal humeral fracture in adults require open surgical reduction and stable fixation, except when there are contraindications to a surgery. The goal of surgical treatment, especially in intraarticular fractures, is to fix the pieces of bone in such a way that elbow joint motion can be initiated as early as possible [5-6]. The elbow joint is particularly susceptible to mobility limitation after surgery, which translates directly into a longer rehabilitation process.

It can be extremely difficult to obtain stable fixation in comminuted fractures, so in exceptional cases a joint prosthesis is being considered [8].

The most commonly used method of surgical treatment of distal humeral fractures is open reduction of bone fragments and fixation with metal connectors (screws and plates). Surgical treatment makes it possible to restore the anatomical structure of the distal humerus, preserve the elbow joint congruency and begin early rehabilitation [4, 8].

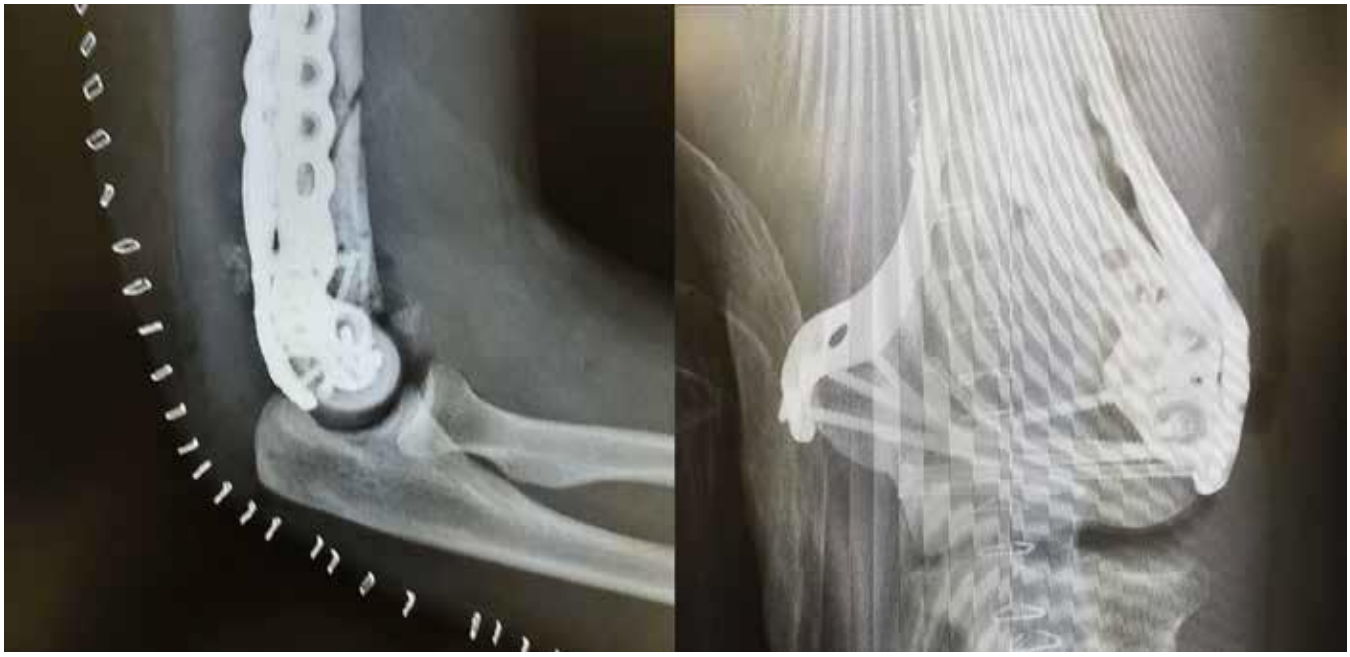

Figure 1. Open reduction internal fixation (ORIF) of a distal humeral fracture.

In the cases of open fractures with extensive bone and soft tissue damage or loss, their contamination without the possibility of immediate soft-tissue coverage of the opening site, damage to blood vessels and in unstable fractures, an external stabiliser should be used. In particular situations, an external hinged elbow brace may be used, as it enables starting the rehabilitation process [5].

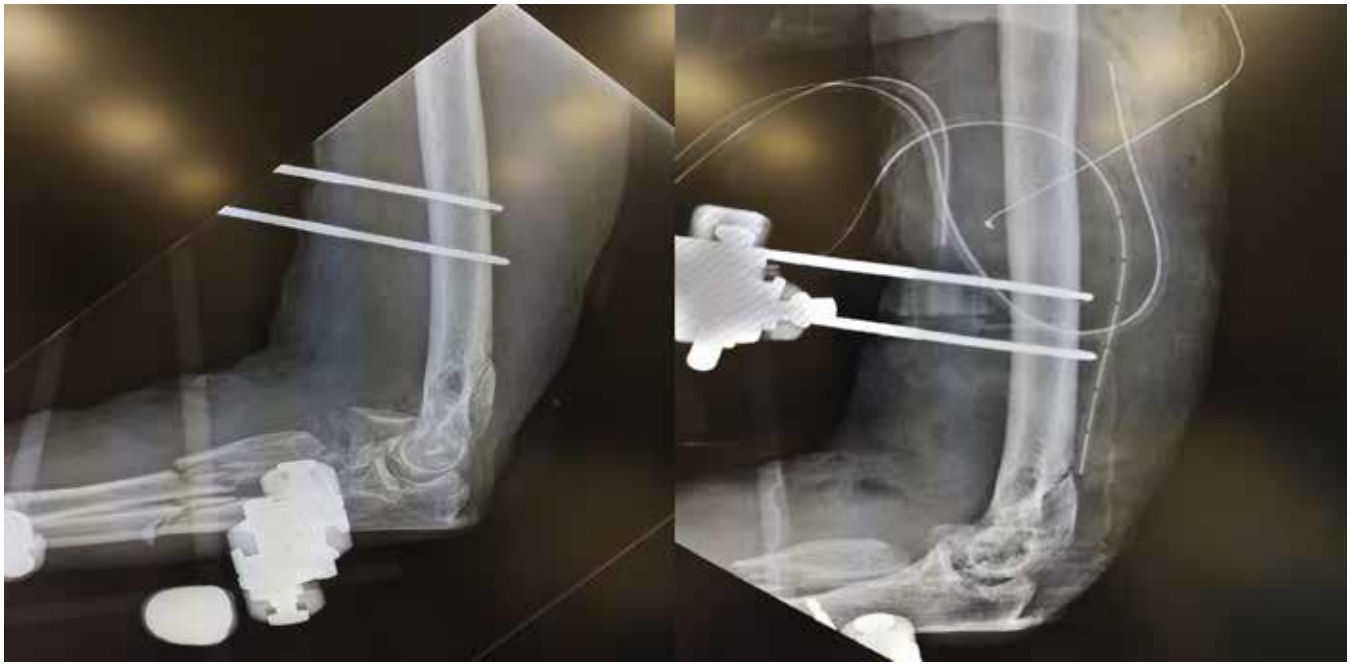

Figure 2 Surgical fixation with an external brace of a distal humeral fracture.

Where anatomical fixation is difficult, an alternative functional treatment method that was introduced by Professor Tylman's team may be applied. A direct traction is applied in the axis of the arm behind the ulnar process in the damaged limb with appropriately selected loading. This method prevents the development of stiffness in the shoulder joint associated with immobilisation after other surgical methods [9].

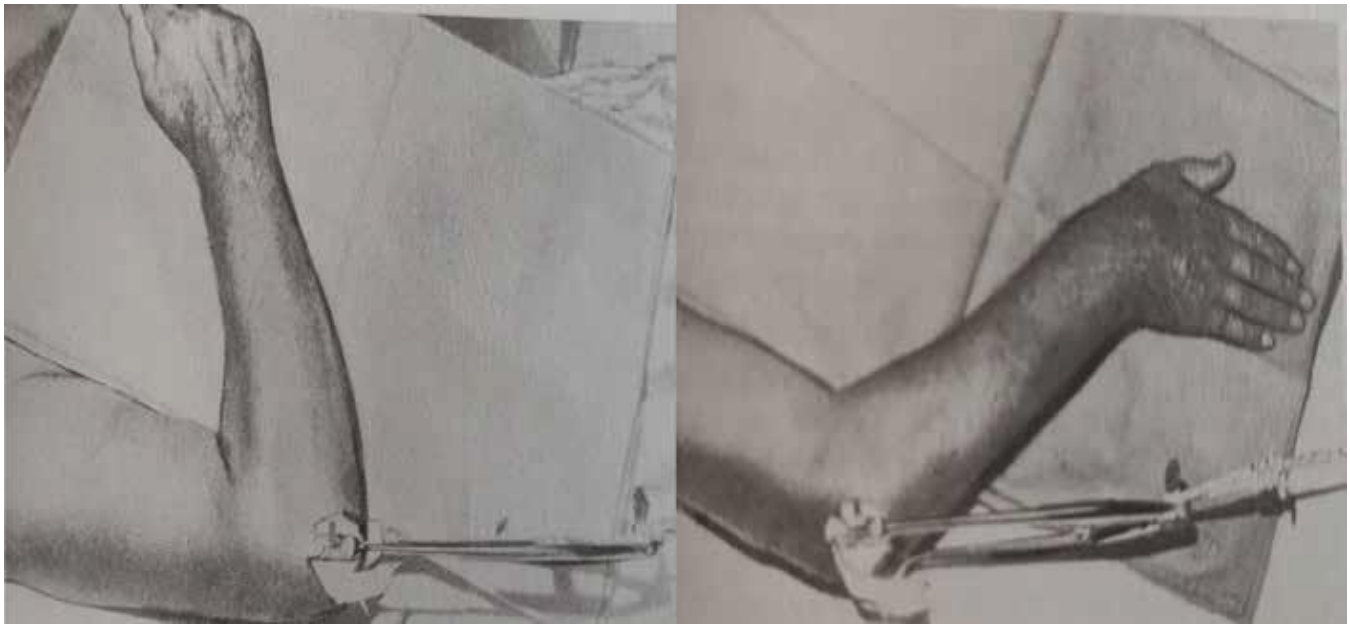

Figure 3 Active exercise of elbow joint extension within functional therapy in the treatment of fractures.

Proper planning of postoperative rehabilitation requires information from the operator regarding: stability of the bone fragments fixation, restoration of the articular surface of the humerus, ligamentous stability, and intraoperative passive mobility of the elbow joint. This information, together with a clinical and radiographic examination, is used for rehabilitation planning [8, 10]. The goal of rehabilitation after elbow surgery is to restore the optimal and pain-free mobility in the joint, considering the patient's individual anatomical, physiological and biomechanical conditions [11]. It should be noted that, compared to the knee or shoulder joint, the elbow joint presents greater variability in bone fusion and a tendency to form scar tissue, which limits the effectiveness of rehabilitation [4].

The literature contains general principles of physiotherapeutic management of distal humeral fractures. The authors divide the healing process into three phases: inflammatory, fibroblastic, and remodelling [8]. In the first one, management is targeted at an effective analgesia and anti-inflammatory effect while maintaining a range of painless motion through the introduction of weight-bearing and self-assisted exercises. Stretching and strengthening exercises are not indicated, as they pose a risk of disturbing the healing of any damaged tissues. In this phase, an effective approach is to follow PRRICEMM (*protection, relative rest, ice, compression, elevation, medications and modalities*) [8].

Once the inflammation has been reduced, the fibroblastic phase involves normal collagen synthesis. The patient can perform equipment-free and assisted active exercises. They can also start increasing the passive range of motion for the elbow joint with the application of limited force. During the remodelling phase, the patient is allowed to do exercises that stretch the muscles and fascia, build up muscle strength and increase the active range of motion to restore the elbow joint function [12-13]. Continuous observation is necessary towards exudation, change in skin temperature and severity of pain. Inflammation can lead to a decrease in the range of motion. In such a case, the PRRICEMM management method should be continued in the process of the elbow joint rehabilitation [8].

The widely published recommendations referred to above seem too general. Rehabilitation requires an individual approach to each patient, taking into account their general condition, as well as data on the operation site. It is difficult to find appropriate guidelines for developing an individualised rehabilitation plan. The publications lack important definitions for physiotherapists regarding the time of rehabilitation and detailed information to determine when to proceed to the next phase. Therefore, we would like to present an original program for elbow joint rehabilitation after fixation and reduction of the distal humeral fracture.

Time intervals during postoperative rehabilitation should be introduced according to the following scheme:

Up to 2 weeks after surgery
(postoperative wound healing period)

The main goal of the first stage of physiotherapy is to improve blood circulation and reduce swelling in the operated limb, which makes the post-operative healing faster and reduces pain. We recommend performing passive/active-passive/active exercises of the arm and shoulder joints, isometric exercises of the muscles of the forearm and shoulder to prevent atrophy. The exercises can

be supported by lymphatic drainage with limb elevation in a drainage position. During this period, the elbow joint is immobilised.

Figure 4 Active exercise of the hand.

From 2 to 6 weeks after surgery (until the first radiological control)

This stage begins after the postoperative wound has healed. It should be noted that passing to the next stage should be conditioned upon the stability of the fixation confirmed by the surgeon. If the fixation stability is sufficient, active-passive movement at the elbow joint should be introduced. We recommend self-assisted exercises in one plane (flexion/extension) with the forearm in an intermediate position. Pronation and supination can be included in rehabilitation after radiological confirmation of fixation stability. In the case of doubtful fixation stability, the first stage management should be continued for another 4-6 weeks, i.e. until the next radiological control.

From 6 to 12 weeks after surgery

If there are no contraindications to starting the next stage of rehabilitation, we recommend active movements of the elbow joint. At the early stage, active movement should be performed in the pain-free range. We recommend rotational movements of the forearm and resistance exercises with loads appropriate to the patient's

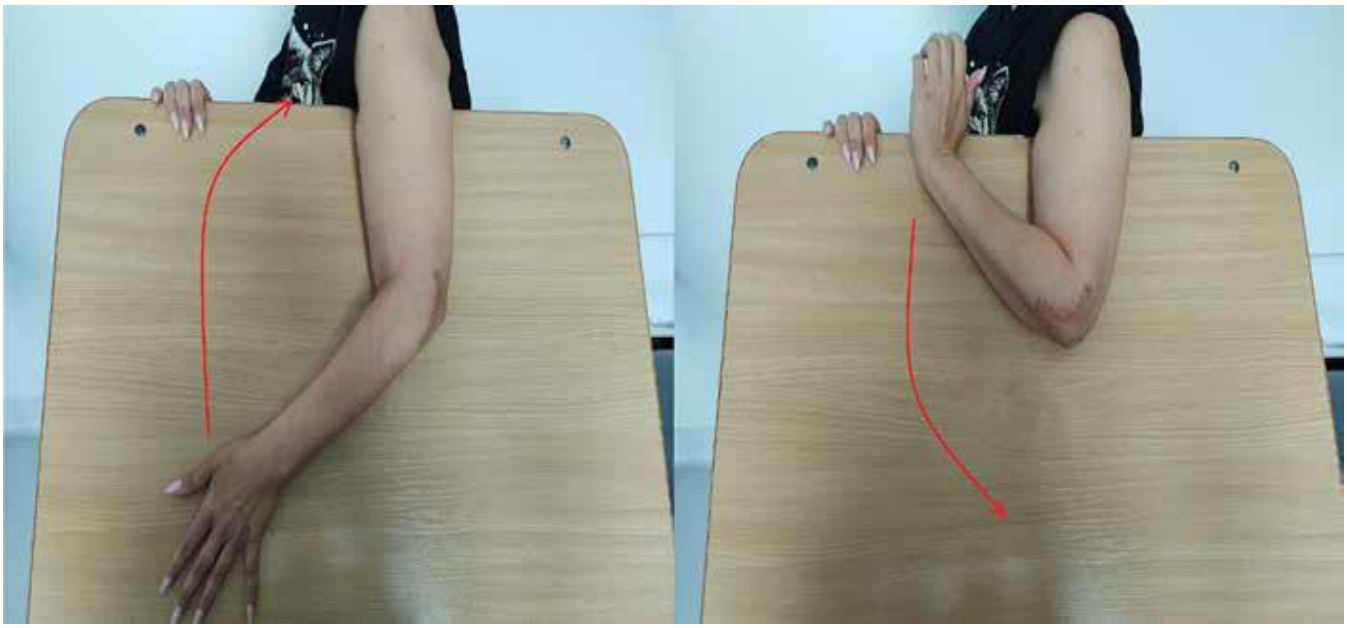

Figure 5 Active exercise of the elbow joint.

capabilities. In addition, to increase mobility, we apply a post-isometric relaxation technique, muscle and fascia stretching and passive stretching of the elbow joint, with the help of specialised instruments.

In the case of incomplete bone fusion or other contraindications to the implementation of further stages of rehabilitation, it is necessary to follow the plan from the first or second stage, waiting for the next radiological control. In such cases, the decision should be taken together with the surgeon.

From 12 weeks to full bone remodelling

If all the stages have passed without worrisome symptoms, we can proceed to the final stage of rehabilitation after surgical fusion. We introduce a rehabilitation plan with a training schedule appropriate for the patient's capabilities, including progressive loading. It involves intensifying the number of repetitions, increasing the load and the number of series, which simultaneously translates into time and intervals between workouts. We use various forms of stretching to achieve the maximum possible range of motion. This stage aims at restoring or achieving limb efficiency as close to the preinjury level as possible.

At each stage, depending on the needs of the patient, kinesiology taping and physical therapy treatments (magnetic field, laser, cryotherapy, etc.) can be implemented. An important part of the rehabilitation is scar management, based on various preparations and silicone plasters. They have anti-oedema, anti-inflammatory effect and accelerate tissue regeneration. It is also important to introduce myofascial techniques, which have been widely used recently in physiotherapy. However, this topic should be discussed separately due to its complexity and possible complications.

Dehghan et al. believe that postoperative immobilisation of the elbow joint should not last longer than 2 weeks. Longer immobilisation can cause significant restrictions in the range of motion and limit limb function [11]. Our experience shows that such management, although correct, is not appropriate in every single case.

Pipicelli et al. point out that rehabilitation should be carried out in close collaboration with the therapist and surgeon. They impose the requirement of providing very important information regarding the fixation stability and the possible passive range of motion after closure of the surgical wound. Other important information regards the elbow joint ligament tension, which determines the planes of passive and active movements during rehabilitation [12]. These principles coincide with the methods of rehabilitation for patients undergoing surgery in our clinic.

Verstuyft et al. recommend referring to general principles of rehabilitation in the case of a distal humeral fracture [13]. The proposed principles are too general to be effectively applied. One example is the suggestion to start mobilizing the elbow joint in the first two weeks in a pain-free active and passive range of motion. Our practice shows that this rehabilitation method can interfere with soft tissue healing and bone fusion.

Conclusions

Development of a standard rehabilitation program in patients after musculoskeletal trauma is associated with numerous disadvantages. In distal humeral fractures, surgical anatomical restoration of the joint surface and stable fixation with simultaneous restoration of soft tissue continuity is crucial to the physiotherapy process in achieving the functional range of motion of the elbow joint. Because of the many variables involved in a bone and soft tissue injury, quality of surgical reduction and bone fusion, creating a universal physiotherapy management protocol is difficult. The presented method of physiotherapy after surgical treatment of distal humeral fractures requires close cooperation between the surgeon and the physiotherapist. Other important factors include diligent information collection, exchanging experiences and dialogue between the centres on the surgical and the rehabilitation management being carried out.

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REVIEW ARTICLE

LASER THERAPY IN THE TREATMENT OF THE INJURIES AND INFLAMMATIONS OF THE ORAL MUCOSA – PART 2

LASEROTERAPIA W LECZENIU URAZÓW I ZAPALENIA ŚLUZÓWKI JAMY USTNEJ – CZĘŚĆ II

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Abstract: The mucous membrane (MM) of the oral cavity is a complex structure and possesses numerous significant functions. Lesions and inflammatory diseases of the oral mucous membrane (oral mucositis, OM) are a common reason for patient consultations. The underlying causes comprise infectious (bacterial, fungal, viral), allergic, reactive, as well as systemic and idiopathic factors. Traumatic stomatitis can be classified into thermal, chemical, and mechanical types. In fact, iatrogenic injuries resulting from dental treatment constitute a particular group. Oral mucositis is manifested by redness, oedema, acute pain and burning, which significantly impairs food intake and hygiene procedures. Low-level laser therapy (LLLT) is applied for both oral cavity injuries and oral mucositits, due to its analgesic, anti-inflammatory, anti-edematous and biostimulative effects. Absorbed by the biological structure, laser radiation induces a number of processes which are either primary / early (up to a few minutes following the procedure), and secondary / delayed (a few / many days). Depending on the level at which the changes occur, they are classified into molecular, cellular, and affecting the tissues. As indicated by numerous studies, LLLT is a non-invasive, low-cost, fast, widely available, and effective form of treatment of oral mucosa inflammatory lesions and injuries.

Streszczenie: Błona śluzowa/śluzówka (ang. *mucous membrane*, MM) jamy ustnej ma skomplikowaną budowę i pełni rozliczne, niezwykle istotne funkcje. Zmiany i choroby zapalne śluzówki jamy ustnej (ang. *oral mucositis*, OM) są częstym powodem zgłaszania się pacjenta na konsultacje. Przyczyną występowania OM mogą być czynniki: infekcyjne (bakteryjne, grzybicze, wirusowe), alergiczne, odczynowe oraz choroby ogólnoustrojowe i idiopatyczne. Urazowe OM można podzielić na: termiczne, chemiczne oraz mechaniczne. Szczególną grupę stanowią uszkodzenia jatrogenne powstałe w wyniku leczenia stomatologicznego. Objawem OM jest: zaczerwienienie, obrzęk, ból ostry i pieczenie MM, które w znacznym stopniu utrudniają przyjmowanie pokarmów i zabiegi higienizacyjne. Laseroterapia niskoenergetyczna (ang. *low level laser therapy*, LLLT) jest wykorzystywana w urazach MM i OM, ze względu na działanie przeciwbólowe, przeciwzapalne, przeciwobrzękowe i biostymulacyjne. Zaabsorbowane przez strukturę biologiczną promieniowanie laserowe indukuje w niej szereg procesów o charakterze pierwotnym/wczesnym (do kilku minut po zabiegu) oraz wtórnym/późnym (kilka/kilkanaście dni). W zależności od poziomu, na którym zachodzą zmiany, dzielimy je na efekty: molekularne, komórkowe i tkankowe. Jak wskazują liczne badania LLLT jest nieinwazyjną, tanią, szybką, powszechnie dostępną a przy tym skuteczną formą leczenia OM i uszkodzeń MM jamy ustnej.

Keywords: mucous membrane, mechanic injury, oral mucositis physiotherapy, low level laser therapy, LLLT.
Słowa kluczowe: błona śluzowa, urazy mechaniczne, zmiany zapalne, fizjoterapia stomatologiczna, laseroterapia niskoenergetyczna.

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Structures and functions of the oral cavity mucosa

The oral cavity extends between the palatal arches (at the back), lips (at the front), soft and hard palate (at the top) and the floor of the mouth (at the bottom) [1]. The normal mucous membrane (MM) lining the oral cavity is moist, smooth, and shiny, and its colour varies from pale pink (white skin/Caucasian race) to dark pink to brown (black skin/Ethiopian race) depending on the population studied [2–4].

MM in the oral cavity is composed of four layers [2, 5–7]:

1. a non-keratinized epithelium (its outermost layer is alive and contains cell nuclei, it becomes flattened and then gradually exfoliates) or a keratinized epithelium (cell nuclei are degraded, keratohyalin granules begin to appear, causing keratinisation which are responsible for the epithelium's lack of transparency) [2, 5, 7-9];
2. a basement membrane is attached to the lamina propria and consists of a single layer of dividing cylindrical epithelium; it is responsible for the formation of the entire epithelium and contains melanoblasts (responsible for melanin formation) [2, 4, 7];
3. a lamina propria is composed of collagen fibres and connective tissue cells (fibroblasts, fibrocytes, as well as macrophages, mast cells, plasma cells, etc.), and it has two layers: the papillary layer (more externally located, with papillae that extend to the epithelium, of variable height and density, depending on the area of the oral cavity) and the reticular layer;
4. a submucous membrane is adjacent to a layer of muscle or periosteum; it is composed of areolar tissue and contains serous, mucous or serous-mucous glands (some areas of the oral cavity, such as the gums, the dorsal surface of the tongue and a large area of the hard palate, are devoid of submucous membrane) [2-3, 8, 10].

Furthermore, MM in the oral cavity can be divided into three types: masticatory MM (its structure prevents mechanical damage during chewing), lining MM (characterised by the translucence of blood vessels) and special MM, characterised by the co-occurrence of the features of masticatory and lining MM as well as other features, such as the presence of gustatory receptors [7, 10] (see the Table).

The primary functions of MM include:

- a covering function provided by the continuity and tightness of the epithelium forming a barrier between the non-sterile interior of the oral cavity and the intraoral environment; it is largely dependent on the proper renewal and regeneration of the mucosa and the exfoliation of the epithelium, as this ensures the removal of microorganisms,
- a renewing function influencing the correct multiplication of epithelial cells and their correct keratinisation; numerous mucosal diseases result from a disruption of the keratinisation process,
- a defensive function resulting mainly from the components of saliva, which also moistens the mucosa and protects it from injury, as well as the role of the reticuloendothelial and reticuloendothelial-lymphatic systems,
- an absorption function thanks to the presence of a thin epithelium and a dense capillary network,
- a sensory function through gustatory receptors (due to the proliferation of taste buds within the oral cavity), thermoreceptors (heat and cold) and sensory receptors (Ruffini and Pacini corpuscles) [2, 9-10].

Inflammatory lesions and oral mucosal diseases

The natural function of the oral cavity is to come into contact with the external environment, including pathogens, which makes it susceptible to damage and infection [1].

Table. Characteristics of the types of MM in the oral cavity [8].

Location MM	Mucous membrane type	Epithelium		Papillae of the lamina propria	Submucosal density
		Thickness	Keratinisation		
lips	lining	moderately thin	non-keratinized	irregular and short	dense
cheek	lining	moderately thin	non-keratinized	irregular and short	dense
red zone of the lip	special	thin	keratinized	long and narrow	dense
vestibule	lining	moderately thin	non-keratinized	short	loose
alveolar gingiva	masticatory	thick	keratinized	long and narrow	no
floor of the mouth	lining	thin	non-keratinized	short and wide	loose
tongue – ventral surface	lining	thin	non-keratinized	short and numerous	no
tongue – dorsal surface (2/3 anterior)	special gustatory	thick	keratinized	long	no
tongue – dorsal surface (1/3 posterior)	lining gustatory	varied	keratinized	short	no
hard palate	masticatory	thick	keratinized	long	no
soft palate	lining	thin	non-keratinized	long	loose

Oral mucositis (OM) is a common reason for patients coming for a consultation. In one study, mucosal lesions and disease were found in 5,179 (34.2%) of 15,154 patients who visited the dentist [7].

OM can be caused by infections (bacterial, fungal, viral), allergies, reactive factors as well as systemic and idiopathic diseases [11]. OM manifests as redness, swelling, soreness (pain described as acute) and burning, which greatly impede food intake and hygiene procedures. Another common symptom is an unpleasant mouth smell [1].

It should be emphasised that in the case of patients with acute and chronic OM, a diagnostic process should exclude infectious diseases, chronic systemic diseases (e.g. lupus, type II diabetes mellitus, bone marrow diseases, Crohn's disease) [11], pre-neoplastic conditions (e.g. leukoplakia, erythroplakia, lichen planus, submucosal oral fibrosis) [12] and tumours (e.g. oral cancer, melanoma) [7, 12].

The most common lesions and inflammatory diseases of MM include: oral candidiasis (29.6%), burning mouth syndrome (10.1%), mucogingival conditions (9.6%), Wilson's lichen planus (9.3%), leukoplakia (5.7%), post-traumatic lesions (5.3%), geographic tongue (3.8%), recurrent aphthous stomatitis (3.6%), fibromas (3.4%) and herpetic lesions (2.7%) [7].

Traumatic OM can be divided into: thermal traumas (caused by exposure to low or high temperatures), chemical traumas (caused by irritation of MM with a chemical substance) and mechanical traumas (caused by a mechanical stimulus).

Mechanical damage to MM of the oral cavity occurs as a result of: poor oral hygiene (e.g. too hard toothbrush bristles, incorrect brushing and flossing technique), cheek and/or tongue biting, bad habits (biting fingernails, pencil or pen, careless use of toothpick, flaking sunflower seeds), denture mismatch and/or improper use (dentures that are too old or do not fit properly, insufficient hygiene, wearing dentures while asleep), jewellery trauma (tongue piercings), eating/chewing hard foods [2-3, 7].

A special group of oral MM and OM are iatrogenic injuries resulting from dental treatment: endodontic, surgical, implantology, orthodontic or prosthetic treatment, of a chemical, mechanical and mixed nature [13-14].

Laser therapy basics and division

The basis of Light Amplification by Stimulated Emission of Radiation is stimulated emission. It is based on the return of a previously excited atom to its original energy level under the influence of externally supplied electromagnetic radiation with simultaneous emission of a radiation quantum. All energy quanta that leave the laser system are characterised by the same phase, frequency, and direction, which determines the essential property of laser light, namely coherence (coherence). Other characteristics of a light beam produced by a laser include: monochromaticity (constant frequency of the generated wave), beam parallelism (meaning that the diameter of the laser beam increases very slowly with increasing distance from the resonator window) and its intensity [15-20].

In terms of the active material (which determines the wavelength of the radiation generated: from UV, through the visible light spectral region, up to IR [infra-red], which is extremely important from a medical point of view) that lasers are divided into:

- solid-state lasers based on crystal or glass: ruby laser, neodymium laser (Nd:YAG), or holmium laser (Ho:YAG),
- gas lasers, whose active medium can be a gas or metal vapour, e.g.: helium-neon (He-Ne), argon (Ar), or krypton (Kr),
- semiconductor lasers – p-n junction),
- liquid lasers (organic dye) [15-17].

He-Ne lasers are usually used to accelerate the healing of wounds and ulcers (due to the properties of red light), while semiconductor lasers are used for pain control and inflammation treatment, as the IR radiation they emit penetrates deeper into tissues than He-Ne laser radiation [19].

In terms of the power of the generated radiation, lasers used in medicine are divided into: low-energy (“soft” 1-6 mW), medium energy (“mid”: 7-500 mW) and high-energy (“hard”: over 500 mW). High-energy lasers (laser lancing devices) are used in surgery for tissue destruction or removal. Low- and medium-energy lasers, on the other hand, belong to the common group of low-level laser therapy, LLLT).

Biological effects of laser radiation on tissue

Laser radiation absorbed by a biological structure induces a number of primary (early) processes that last up to a few minutes after treatment, as well as secondary (late, distant) processes that can be observed even several days after the end of irradiation. Depending on the level of the changes, they are divided into: molecular, cellular and tissue effects of laser therapy [15, 17, 19]. What is more, laser radiation causes a number of changes in the cells, which can be divided into biostimulative, photothermal, photochemical and photoionisation effects.

Biostimulative (photo-bioactivation) effects can be divided into non-thermal and thermal effects. Non-thermal biostimulation occurs with low energy doses (below 6 mW/cm2); the temperature increase in the irradiated tissues is minimal and does not exceed 1°C. “Thermal biostimulation” means a local increase in tissue temperature under the influence of medium-power laser light, but only up to 43°C. At these energy levels, the effects of laser radiation are not visible macroscopically and can only be confirmed by microscopic examination, based on changes in certain cell organelles [21].

Photothermal effects are the result of a further increase in the temperature of the irradiated tissue, which include: photo-hyperthermia (43–60°C), photo-denaturation (60–80°C), photo-coagulation (60–100°C), photo-deposition of

water and tissue (respectively: 90–100°C and 100–300°) and tissue charring (above 300°C) [15, 17–18, 20].

Photo-ionisation effects are associated with laser radiation of more than 106W/cm2 (dissociation and ionisation of the irradiated tissue with disruption of chemical bonds, while photochemical effects are used in photodynamic therapy (PDT) for cancer diagnosis and therapy [21-23].

LLLT in the treatment of trauma and inflammatory diseases of the oral mucosa

Particular attention should be paid to the use of laser therapy in dentistry as a complementary treatment method (to pharmacology, surgery, manual therapy, and osteopathy) and sometimes as the main form of treatment [23-24]. Laser therapy is used to treat soft tissue, hard tissue, and the temporomandibular joint both by intraoral application and externally. Additionally, LLLT physiotherapy procedures have been successfully used in MM and OM injuries due to their analgesic, anti-inflammatory and biostimulatory effects [24-25].

The use of LLLT in the treatment of mechanical injuries and in accelerating the wound healing process is one of the best-studied properties of this physical therapy method. Promising research results were reported by Hopkins et al. [26], who demonstrated the positive effects of LLLT in accelerating wound healing. The study was conducted in a group of 22 healthy young volunteers (age: 21 ± 1 years) with a normal body build (height: 175.6 ± 9.8 cm; body weight: 76.2 ± 14.2 kg), who were divided into two study groups: studied (n = 11; 5 women and 6 men; LLLT) and control (n = 11; 7 men, 4 women; placebo). In all subjects, two superficial circular wounds (using abrasive material) were made on the forearm of the dominant hand, with an area of 1.27 cm2. The wound sites were anaesthetised with an ointment (composition: 2.5% lidocaine and 2.5% prilocaine). Volunteers then reported daily for LLLT/placebo application and assessment of wound area and colour. Final readings were taken on day 20 after the first treatment. The researchers showed that in the group treated with LLLT (dose: 8 J/cm2; treatment time: 125 s) a significant reduction and shrinkage of the wound was observed compared to the control group.

Another important aspect is the demonstration of the analgesic effect of LLLT in endodontic treatment, which has been confirmed in studies conducted by Assnahaari et al. [27]. The researchers confirmed pain reduction in patients after endodontic treatment of the molars after using LLLT. The group consisted of 80 patients who were randomly assigned to the study group (n = 40; LLLT) or control group (n = 40; placebo). Five LLLT procedures were performed in the study group, at: 4, 8, 12, 24 and 48 hours after dental treatment (70 J/cm^2, time: 80 s; direct application to the tooth). Pain intensity after treatment was checked 5 times using the McGill Pain Questionnaire and a numerical VAS rating scale (at: 4, 8, 12, 24 and 48 hours after the dental treatment). The study group showed a significant ($p < 0.05$) reduction in pain in the first hours compared to the control group.

Promising studies using LLLT have been conducted in oncology patients with oral cancers and acquired oral mucosal lesions resulting from chemotherapy or immune system impairment. In the analysis produced by Jadaud and Bensadoun [28], in a selected 11 randomised trials involving a total of 415 patients with head and/or neck cancer treated with chemotherapy and/or radiotherapy, the relative risk of developing OM was significantly reduced after LLLT (for a dose of 1-6 J/point). Significant reductions in pain and in the severity and duration of severe OM (> grade 2) were also reported, more importantly without adverse effects (compared to the placebo).

It is worth paying attention to the triple-blind randomised study conducted by Gautan et al. [29], who in 221 patients with head and/or neck cancer treated with conventional radiation therapy (66Gy, 33 fractions, 5 fractions/week, 45 days) and cisplatin (every 3 weeks) were randomly divided into: a study group (n = 111; LLLT) and a control group (n = 110; placebo). It was shown that LLLT (He-Ne, wavelength: 632.8 nm, 24 mW, 3 J/point, 36-40 J/treatment, spot size: 1 cm^2, 5 treatments/week) significantly reduced the incidence of OM ($p < 0.0001$), associated pain ($p < 0.0001$), dysphagia ($p < 0.0001$) and the need for opioids ($p < 0.0001$) in the patients compared to the control group.

Similar conclusions were based on a case report presented by Ramalho et al. [30]. A patient aged 47 years, after surgical treatment and chemotherapy (6-month cycle) for squamous cell carcinoma of the tongue. At the treatment site, there was chronic inflammatory infiltration (confirmed by biopsy) around the residual polyglactin suture. In addition, after 2 months, the biopsy site developed a painful mucosal dehiscence. Ten LLLT procedures were performed (InGaAlP visible semiconductor laser wavelength: 660 nm, spot size: 0.04 cm^2, 40 mW, 4 J/point, 16 J/point, 2.4 J/treatment) using a contact, point procedure above and around the lesion (15 points, 4 s/point). As a result of LLLT application, the wound healed completely, based on which the researchers arrived at the conclusion that this procedure is effective in the treatment of chronic wounds in tissue previously treated with radiotherapy.

The very encouraging results of LLLT in the prevention (dose: 2 J/cm^2) and treatment (dose: 4 J/cm^2) of OM in oncology patients may soon become the basis for development of a new standard of care, in line with the Multinational Association for Supportive Care in Cancer (MASCC) criteria [28].

Conclusions

The MM lining the oral cavity is, both anatomically and functionally, the initial element of the gastrointestinal and respiratory systems. Its functional status reflects the well-being of the whole organism and may also influence it. Untreated damage to the oral MM can lead to serious diseases in further sections of the respiratory and gastrointestinal systems and in the whole body. This is particularly relevant for oncology patients (especially those suffering from the head and neck cancers and

haematopoietic malignancies) and those with immune disorders.

LLLT is a non-invasive, low-cost, fast, widely available, and yet effective form of treatment. Importantly, LLLT influences the oral MM at a cellular level, exerting regenerative and nutritional effects. According to numerous sources, the use of LLLT effectively reduces inflammation and swelling as well as alleviating/eliminating any accompanying pain and discomfort.

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CRIMINAL LIABILITY OF A MILITARY DOCTOR AS A PUBLIC OFFICIAL DUE TO THE CONSEQUENCES OF MEDICAL ERRORS

Odpowiedzialność karna lekarza wojskowego jako funkcjonariusza publicznego za skutki błędów medycznych

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Abstract: Military doctors, if on active military duty, have the status of a public official within the meaning of the Criminal Code. They are entitled to enhanced criminal-law protection, but they may be liable for official offences. One of them is the act described in Article 231 of the Criminal Code, which consists in exceeding powers or failing to fulfil duties and thus acting to the detriment of public or private interests. The question arises whether, if a military doctor commits a medical error, he can be held liable for this act, or only for crimes against the life or health of the patient, as is the case with civilian doctors. The article shows the judicial practice in this regard, from which it follows that military doctors in leadership positions and committing irregularities in this area and soldier doctors providing medical services are treated differently. It can be deduced from this that only with regard to the former group of military doctors is it permissible to charge them with the offence listed in Article 231 of the Criminal Code. The article presents arguments justifying such a thesis.

Streszczenie: Lekarze wojskowi, jeśli pełnią czynną służbę wojskową, posiadają status tzw. funkcjonariusza publicznego w rozumieniu Kodeksu karnego. Z jednej strony przysługuje im wzmożona ochrona karnoprawna, z drugiej jednak mogą ponieść odpowiedzialność za przestępstwa urzędnicze. Jednym z nich jest czyn opisany w art. 231 K.k., a polegający na przekroczeniu uprawnień lub niedopełnieniu obowiązków i działaniu w ten sposób na szkodę interesu publicznego lub prywatnego. Powstaje pytanie, czy w przypadku popełnienia przez lekarza wojskowego błędu medycznego, może on odpowiadać za ten czyn, czy tylko za przestępstwa przeciwko życiu lub zdrowiu pacjenta (jak ma to miejsce w odniesieniu do lekarzy cywilnych). W artykule ukazano praktykę sądową w tym zakresie, z której wynika, że inaczej traktowani są lekarze wojskowi pełniący funkcje kierownicze i dopuszczający się nieprawidłowości w tym obszarze oraz lekarze-żołnierze udzielający świadczeń zdrowotnych. Można z tego wywieść, że jedynie w odniesieniu do tej pierwszej grupy lekarzy wojskowych dopuszczalne jest postawienie zarzutu popełnienia występku spenalizowanego w art. 231 K.k. W artykule przedstawiono argumentację uzasadniającą taką tezę.

Keywords: criminal liability, medical error, dereliction of duty, public official.

Słowa kluczowe: odpowiedzialność karna, błąd medyczny, niedopełnienie obowiązków, funkcjonariusz publiczny.

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Introduction

Polish criminal law does not provide for strict liability in terms of a medical error. This is because the legislator has not criminalised the act of committing such an error. However, a person may be held liable for its consequences. Thus a doctor who commits a medical error may be liable for the material offence against life or health, as described in Chapter 19 of the Criminal Code ("CC"). Thus, they may be liable for the misdemeanour of exposure to an imminent risk of loss of life or grievous bodily harm, as defined in Article 160 of the CC. If this risk materialises, a doctor may be held liable for various forms of bodily harm (minor and moderate bodily harm according to Article 157 of the CC and severe health impairment according to Article 156 of the CC) or manslaughter according to Article 155 of the CC. However, in the case of military doctors, who have the status of a public official, we can additionally consider liability for the offence of exceeding powers or failing to fulfil duties, which is criminalised in Article 231 of the CC.

The subsequent part of the argumentation presents example judgements of the criminal courts in cases where military doctors were accused and charged with this offence. It should be considered whether the mere fact of having the status of a public official, which is enjoyed by a person performing active military service and being a doctor at the same time, justifies liability under this provision. Thus, whether military doctors may be held

additionally liable compared to civilian doctors for the consequences of their medical errors.

At this point, it is worth clarifying that the offence of exceeding powers or failing to fulfil duties is an individual misdemeanour. This means that it can only be perpetrated by a person who has a particular characteristic set out in the relevant provision. The act in question can only be perpetrated by a public official. This notion has been defined in Article 115(13) of the CC. This category includes a person performing active military service with the exception of territorial military service performed at the disposal. It is therefore a soldier within the meaning of Article 115(17) of the CC. However, this does not specify what this active military service means. In order to clarify this term, we therefore need to refer to separate provisions, and currently to the Act of 11 March 2022 on Homeland Defence [1]. According to Article 130, active military service consists of performing the following: basic military service, territorial military service, active reserve service on specified days, and participating in military exercises within the passive reserve, professional military service, service in the event of the mobilisation announcement of and during a war. In turn, basic military service consists of either: compulsory basic military service or voluntary basic military service.

Anyone performing any type of this service has the status of a soldier within the meaning of the Polish Criminal Code, and thus a public official, as referred to in Article 231 of the CC. According to Article 90 of this Act, anyone called up for active military service becomes a soldier upon reporting for such service at a specified date and place. However, someone does not have the status of a soldier if they are a reservist or have left the service. Furthermore, someone performing military service in armed formations but not included in the armed forces is not a soldier. A military doctor will therefore have the status of a soldier within the meaning of the provisions of the Polish Criminal Code if they meet the aforementioned conditions, i.e. while performing medical duties within the framework of the service referred to in the quoted provision.

The paper will first discuss the essence of criminal liability for the consequences of a medical error, and then, on the background of these considerations, show examples of specific cases concerning such errors perpetrated by military doctors. The last section will present considerations concerning the liability of a military doctor for a crime defined in Article 231 of the CC. The arguments will be based on the analysis of the normative material, doctrine and judicial decisions. The provisions will be analysed using a formal dogmatic approach.

Concept and typology of medical errors

Before discussing the liability of military doctors for the consequences of medical errors, we should introduce the concept of a medical error and the typology of such errors. This term is not statutorily defined, nor does the legislator use such a term in any regulations. It is used for the purposes of the literature and judicial practice. An explanation of the term can therefore be sought in these sources. It is discussed in both the medical and legal literature.

In the medical literature, we can refer, for example, to the definition proposed by B. Popielski, who understands such an error as: "Conduct contrary to the generally recognised principles of medical knowledge in an action or omission harmful to a patient, which could have been avoided by following the rules corresponding to the state of medical knowledge" [2-3]. Similar terms can be found in the literature related to criminal law. For example, M. Filar understands "malpractice" as: "a violation by a doctor performing a medical practice activity based on a set of rules and principles of professional conduct applicable in relation to that activity, the source of which is medical science and practice". Similarly, this notion is defined by R. Kędziora [4, p. 199] and A. Liszewska, who adds that these rules are supposed to concern "legal interests in the form of human life and health", while their violation "according to legal provisions constitutes a case of breach of the due care obligation" [5, p. 28]. The term "medical malpractice" has also been introduced by the Supreme Court. In its judgement of 1 April 1955, the court indicated that: "medical malpractice is an act (omission) of a doctor in the field of diagnosis and therapy which is non-compliant with the medical science to the extent available to the doctor". However, the court excluded organisational negligence in patient care and guaranteeing hygiene from this category [6].

It can be inferred from these statements that such an error would be a conduct contrary to the accepted approach remaining in accordance with the current medical knowledge and practice of performing specific diagnostic and therapeutic procedures, i.e. conduct *contra legem artis*. However, in the context of criminal law, the issue is more complex. As already mentioned, the Criminal Code does not criminalise the act of performing a medical error. The person will therefore be liable for its effect and not for the conduct itself, which is not in accordance with the current medical knowledge. Besides, the legislator does not use the concept of medical knowledge in the Criminal Code. The conduct which is non-compliant with the standard established according to the medical knowledge should therefore be seen in the light of the rules of caution, the observance of which is a prerequisite for the exclusion or reduction to a socially accentuated level, the risk to the legal interest. The literature indicates that there are different sources of these rules. They may take a normative form of legal acts of various ranks, they may result from conclusions in a given field or they may be developed on the basis of experience in a particular sphere of human activity [7]. In medical matters, it will rarely be possible to find regulations governing the principles of performing a given type of procedure. Such norms are more likely to refer to organisational and administrative issues and may be a determinant for the assessment of the occurrence of so-called organisational errors (which will be discussed later). On the other hand, a method of performing a medical intervention will most often be based on empirical knowledge, sometimes presented in the form of guidelines

and recommendations of various recognised bodies, e.g. scientific societies, academic centres, etc.

The code of practice is therefore established based on the state of medical knowledge. In general, the state of medical knowledge can be understood as "theories, views or principles, which have either been verified, empirically tested, or have defended itself against critics, or have been pronounced or promulgated by persons or scientific institutions enjoying particular authority due to their high scientific level and reliability" [8]. The literature indicates that the state of medical knowledge includes information contained in medical textbooks and obtained by the doctor during their studies. Therefore, they do not have to demonstrate knowledge that is only available to eminent scientists and specialists [9]. It seems to be an oversimplification, as it does not take into account the group to which a doctor belongs, in particular the specialisation they hold. It can therefore be assumed that the need-to-know textbook information is a form of minimum and a doctor cannot make excuses for the lack of this elementary knowledge [10].

The conduct of a perpetrator (doctor) of a possible medical error will be compared to such a norm constructed on the basis of the current state of medical knowledge. However, it should be mentioned that a breach of the rules of caution does not always coincide with acting *contra legem artis* in the medical sense. These ranges can be graphically presented in the form of concentric circles, with the circle containing medical error cases placed within the wider circle of any breach of the rules of caution. This is because there may be breaches of the required rules of caution that will not be regarded as a medical error, e.g. the performance of a surgical procedure by an intoxicated doctor will naturally be considered a gross breach of the rules of caution, but will not be treated as acting *contra legem artis* in the medical sense (similarly, technical errors, such as leaving foreign bodies in the operating field). This is because there are no points of contact with current medical knowledge. On the other hand, it can be assumed that a violation of the standard of medical conduct will at the same time be a violation of the required rules of caution. This is because the medical rules of conduct are established to guarantee the most effective action of the doctor aimed at achieving a therapeutic goal. They therefore protect the interest. Their violation is therefore automatically in conflict with the rule of caution, which is also intended to protect this interest. It should be noted, however, that these rules are not constructed in an abstract sense and are not identical for every case. Indeed, in defining the concept of unintentional perpetration the legislator indicates that there must be a breach of the rules of caution "required under the specific circumstances". It therefore mandates that the rules be relativised, taking into account the circumstances of the case.

When building a particular standard of conduct, we need to take into account, for example, the qualifications of the health care professional, the equipment of the facility in question, the dynamics of the situation, etc. [11]. However, these rules cannot be unduly individualised, but should be related to a certain objective standard of conduct (e.g. the requirements taking into account the qualifications of a doctor should be established on the basis of the specialisation of the doctor who is the perpetrator of the potential error). Issues concerning the personal predisposition of the doctor, their psycho-physical condition, perceptual capabilities, limited, for example, by fatigue, illness, stress, etc., are also considered when determining criminal liability, but on the level of guilt. However, the determination that an error has been perpetrated (the obligatory rules of caution have been breached) is objectivised. Assessments in this regard are formed on the basis of the figure of the model doctor, mentally placed in the reality of the event in question. Negative deviations from such a model will be considered a violation of the aforementioned rules and thus as a medical error [12].

In order for criminal liability to arise, the life or health of the patient must, as a consequence, be adversely influenced. There must therefore be a causal link between the violation of the required rules of conduct and this negative effect.

As already mentioned, the violation of these rules may relate to medical treatment, in which case we may speak of a "knowledge error" (e.g. prophylactic, diagnostic, therapeutic, surgical and rehabilitation errors), as well as technical and organisational issues. Hence, in addition to errors in the narrow sense, the literature distinguishes what are called organisational errors. A. Liszewska points out that this term is used to describe the "faulty organisation of medical assistance, which impacts the life and health of patients" [5, p. 196]. The literature clarifies that such an error consists in "a failure to perform or inadequate performance of administrative or organisational functions, not in defective treatment" [4, p. 228]. The essence of this error is therefore embodied in the incorrect organisation of the process of providing medical services, which ultimately leads to negative consequences for the patient's health or life. Naturally, such irregularities may cause errors committed already at the stage of diagnosis or treatment, e.g. lack of appropriate diagnostic equipment, its malfunction, etc., which may lead to the omission of certain (e.g. radiological) diagnostic tests and ultimately to the patient's death.

The distinction between these two types of errors is also pointed out in judicial practice. For example, we can quote the judgement of the District Court in Zgorzelec, in which the court noted that "an organisational error is not a case of medical malpractice, although it may be associated with a technical, therapeutic or diagnostic error" [13]. The doctrine emphasises that this kind of error is very dangerous, as it may imply the repeated commission of a medical error in the strict sense. This is because, if the organisation of the provision of medical services is flawed, it may lead to the repetition of incorrect activities by multiple doctors. For example, failure to introduce or enforce appropriate procedures, staff shortages, or inadequate equipment may induce the repetition of errors [14]. Failures in this field may result in the liability of those who are in charge of the treatment process, in particular the

managers of the given medical entities or their organisational units [15]. Such a liability may therefore also apply to military doctors who are the heads of medical facilities or their departments.

A distinction between medical errors in the strict sense and organisational errors is therefore important for determining the circle of entities that may incur criminal liability. Moreover, it may be important in the context of attributing liability to a military doctor for exceeding powers or failing to fulfil duties, i.e. for an act defined in Article 231 of the CC.

Criminal liability of a military doctor seen in judicial practice

Criminal rulings on the liability of military doctors for medical malpractice can rarely be found in judicial practice.

An example of such a case may be the following factual circumstances, which formed the basis of the Supreme Court judgement of 26 March 2007 [16]. According to the case file, the emergency medical team was called to a patient with a stab wound to the chest in the left clavicular region. After initial treatment of the wound, the patient was transported to the emergency department (ED) of a military hospital with a referral to the surgery department. According to the referral, the patient was in shock. The patient was admitted to the ED at approximately 08:40. At that time, the head of the department and a senior assistant, both military doctors, were present. These doctors were accused of failing to fulfil their duty of due diligence, as referred to in Article 4 of the Act of 5 December 1996 on the Professions of Doctor and Dentist [17], by failing to take effective measures to perform immediate surgery aimed at revising the wound, despite the absolute indications for surgery arising from the nature of the patient's injuries. It was evident from the medical records and witness statements that the senior assistant contacted the surgical department a few times to request a consultation. However, these efforts were unsuccessful. In turn, the head of the department, seeing these efforts and their ineffectiveness, did not take any steps to either obtain such a consultation or, in the absence of such a consultation, to perform the surgery immediately. It was clear from the circumstances of the case that the patient's condition was very serious and that an important organ had been damaged as a result of the stab wound. As a result of this delay, the patient remained in the hospital emergency department for about three hours and was then transferred to the surgical department and later to the anaesthesiology and intensive care department, where resuscitation efforts were undertaken. However, this proved ineffective and the patient died. In this case, the assistant doctor was charged with the offence described in Article 160 of the CC, i.e. exposure to direct danger of loss of life or severe health impairment, and manslaughter, i.e. the offence stipulated in Article 155 of the CC. The same charges were brought against the head of the department. In addition, however, he was accused of committing the offence defined in Article 231(1) of the CC. The Court of First Instance acquitted both doctors, although as a result of the appeal, the case was referred for reconsideration. The Court of Appeal made the order to reconsider the case and examine whether both defendants had breached the required standard of conduct by failing to take certain steps to obtain a consultation or, alternatively, to contact a doctor of the surgical department in person, which would have made it possible to perform the necessary surgical procedure faster. Without analysing the substantive issues related to the appropriate attitude of the two doctors, we should note that the judicial bodies, the courts of both instances, put the scope of liability of the assistant doctor and the person occupying a managerial position differently – the head of the department, who was also charged with committing the act described in Article 231 of the CC.

Another case concerned the head of the urology department of one of the military hospitals – a military doctor. He was accused of failing to fulfil official duties by failing to draw up a work plan and timetable for the department staff, thereby exposing a patient to danger of loss of life by failing to provide adequate care to the nursing staff required immediately after the surgery. According to the prosecutor, the head of the department should have produced and implemented appropriate documents setting out the rules of conduct for the post-operative care provided by the nursing staff. In the factual circumstances, the defendant did not produce such documentation. The patient should have been under the care of a nurse for at least two hours immediately after the surgery. In the factual circumstances, the nurse providing such care had to provide care to another patient, leaving the operated patient unattended. Although she was absent only for a few minutes, the patient's condition rapidly deteriorated and caused his death. In this case, the head was charged not only with the offence of exposure to direct danger according to Article 160 of the CC, but also with the offence specified in Article 231(1) of the CC, i.e. failing to fulfil duties. Without analysing the circumstances of this case and the justification of the acquittal in more detail, we need to emphasise that the charge concerned not so much the medical practice activity of the military doctor, but his duties in the administrative sphere.

Criminal liability of a military doctor for the misdemeanour criminalised in Article 231 of the CC.

Based on the factual circumstances and the views of the courts hearing these cases, it can be concluded that the liability of a military doctor for the offence referred to in Article 231 of the CC depends on whether they perform only therapeutic activities in the strict sense or whether they are charged with administrative and organisational duties. Only in the latter case are the courts inclined to attribute this act. Such a position should be regarded as correct.

It is therefore worth examining the said Article 231 of the CC in more detail. It is placed in Chapter 29 of the CC: "Offences against State and Local Government Institutions". The doctrine of criminal law explains that giving a title to the chapter containing a provision criminalising a specific act is helpful in determining the legal

interest that is protected by this provision. In the context of the offence in question, the literature indicates that the object of criminal law protection is "the proper functioning of state and local government institutions and the related public authority" [18, p. 1204]. The protected interests are similarly defined in judicial practice. For example, we can refer to the judgement of the Supreme Court of 27 October 2014 [19], in which it was explained that "the object of protection under Article 231 of the CC is any legal interest, regardless of whether it belongs to the private or public sphere. This provision directly protects the proper functioning of state and local government institutions and the related public authority. A characterising feature of the prohibited act is acting to the detriment of public or private interests in a strictly determined manner, namely by exceeding powers or failing to fulfil duties. It is further indicated in the doctrine that, in addition to the aforementioned main object of protection, there is an additional object of protection, namely public and private interest. This may be established *in concreto* in a particular case [20, p. 1512]. The performed action (non-performance of duties or exceeding powers) harms such an interest.

The perpetrator's conduct may consist both in acting (exceeding powers) and in failing to perform certain duties, including in the organisational field. This issue was pointed out by the Supreme Court in its judgement of 14 November 2001 [21]. It explained that "a failure to fulfil duties that meet the features contained in Article 231 of the CC may also relate to the improper organisation of the work of the personnel subordinate to a public official or failure to control the performance of their official duties".

These issues are relevant for determining the liability of a military doctor performing managerial functions in a medical facility. As explained above, they have the status of a public official and may therefore be the perpetrator of the offence in question. Liability may arise if they fail to fulfil the duties incumbent upon them. The literature explains that an obligation is an order to act in a certain way, resulting from the professional duties of a given official related to their function and position. The obligation may result from both generally binding acts, such as laws, regulations, intra-organisational acts, e.g. regulations issued in a given institution, and civil law contracts. On the other hand, failing to fulfil duties consists in complete non-fulfilment or performing them in an incorrect, incomplete manner [22]. Judicial practice clarifies that in order to determine whether a doctor has failed to fulfil their duties, it is necessary to use an appropriate model of a good host, a reliable official and compare the conduct of the alleged perpetrator to them [23]. Any negative deviation from such an imagined model may be considered a misconduct in the performance of a duty.

With regard to military doctors in a managerial position, we can therefore deduce that the source of their duty can be both acts issued by public authority, e.g. decrees of the Minister of Health, as well as intra-hospital regulations, e.g. defining the scope of duties of a head of the department. In addition, duties in this respect may arise from tasks defined by military regulations in relation to the position in question. Failure to perform these tasks or performing them in an inaccurate, incomplete manner may be regarded as the concept of failing to fulfil duties. We should emphasise, however, that they are duties in the managerial, organisational and supervisory area, and not in the area of providing medical services.

This thesis is also confirmed by the judgement of the Supreme Court of 12 March 2002 [24], in which the Court upheld the judgements of the courts of lower instances convicting a military doctor, the commander of a military specialist medical centre. He was accused of failing to fulfil duties by failing to produce appropriate organisational and order documents defining the procedure for the provision of standard services at the medical centre that he was in charge of, as well as failing to introduce a legally compliant cost account for the medical centre in the form of a lack of priced lists of medical procedures and a list of quantities of resources consumed in their performance divided into time and the materials used, and, moreover, concluding an employment contract for the position of chief accountant with a person who did not possess the qualifications required for this position. Thus, the doctor not only failed to fulfil his organisational duties but also exceeded his powers. In the Court's opinion, he therefore committed the offence defined in Article 231
of the CC. However, these acts were clearly connected with his administrative duties and not with the provision of medical services.

With regard to the appropriate organisation of the provision of medical services, failing to fulfil duties would therefore be, for example, a failure to provide appropriate staffing, a failure to introduce appropriate procedures or a failure to enforce them. Thus it would be possible to conclude that the failure to fulfil duties occurred, and consequently, that the features of the offence described in Article 231 of the CC were met.

However, not every case of exceeding powers or failing to fulfil duties justifies itself would incur liability for the offence in question. The legislator additionally requires that the perpetrator act to the detriment of a public or private interest. The use of the phrase "act to the detriment" in the description of the tort has provoked a dispute in doctrine and judicial practice about the nature of this offence, i.e. whether it causes a true exposure, being a material offence or an abstract exposure, being a formal offence. The resolution of these doubts is of major procedural importance, since in the case of adopting the former approach, it would be necessary to prove that the offender caused a risk of damage. The authors supporting the concept of a material offence argue that, although the law does not require the effect in the form of damage, it is necessary for the perpetrator to cause a real risk of damage. A general risk is therefore not sufficient [20, p. 1514]. This view is also shared in the judicial practice of the Supreme Court [25]. However, the prevailing view in the doctrine is that the misdemeanour in question is formal in nature, which means that the perpetrator does not have to cause a specific threat. It is argued that the phrase "acts to the detriment" does not describe the effect that the

perpetrator is supposed to bring about, but rather specifies the punishable conduct. Indeed, not every case of exceeding powers and failing to fulfil duties justifies incurring criminal liability, but only those which, in a specific situation, pose a risk of violating public or private interests. In other words, the act is formal [18, pp. 1208-1209]. Such a view has also been shared in the judicial decisions. For example, reference may be made to the judgement of the Supreme Court of 2 December 2002 [26], in which the Court emphasised that "the legislator has defined the offences specified in Article 231(1) and 231(2) of the CC as formal offences. Acting to the detriment of public or private interest is not a characteristic feature of the effect, but of the perpetrator's conduct. The mere occurrence of damage, or even its imminent risk, is not a characteristic feature of these types of prohibited acts".

It is therefore apparent from the summary report presented that both the doctrine and the judicial decisions express clashing views regarding the nature of this act. However, this issue is not particularly significant in the context of the subject matter under discussion, as the possible liability of a military doctor for exceeding powers or failing to fulfil duties, considered in the category of an organisational error, refers to an unintentional act.

The unintentional variant of the offence in question is contained in Article 231(3) of the CC. In describing the offence, the legislator unequivocally indicated that the perpetrator is to cause severe damage. Therefore, there is no doubt that it is a material offence. It is committed at the moment of causing such damage. It may be a property and non-property damage. In the latter form, it may consist in causing suffering and other ailments to the victim. This thesis is relevant in the context of organisational errors, as they may result in bodily injury or disorder of the patient, leading to such suffering. As indicated, the risk must be significant. If it refers to property, this significance is assessed in particular on the basis of the material value of the damage caused. On the other hand, if the risk does not refer to property, the significance is assessed, taking into account the discomfort caused to the injured person by the perpetrator, e.g. a degree of physical and mental suffering of the patient as a result of the organisational error committed by a military doctor [27]. Since the offence in question is material, from a procedural point of view, the burden of proof with regard to severe damage lies with the prosecutor.

Thus, if, as a result of exceeding powers or failing to fulfil duties, the life or health of a patient is endangered or violated, a public official being a military doctor may be held liable for the presented misdemeanour.

The situation is different in the case of military doctors providing medical services. Although they have the status of a public official and thus may be perpetrators of the offence in question, it seems that it would not be correct to attribute liability for this act to them. At first sight, committing a medical error may be treated as failing to fulfil duties of due diligence resulting from current medical knowledge. In turn, the effect of such an error could be the breach, or at least the exposure to harm of a private interest, which, as mentioned above, could be the patient's health. Such a doctor could therefore meet the features of the offence in question. However, these issues should also be considered from the perspective of the object of protection. As indicated, it is the proper functioning of state and local government institutions. Apart from the fact whether a medical facility is such an institution (especially if it is an institution not financed from public funds), we should consider whether an individual medical malpractice, resulting even in the death of a patient, can be treated as a harm to the proper functioning of the said institutions. Of course, spectacular medical errors may affect the negative opinion about the work of medical personnel in a given medical facility, but they do not seem to interfere with its proper overall functioning. Such an assumption leads to the conclusion that the legal interest protected by the provision in question is not attacked. In other words, a military doctor who, in connection with the provision of medical services, has violated the required standard of conduct and, for example, has not fulfilled their duty of taking care of the patient, cannot be held liable for the act defined in Article 231 of the CC.

This thesis is also confirmed by the consideration of justice. We can imagine that the same procedure is performed by two doctors, one of whom is a military officer and the other a civilian. If a medical error was committed in such a team, both doctors could be held liable for a material offence against life or health. However, if a military doctor were also the perpetrator of the act described in Article 231 of the CC, their liability would be more severe. In turn, it seems that such differentiation is not justified, since the mere fact of having the status of a public official should not prejudge the scope of the liability. Therefore, it seems more reasonable to make the scope of the liability of both these doctors equal.

The counter-argument for such equal treatment could be the increased criminal law protection enjoyed by a public official. Indeed, in the case of attacks on honour or bodily integrity, these acts are more severely punished than if committed against a person without such a status. Moreover, they are indictable offences and not offences prosecuted under private prosecution proceedings as is the case for other persons [28]. The reasoning, therefore, could be that since a public official being a military doctor has stronger criminal law protection, their liability should also be stricter. However, such an assumption could be falsified due to the fact that the medical and legal provisions also provide for enhanced protection for civilian doctors even though they do not have the status of a public official. Such a construct is described in Article 44 of the Act of 5 December 1996 on the Professions of Doctor and Dentist [29], and also follows from Article 15a of the Act of 15 April 2011 on Medical Activity [30]. In general, therefore, civilian and military doctors are also equalised in this respect. Therefore, there is no justification for differentiating their scope of criminal liability for the consequences of a medical error.

Conclusions

Polish criminal law does not define the concept of a medical error; however, it can be assumed, based on the statements of doctrine and judicial decisions, that it means conduct inconsistent with the current state of medical knowledge and medical practice, which leads to negative consequences for the life or health of the patient.

A doctor who commits a medical error may incur liability for a material offence against life or health described in Chapter 19 of the CC.

A military doctor, i.e. a soldier in active military service, has the status of a public official. Therefore, they may incur liability for the misdemeanour defined in Article 231 of the CC, i.e. for failing to fulfil duties or exceeding powers.

Liability under Article 231 of the CC, which describes an official offence, is limited to military doctors performing duties in the organisational and administrative area. On the other hand, military doctors providing medical services should be equalised with civilian doctors in terms of liability for the consequences of a medical error. It is because their conduct does not harm the legal interest protected by the aforementioned provision, i.e. the proper functioning of a state or local government institution. Such a limitation of liability also results from the judicial decisions, in which liability based on Article 231 of the CC was attributed only to those military doctors who performed managerial and administrative functions in a medical institution.

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26. File No.: IV KKN 273/01, LEX No. 74484

27. Cf. the resolution of the Supreme Court of 29 January 2004, ref: I KZP 37/03, court calendar 2004/5/16
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    - performs activities in the framework of emergency services or in the case referred to in Article 30 (i.e. in any case where delay in rendering assistance to a patient could result in danger of loss of life, grievous bodily harm or serious health disorder),
    - practises a profession in a health care facility contracted to provide medical services financed from public funds in connection with the provision of medical services in that facility.
30. Journal of Laws of 2023, item 991, as amended This provision stipulates that a medical practitioner who provides medical services outside a medical facility is given the legal protection provided by the Act of 6 June 1997.
    - Polish Criminal Code for public officials

Hyperbaric Oxygen Therapy – Part 1. historical outline, the principle of operation of a hyperbaric chamber, indications and contraindications

Hiperbaryczna terapia tlenowa – cz. 1. Zarys historyczny, zasada działania komory hiperbarycznej, wskazania i przeciwwskazania

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Abstract: The increased interest in the use of hyperbaric oxygen therapy (HBOT) in medicine prompted the authors to analyse the available research reviews and meta-analyses, and to rank the data on HBOT. The first part of the article presents a historical outline of research on HBOT, the principles of operation of hyperbaric chambers, as well as indications and contraindications for the use of this form of treatment.

Streszczenie: Wzrost zainteresowania wykorzystaniem tlenu hiperbarycznego (ang. *hyperbaric oxygen therapy*, HBOT) w medycynie skłonił autorów do przeanalizowania dostępnych przeglądów badań i metaanaliz oraz uszeregowania danych dotyczących HBOT. W pierwszej części artykułu przedstawiono: zarys historyczny badań na HBOT, zasady działania komór hiperbarycznych oraz wskazania i przeciwwskazania do stosowania tej formy leczenia.

Keywords: hyperbaric oxygen therapy, history, hyperbaric chamber, indications, contraindications.

Słowa kluczowe: tlenowa terapia hiperbaryczna, rys historyczny, komora hiperbaryczna, wskazania, przeciwwskazania.

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Introduction

In recent years, the interest in hyperbaric oxygen therapy (HBOT) has increased significantly, which can be seen in the number of publications on the subject in scientific databases: a total of 15,325 records between 1965 and 2023, with 4,421 (29%) in the last 10 years (2013-2023). The largest increase in interest in HBOT was recorded between 2020 and 2021, probably as an aftermath of the search for a treatment for the sequelae of COVID-19 [1] (PubMed search/05.2023, search term: "hyperbaric oxygen therapy").

There is also a huge increase in centres offering HBOT treatment commercially (Google/05.2023, number of records per keyword: "hyperbaric oxygen therapy" at 6,690,000 and "hyperbaric chamber" at 2,590,000). It is also noticeable in Poland (Google/05.2023, number of records per keyword: "terapia tlenowa" at 83,700, per "leczenie tlenem" at 82,400, and per "komora hiperbaryczna" at 65,000). Encouraged by advertisements, patients use HBOT to treat conditions for which its efficacy has not been sufficiently established, has never been studied or for which the therapy is not even recommended. Another issue is the lack of regulation regarding the training standards for the personnel involved in HBOT [2], the conditions under which HBOT is performed, and the technical capacity of the equipment used (often inadequate, not allowing a therapeutic oxygen pressure to be achieved).

Historical outline of research on hyperbaric oxygen therapy

Compressed air was first used to treat medical conditions in 1662 by the British physician, Nathaniel Henshaw [3], who in 1664 published a treatise describing "*domicilium* or oxygen chambers", where air at atmospheric pressure could be condensed or evaporated to treat disease and improve health [4]. Over 100 years later, in 1775, John Priestly discovered oxygen. However, early reports of the harmfulness of concentrated O2 delayed the development

of research on hyperbaric oxygen therapy until the 19th century [3]. In 1877, Fontaine developed the first mobile hyperbaric chamber [5]. Since then, work on various hyperbaric chambers has been developed with simultaneous studies of their therapeutic effects. As a result of all this work a hyperbaric hotel was built in Cleveland in 1928 (for about 70 guests), HBOT was used to treat decompression sickness in US Navy divers during World War II, and the results of Boerema's famous study on pigs were published in 1959 in the paper "*Life without blood*" (its topic was keeping animals alive with HBOT despite haemoglobin levels preventing survival under normal conditions) [4-6]. Since the first successful treatment of decompression sickness in 1937, [3] HBOT has been used and studied in increasing numbers of therapeutic areas.

Hyperbaric chamber - principle of operation

The hyperbaric chambers used in HBOT are divided into monoplace and multiplace units. Regardless of their type, the treatment procedure is the same. A patient breathes 100% O_2 at a pressure 1.5–3 times higher than the pressure above sea level (1.5–3 atm) [7]. In monoplace units, a patient breathes O_2 which directly fills the chamber. In multiplace units, O2 is administered directly through a special mask or head hoods [8]. There are also monoplace chambers with a pressure range of 1.2 to 1.3 atm. They are usually folding, portable devices made of plastic [3].

The principle of the method focuses on improving O_2 delivery to the tissues. This improves the healing process for inflammations, circulatory disorders, and other ailments. Oxygen delivery to the tissues is influenced by many factors, including the oxygen-carrying capacity of the blood and tissue perfusion [7].

The physical aspects are also significant. Oxygen delivery is influenced by its concentration in the solution, as well as the oxygen diffusion effectiveness. The relationship between gas pressure and its concentration in a solution (serum/tissue) is described by Henry's law. According to this, the concentration of gas in a dissolved state (C_{gas}) is equal to the pressure (P) multiplied by the solubility coefficient (S) of the gas (measured in this case at the normal temperature of the human body) [3].

$$C_{gas}=PS$$

The solubility coefficients of the three main gases contained in the atmospheric air mixture, measured at human body temperature, are as follows [9]:

Oxygen	0.024
Carbon dioxide	0.57
Nitrogen	0.012

Fick's law describes the speed of the flow process of a gas across a tissue/fluid. According to it, the volume of gas moving through the membrane (V_{gas}) is equal to the quotient of the surface area (A) and thickness (T) of the membrane multiplied by the product of the diffusion coefficient (D) and the pressure difference on both sides of the membrane (P_1-P_2) [17, 24].

$$V_{gas}=\frac{A}{T}D(P_1-P_2)$$

Due to the almost unmeasurable values of membrane thickness and surface area, this formula is simplified to:

$$V_{gas}=D\,(P1-P2)$$

The diffusion coefficient takes the same value as the quotient of the solubility coefficient (S) and the square root of the molar mass of the gas ($\sqrt{MW}$) [3].

$$V_{gas}=\frac{S}{\sqrt{MW}}(P_1-P_2)$$

The molar mass of carbon dioxide (CO_2) is 44 g/mol and molar mass of oxygen (O_2) is 32 g/mol. This difference does not compensate for the almost 24 times higher solubility coefficient of CO2. Thus, under the same conditions, the O_2 that reaches the tissues is less than the CO_2, both because of the lower dissolved gas concentration (Henry's law) and the less efficient diffusion process (Fick's law).

The hyperbaric chamber generates a high pressure of 100% O_2, increasing the pressure gradient [7]. As a result, the process of the saturation of fluids with oxygen and the diffusion of this gas are accelerated. This causes a cumulative effect of O_2 delivery to the tissues [10–11].

The need for a more efficient delivery of O_2 to the tissues is attributable to its deficiency under pathological conditions (e.g. trauma, hard-to-heal wounds, or gas embolism). A higher O2 supply to the cells improves the processes of the formation of the energy carrier, adenosine triphosphate (ATP), synthesised in the mitochondria [3, 7].

In addition, many inflammatory, rheumatic, or autoimmune processes can disrupt O2 transport in the body. Consequently, its maximum concentration, at elevated pressure, provides an improvement in the physiological processes concerned [11].

Recommendations on the clinical indications for HBOT

The Tenth European Consensus Conference on Hyperbaric Medicine published Recommendations on accepted and unaccepted clinical indications and practice of hyperbaric oxygen treatment (HBOT) ([12], as amended [13]) - Table.

Contraindications and precautions for HBOT

Increased partial pressure of O_2 in the blood (hyperoxaemia) and tissues (hyperoxia) supports the healing process of many diseases; however, it must be remembered that excess reactive O_2 forms and/or associated deficiencies in antioxidant activity have cytotoxic effects and may cause HBOT complications. The issue is all the more complicated because, in the case of HBOT, it is not possible to determine precisely what ultimate O_2 pressure will be achieved in the tissues [14].

Table. Recommendations on the clinical indications for HBOT [12-13].

Recommen-dations for HBOT	**Strongly recommended*** (strong recommendation)	• CO poisoning, • open fractures with crush injury, • prevention of osteoradionecrosis after dental extraction, • osteoradionecrosis (mandible), • soft tissue radionecrosis (cystitis, proctitis), • decompression illness, • gas embolism, • anaerobic or mixed bacterial infections, • sudden idiopathic deafness.
	Recommended (weak recommendation)	• diabetic foot lesions, • femoral head necrosis, • compromised skin grafts and musculocutaneous flaps, • central retinal artery occlusion (CRAO), • crush Injury without fracture, • osteoradionecrosis (bones other than mandible), • radio-induced lesions of soft tissues (other than cystitis and proctitis), • surgery and implant in irradiated tissue (preventive treatment), • ischaemic ulcers, • refractory chronic osteomyelitis, • burns, 2nd degree more than 20% BSA, • pneumatosis cystoides intestinalis, • neuroblastoma (stage IV).
	Optional (neutral recommendation)	• brain injury (acute and chronic TBI, chronic stroke, • post anoxic encephalopathy) in highly selected patients, • radio-induced lesions of larynx, • radio-induced lesions of the central nervous system (CNS), • limb replantation, • selected non-healing wounds secondary to systemic processes, • sickle cell disease, • interstitial cystitis.
Not recommended		• post sternotomy mediastinitis, • malignant otitis externa, • acute myocardial infarction, • retinitis pigmentosa, • facial (Bell's) palsy.
Recommendations concerning those indications for which HBOT should not be used		• autism spectrum, • placental insufficiency, • multiple sclerosis, • cerebral palsy, • tinnitus, • acute phase of stroke.

** Recommendations for the use of HBOT: strongly recommended ("We recommend…"); recommended ("We suggest…"); optional ("It would be reasonable…").*

The complications of HBOT include: cataracts, macular degeneration and keratoconus (oxidative stress enhances apoptosis of the retinal pigment epithelial cells [15]) and retinopathy of prematurity (in pregnant women receiving HBOT [14]); and, in addition, pressure injury (barotrauma), which occurs in response to failed equalization of the pressure between the external space (here the hyperbaric chamber) and the part of the patient's body containing gas (even a trace amount); most commonly, an injury is caused to the ear, but also to the teeth (previously treated), paranasal sinuses and lungs [16].

Other dangerous complications of HBOT include acute CNS oxygen poisoning, known as the Paul Bert effect, occurring when O2 is breathed at pressures in excess of 1 atm, which causes CNS oxygen toxicity. Its manifestation is almost immediate seizure (transient) and negative behavioural patterns and cognitive impairment (it has not been established whether it is permanent or transient [17], although increased apoptosis of hippocampal neurons has been noted in mouse models when exposed to O_2 at a pressure of 6 atm [18]). The main contraindications to using HBOT include claustrophobia, hypertension, pulmonary embolism, hypoglycaemic episodes, seizures, and an implanted pacemaker [19].

The complication rate is estimated to increase with the number of HBOT treatments and is 8% for 11-29 treatments and 17% for above 30 treatments. Most of the reports referred to in this study recommend treating a patient with 20 to 40 HBOT sessions [20], which should

make us reflect on the ad hoc and not fully justified use of this method (see the Table).

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REPURPOSING OF MULTIPLE SCLEROSIS (MS) AND GRAFTS VERSUS HOST DISEASE (GVHD) THERAPEUTICS TO INHIBIT THE CHRONIC REJECTION OF TRANSPLANTED ORGANS

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Abstract: Chronic rejection of transplanted organs is an incurable event in transplantation. The macrophages infiltrating an allograft induce vessel occlusion and tissue fibrosis, which over the months/years in the post-transplantation period lead to organ failure. This means that patients require re-transplantation, which is extremely problematic due to the permanent lack of organ donors. Our studies show that chronic rejection depends on the function of the macrophages and the RhoA/ROCK pathway. Genetic (RhoA knockout) or pharmacological (ROCK inhibitors) interference with the RhoA pathway inhibits macrophage functions and prevents chronic rejection in the rodent transplantation model. Most commercially available RhoA pathway inhibitors are not approved for clinical use. However, we found two compounds: fingolimod (Gilenya, FTY720) and belumosudil (Rezurock), which are clinically approved for relapsing multiple sclerosis (MS) and chronic graft versus host disease (cGVHD), respectively, which also inhibit the RhoA pathway. We tested these two drugs in the rodent transplantation model, and both inhibited chronic rejection. We therefore proposed to repurpose these drugs for organ transplantation. A clinical trial on the effect of fingolimod in kidney transplant patients is ongoing, and the belumosudil trial is pending.
Keywords: organ transplantation, macrophage, fingolimod, belumosudil, RhoA pathway.

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Introduction

Despite the enormous progress in medicine, the number of terminally ill patients is increased by obesity, lengthening of the human lifespan, the side effects of overmedication, and environmental factors. For many of them, the only chance for survival is organ transplantation. According to the 2021 statistics, there were over 144,000 transplantations performed worldwide [1]. Unfortunately, lifesaving organ transplantation is limited by the lack of organ donors. Currently, the USA has over 100,000 people on the transplant waiting list, and a new patient is added to the list every 10 minutes. Because of this huge demand, there is an urgent need to find new therapies that improve transplanted organ health and longevity. All transplanted organs, if they do not derive from genetically identical donors, such as identical tweens, undergo a process of immune rejection. There are two main phases of organ rejection: acute and chronic rejection [2]. While acute rejection occurs a few days after transplantation, chronic rejection develops much later, usually months or years post-transplantation. Ten years after transplantation, approximately 70% of all organs fail due to chronic rejection. Nowadays, acute rejection, which is T- and B cell-dependent, can be successfully managed by a variety of available immunosuppressive drugs [3]. Unfortunately, there is no cure for chronic rejection, which mainly depends on the activity of macrophages [4]. Here we describe our research into the chronic rejection field and our most recent efforts in repurposing the existing clinically approved therapies from other diseases to clinical transplantation.

The chronic rejection of transplanted organs is driven by macrophages

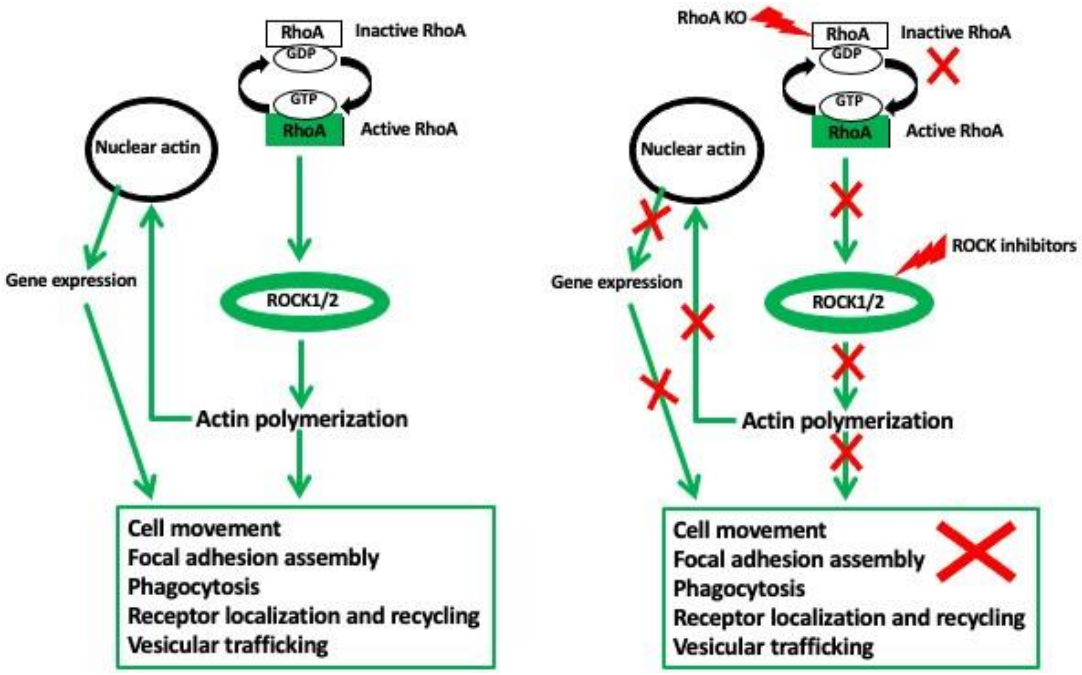
Chronically rejected organs display two main signs of chronic rejection: vessel occlusion and fibrosis. Occlusion of the blood vessel lumen cuts off the blood flow to the transplant, and tissue fibrosis destroys organ architecture, resulting in organ failure. Our laboratory has studied chronic rejection of transplanted organs for over a decade. We use a rodent (rat and mouse) cardiac transplantation model and the *in vitro* cultures of isolated mouse monocyte/macrophages and the RAW 264.7 mouse macrophage cell line. In a rodent transplantation model, the transplanted heart from a genetically different donor is placed in the abdominal cavity of the recipient and anastomosed to its circulatory system via the infrarenal aorta and *vena cava*. Subsequently, the development of chronic rejection is monitored for 100 days post-transplantation. Using such transplantation models, we have demonstrated that the allograft is infiltrated by the recipient macrophages and that the application of RhoA pathway inhibitors (in conjunction with the inhibitors of acute rejection: the low dose cyclosporin or mTOR inhibitor

(everolimus) in rats and CTLA4-Ig in mice) within the first week after transplantation inhibits macrophage infiltration and reduces or prevents subsequent chronic rejection [5-7]. The RhoA is a small GTPase that, through its downstream effector ROCK1/2 kinases, regulates actin polymerization, actin cytoskeleton, and all actin-dependent cell functions, such as cell shape, motility, receptor expression and recycling, phagocytosis, vesicular trafficking, and organelle positioning and integrity. It also controls the expression of pro and anti-inflammatory genes in macrophages by affecting the nuclear actin (which regulates chromatin structure) and the nuclear influx of unpolymerized G-actin (Fig. 1).

Mechanism of macrophage entry into the graft

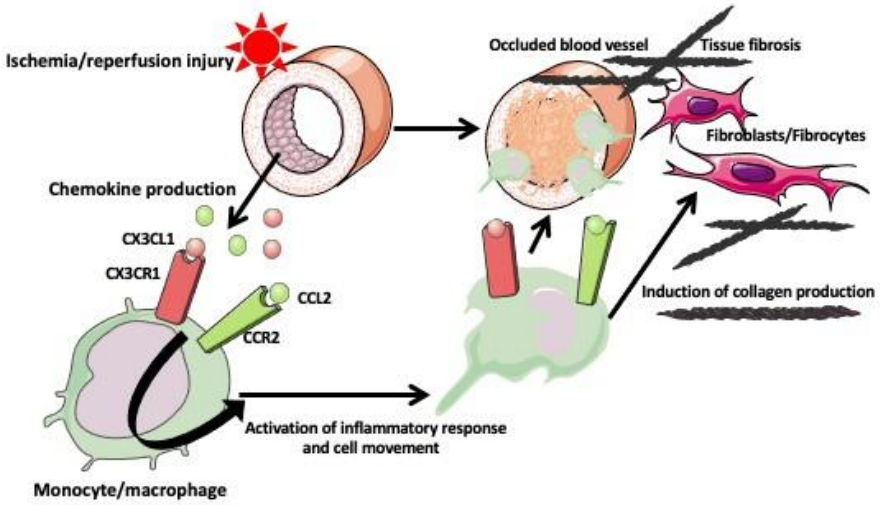
From the moment the organ is procured from the donor and connected to the recipient circulation, it undergoes ischemia/reperfusion injury that causes cell death and the production of inflammatory factors. The injured endothelium of the graft blood vessels produces chemokines, such as fractalkine (CX3CL1) and the monocyte chemoattractant protein (CCL2), which are the ligands for their respective receptors: CX3CR1 and CCR2 are expressed at the surface of monocytes and macrophages [8]. The binding of these chemokines to their receptors activates monocyte/macrophage movement into the graft and their aggregation around the injured blood vessels. While both pathways operate in targeted macrophage migration, the CX3CL1/CX3CR1 pathway dominates in the chronic rejection scenario [9, 10]. While in the graft, macrophages induce the over-proliferation of muscle cells in the artery walls, causing, over time, a decrease and, eventually, total occlusion of the arteries' lumen. Additionally, activated macrophages induce the fibrotic pathways that produce collagen within the graft tissues (Fig. 2, Fig. 3). We showed that in the rodent model system, the application of RhoA/ ROCK inhibitor Y27632 (in conjunction with the T cell inhibitors to prevent acute rejection) to the graft recipient within the first week after transplantation inhibited monocyte/macrophage movement to the graft [5–7]. To confirm the involvement of RhoA in the macrophage movement, we created the knockout (KO) mouse with the RhoA gene deleted in the macrophages, and we used these KO mice as the graft recipients [11]. These studies showed that macrophage-specific deletion of RhoA inhibited macrophage infiltration, abrogated vessel occlusion and fibrosis, and inhibited chronic rejection of the graft [11]; (Fig. 3). The question was why and how the pharmacological (Y27632 inhibitor) or genetic (RhoA deletion) interference with the RhoA pathway prevents macrophage movement to the graft. Knowing that the RhoA pathway regulates actin, we studied the effects of RhoA interference on macrophage actin-dependent features and functions. We showed that macrophages treated *in vitro* with the Y27632 inhibitor and RhoA-deleted macrophages from the KO mice were abnormally elongated, and their organelles, such as Golgi, mitochondria, and nuclei, were displaced from their proper locations within the cell. While the average length of mouse macrophages is ~50 µm, the RhoA-inhibited macrophages were over 700 µm in length [11]. The macrophage

Figure 1. RhoA/ROCK pathway and actin-dependent cell functions.



Exchange of GDP to GTP activates RohA. Active RhoA, through its downstream effector ROCK kinase 1 and 2, activates actin polymerization and dynamics between globular (G) and filamentous (F) actin and thus regulates all actin-dependent cell functions, such as cell movement, focal adhesion assembly/disassembly, phagocytosis, vesicular trafficking, receptor localization at the cellular membrane, and receptor recycling. It also regulates the influx of G-actin to the nucleus, where actin regulates chromatin condensation and gene transcription. Interference with the RhoA pathway, either by RhoA knockout or pharmacological inhibition of ROCK1/2 deregulates actin polymerization and all actin-dependent cell functions.

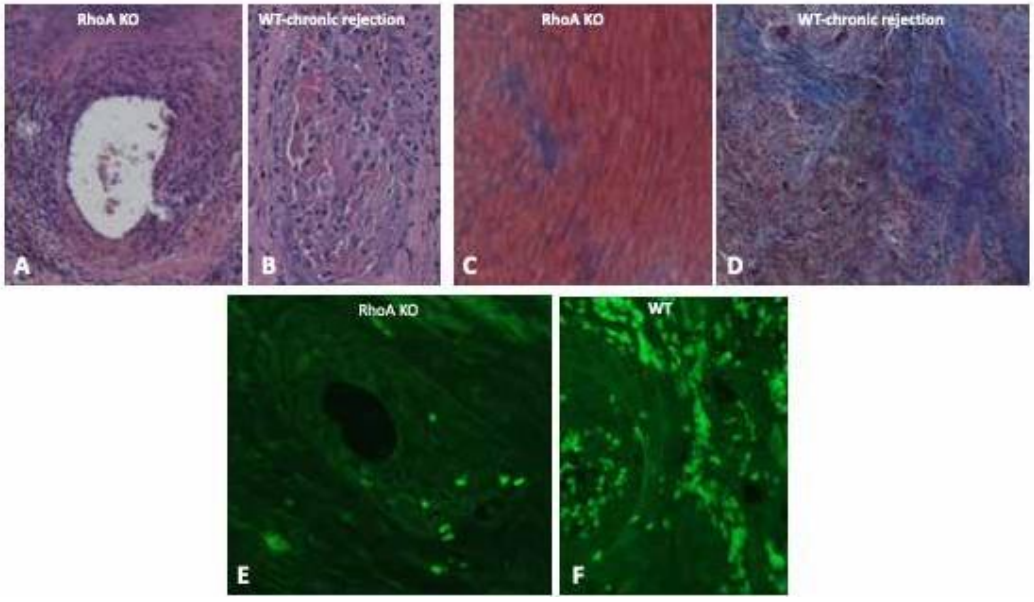
Figure 2 Mechanism of macrophage movement to the allograft.



Procurement of an organ causes ischemia/reperfusion injury. After transplantation, the chemokines produced by the endothelium of the injured blood vessels, such as CXCL1 and CCL, bind to their respective receptors, CX3CR1 and CCR2, on monocytes and macrophages, which activates an inflammatory response and initiates targeted movement toward the injured blood vessels. Macrophages aggregated around the arteries induce the over-proliferation of smooth muscle cells in the arterial wall, causing vessel lumen occlusion. Additionally, activated macrophages induce fibroblasts/fibrocytes to produce collagen, causing tissue fibrosis.

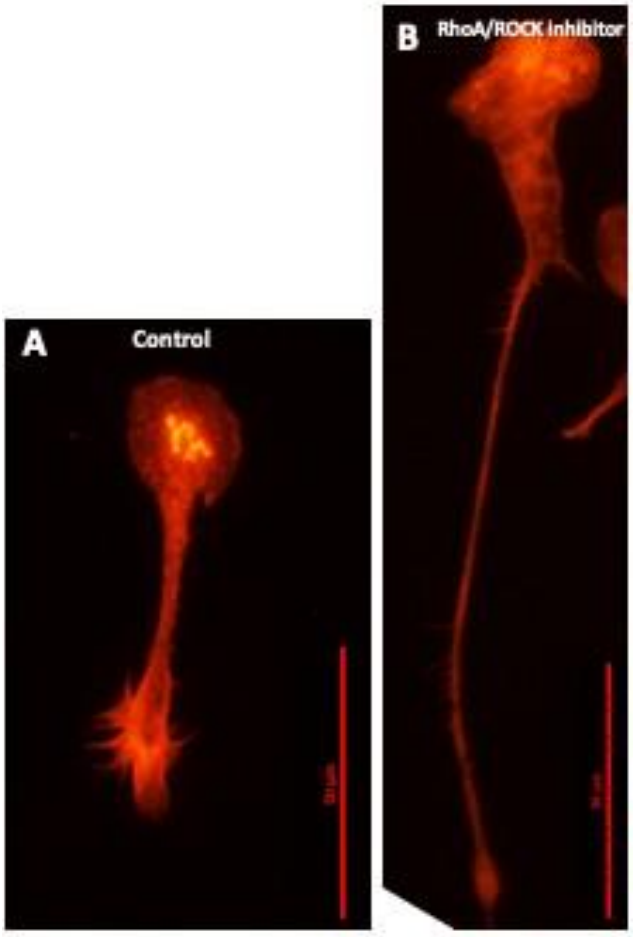
movement forward depends on a cyclical attachment/detachment of the end of the tail to the substrate, which is facilitated by the cyclical formation/disassembly of focal adhesions in the tail. We showed that in the RhoA-inhibited macrophages, the focal adhesions do not disassemble, thus, the tail remains permanently attached to the substrate while the macrophage front is trying to move forward until physical overstretching causes the tail to break. Because such a futile movement forward with the attached tail mimics the movements of the feeding hummingbird, we called this macrophage phenotype the "hummingbird phenotype"

Figure 3 RhoA pathway interference inhibits macrophage infiltration and chronic rejection.



Microscope images of the cross-sections of the control and chronically rejecting of mouse hearts.
A) Non-occluded blood vessel in the mouse heart transplanted to the recipient which macrophages the RhoA deletion (RhoA KO). B) Occluded blood vessel in the heart transplanted to the wild-type recipients. C) Fragment of tissue with very little collagen (stained blue) in the heart transplanted to the RhoA KO recipient. D) Heart transplanted into the wild-type recipient showing a massive disposition of collagen. E) Heart transplanted to the RhoA KO recipient showing a very low number of macrophages (immunostained green with F48 macrophage marker). F) Heart transplanted to the wild-type recipient showing massive infiltration of macrophages (green).

Figure 4 Hummingbird phenotype of RhoA-inhibited macrophages.



A) The macrophage from a control mouse is around 50 µm long.
B) Incubation of macrophages with RhoA/ROCK inhibitor Y27632 causes extreme elongation, the so-called hummingbird phenotype.

[11]; (Fig.4). We also showed that the expression and localization of the CX3CR1 fractalkine receptors (which direct macrophages to the blood vessels of the graft) were abnormal in the RhoA-deleted macrophages. We concluded that interference with the RhoA pathway affects actin-dependent targeted cell movement and prevents macrophage infiltration to the graft [11].

Results of screening RhoA/ROCK inhibitors for the ability to prevent chronic rejection

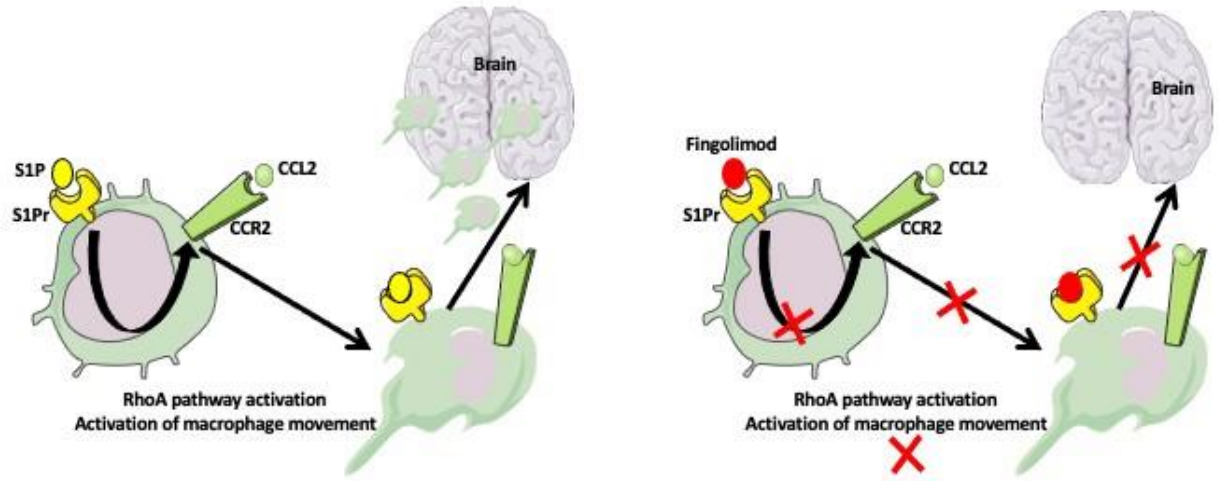
To further confirm that, besides the Y27632, other ROCK inhibitors also abrogate chronic rejection, we tested several commercially available inhibitors in the mouse cardiac transplantation model. We found that out of the four tested RhoA/ROCK inhibitors, fasudil and azaindole inhibited vessel occlusion, tissue fibrosis, decreased macrophage infiltration, and abrogated chronic rejection of mouse cardiac allografts. The remaining inhibitors, SAR-407899 and SLX-2119 (belumosudil), decreased the tissue fibrosis and, at least at the tested doses, were less effective in inhibiting vessel occlusion [5]. Although these studies confirmed that RhoA/ROCK inhibition abrogates chronic rejection in the mouse model, we do not know if this also will be true for human transplantation. Thus the next step should be clinical trials testing these inhibitors in transplantation patients. Y27632 was tested in clinical trials without success due to severe side effects, yet it is approved in Japan for ocular disease treatment. Other ROCK inhibitors available for clinical use outside of the USA are: fasudil, approved in Japan and China to treat cerebral vasospasm ischemic symptoms [12], and ripasudil, a derivative of fasudil, approved in Japan for the treatment of ocular hypertension and glaucoma [13, 14]. Fortunately, we found two RhoA/ROCK inhibitors clinically approved in the USA for treatments irrelevant to the chronic rejection of transplanted organs, fingolimod and belumosudil.

Clinically approved therapies with fingolimod and belumosudil

Fingolimod (Gilenya, FTY720) is a derivative of fungal metabolite myriocin, where the structure resembles sphingosine (15, 16). Fingolimod (Gilenya, FTY720) and its familial compound siponimod (Mayzent) are used for the treatment of multiple sclerosis (MS) [17, 18]. MS is a chronic and debilitating autoimmune disease of the central nervous system. It causes inflammation and damage to the myelinating cells - oligodendrocytes, myelin, and nerve fibers. MS affects over 2.5 million people worldwide, with the highest prevalence in North America and Europe. There are three main forms of MS: primary progressive MS (PPMS), characterized by a rapid progression, affects only 10–15% of MS patients, the relapsing-remitting MS (RRMS) consists of episodes of deterioration interrupted by periods of partial or complete recovery and affects ~85% of the MS population, and the secondary progressive MS (SPMS), characterized by a steady deterioration, which usually develops after two decades of RRMS [19]. In MS, the immune cells exit from the blood and lymphoid organs and enter the central nervous system (CNS), causing inflammation and damage. The movement of immune cells, including macrophages, to the CNS depends on the sphingosine 1-phosphate (S1P) and CCL2/CCR2 pathway. S1P binding to its receptors expressed on the surface of immune cells activates the chemokine CCL2 pathway signaling. The binding of CCL2 to its receptor CCR2 induces translocation of immune cells to the CNS. Fingolimod binds to the S1P receptors, inhibiting the activation of CCL2 signaling and preventing immune cell translocation (Fig.5). Fingolimod binds to four out of five S1P receptors: S1P1, S1P3, S1P4, and S1P5, [20]. Siponimod is selective for S1P1 and S1P5 receptors, and this specificity decreases the adverse effects of the drug [18]. Beside inhibiting the S1P pathway, fingolimod also inhibits the RhoA/ROCK pathway [21].

Belumosudil (Rezurock) is used for the treatment of the chronic graft versus host disease (cGVHD), (22). The cGVHD is a long-term (beyond 100 days) complication following allogeneic hematopoietic cell transplantation. The hallmark of chronic GVHD is inflammatory fibrosis of the skin, joints, and internal organs (mostly the lungs). While

Figure 5 Fingolimod effect on macrophages.



In multiple sclerosis (MS), the binding of the S1P ligand to its S1P receptor activates CXCL1/CCL and RhoA pathways in macrophages and induces the macrophage movement to the central nervous system. Fingolimod, because of its similarity to S1P, binds to the S1P receptor. Fingolimod – S1Pr binding prevents the activation of RhoA and CXCL1/CCL pathways, preventing macrophage movement to the central nervous system. Thus fingolimod therapy is beneficial for MS patients.

the acute form of GVBD is caused by the T cells and B cells, chronic GVBD mostly depends on macrophages. Activated macrophages infiltrate various organs and tissues and produce the transforming growth factor - β (TGF-β), leading to fibroblast activation and the overproduction of collagen [23–25]. Belumosudil, through the inhibition of the RhoA/ROCK pathway, reduces cGVBD fibrosis by downregulating the TGF-β signaling and inhibiting the expression of profibrotic genes and collagen production [26].

Repurposing fingolimod and belumosudil therapies from MS and cGVBD to transplantation

Because fingolimod and belumosudil inhibit the RhoA/ROCK pathway and affect macrophage migration and activation, we hypothesized that they might also inhibit the chronic rejection of transplanted organs and, because they are clinically approved, they can be repurposed from MS and cGVHD applications to clinical transplantation. However, before starting relevant clinical trials, we wanted to be sure that these drugs could inhibit chronic rejection in animal models. The animal studies showed that fingolimod inhibited vessel occlusion and allograft fibrosis, and belumosudil (Rezurock) (at least at the tested dose) was especially effective in inhibiting fibrosis but less effective in preventing vessel occlusion [21, 27]. We also performed a global transcriptome analysis of mouse macrophages treated with fingolimod and belumosudil. This analysis showed that both drugs downregulated the GTPase and the actin pathway genes involved in cell migration and immune response, but they differentially affected the fibrotic pathway genes. Belumosudil specifically downregulated the fibrotic pathway genes, pentraxin 3 (PTX3, which promotes fibrocyte differentiation), CCR2, and CCL2, while fingolimod specifically downregulated NOTCH1, which is a known target of many antifibrotic therapies [28, 29]. All these studies strongly suggested that fingolimod and belumosudil should be tested in clinical trials in transplanted, and maybe even COVID-19 patients [30]. Currently, at the Methodist Hospital in Houston, Texas, USA, we have ongoing fingolimod clinical trials in kidney transplant recipients, and the belumosudil clinical trials are pending. The next step would be to test the effect of fingolimod with belumosudil combination on macrophage infiltration, fibrosis, vessel occlusion, and the inhibition of chronic rejection in animal models and, ultimately, in clinical trials.

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SARCOPENIA IN CHRONIC KIDNEY DISEASE – THE ASSUMPTIONS, AIMS AND METHODOLOGY OF THE RESEARCH PROJECT "THE ROLE OF THE microRNA AS A BIOMARKER OF SARCOPENIA IN CHRONIC KIDNEY DISEASE PATIENTS"

Sarkopenia w przewlekłej chorobie nerek – założenia, cele i metodyka projektu badawczego „Rola mikroRNA jako biomarkerów sarkopenii u pacjentów z przewlekłą chorobą nerek"

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Abstract: Sarcopenia is defined as a syndrome characterized by progressive and generalized loss of muscle mass and strength, with an increased risk of adverse events, such as impaired physical activity that often requires assistance. It also leads to falls, degradation in the quality of life, and increased mortality. Sarcopenia is one of the complications occurring in patients with chronic kidney disease, and significantly worsens their prognosis. The causes of sarcopenia in chronic kidney disease are numerous and include an intensified subclinical inflammatory state as well as hormonal and metabolic disturbances. Early diagnosis of sarcopenia or the risk of sarcopenia development in chronic kidney disease allows for the earlier implementation of lifestyle changes and therapeutic procedures aimed at preventing muscle mass and strength loss, or, in the case of already diagnosed sarcopenia, slowing its progress. Studies involving patients with chronic kidney disease are needed to enable a detailed understanding of the mechanisms of sarcopenia in this group of patients, as well as the identification of new markers of sarcopenia. The paper presents the project "The role of microRNAs as biomarkers of sarcopenia in chronic kidney disease patients" which has been submitted to the MINIATURA 7 competition organized by the National Science Centre and has been positively evaluated, obtaining registration number 2023/07/X/NZ5/00637. The study will be conducted at the Department of Internal Diseases, Nephrology and Dialysis, Military Institute of Medicine – National Research Institute, Poland. The aims and methodology of the study have been presented here.

Streszczenie: Sarkopenia jest definiowana jako zespół charakteryzujący się postępującą i uogólnioną utratą masy oraz siły mięśniowej ze zwiększonym ryzykiem niekorzystnych zdarzeń obejmujących ograniczoną aktywność fizyczną z nierzadką koniecznością korzystania z pomocy osób trzecich. Prowadzi także do upadków, pogorszenia jakości życia i zwiększenia śmiertelności. Sarkopenia jest jednym z powikłań występujących u pacjentów z przewlekłą chorobą nerek, znacząco pogarszającą rokowanie chorych. Przyczyny sarkopenii w przewlekłej chorobie nerek są liczne i obejmują nasilony subkliniczny stan zapalny, zaburzenia hormonalne oraz metaboliczne. Wczesne rozpoznanie sarkopenii lub ryzyka rozwoju sarkopenii w przewlekłej chorobie nerek umożliwiłoby szybsze wprowadzenie zmian stylu życia pacjentów oraz procesów terapeutycznych mających na celu zapobieganie utracie masy i siły mięśniowej, lub – w przypadku sarkopenii już rozpoznanej – spowolnienie jej przebiegu. Potrzebne są badania z udziałem pacjentów z przewlekłą chorobą nerek, które pozwoliłyby na dokładne poznanie mechanizmów sarkopenii w tej grupie chorych oraz nowych markerów sarkopenii. W pracy przedstawiono projekt pt „Rola mikroRNA jako biomarkerów sarkopenii u pacjentów z przewlekłą chorobą nerek", który został złożony do konkursu MINIATURA 7 organizowanego przez Narodowe Centrum Nauki i został rozpatrzony pozytywnie, uzyskując numer rejestracyjny 2023/07/X/NZ5/00637. Badanie będzie przeprowadzone w Klinice Chorób Wewnętrznych, Nefrologii i Dializoterapii Wojskowego Instytutu Medycznego – Państwowego Instytutu Badawczego. W pracy zostały przedstawione cele i metodyka badania.

Keywords: chronic kidney disease, project, sarcopenia, microRNA.

Słowa kluczowe: przewlekła choroba nerek, projekt, sarkopenia, mikroRNA.

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Sarcopenia in the course of chronic kidney disease

Chronic kidney disease (CKD) is increasingly recognised as a global public health problem. Irreversible kidney damage occurs in almost 13% of the population [1]. Impaired renal function cause electrolyte imbalances, metabolic, endocrine and bone disorders, anaemia, calcium and phosphorus metabolism disorders and numerous other complications, particularly involving the cardiovascular system, as well as sarcopenia.

Skeletal muscles account for approximately 30–40% of body weight. Their main function is to maintain correct posture and body balance, control movement as well as a variety of activities including eating and speech. Sarcopenia is defined as loss of muscle mass or abnormalities of muscle structure and decreased muscle strength and deterioration of skeletal muscle function. The term "sarcopenia" was first introduced in 1988 by Rosenberg to describe the loss of skeletal muscle mass in older people [2]. The loss of muscle mass is observed during the ageing process, in neuromuscular and chronic diseases [3]. As in the general population, sarcopenia also affects patients with CKD. The prevalence of sarcopenia in this patient group ranges from 5.9% to 55%, the value depending on various different studies [4-6]. The diagnostic criteria for sarcopenia are based on the 2018 guidelines of the European Working Group on Sarcopenia in Older People (EWGSOP2) [7]. These guidelines are used in many sarcopenia studies, also in patients with CKD. However, there are no specific criteria for the diagnosis of sarcopenia in individuals with CKD, who are particularly vulnerable to deterioration of muscle strength, a loss of muscle mass and impaired muscle architecture. Sarcopenia is associated with the process of protein-energy wasting (PEW), which is also observed in CKD. Decreased muscle mass and strength leads to reduced physical activity, high susceptibility to injury, and an increase in hospitalisations and mortality [4, 8]. Loss of muscle mass is also one of the causes of frailty syndrome, which is characterised by increased susceptibility to multiple physical stressors, such as illnesses or injuries. Frailty syndrome mainly affects the elderly but is also associated with impaired renal function [9]. There are numerous causes of muscle mass loss in patients with CKD. The presence of a subclinical inflammatory process in patients with impaired renal function leads to increased protein catabolism and inhibits anabolic processes in muscle tissue, leading to a decrease in muscle mass [10]. Metabolic acidosis also intensifies proteolytic processes [11]. Insulin resistance significantly contributes to the development of sarcopenia in patients with CKD, as does secondary hyperparathyroidism, which increases energy expenditure and is involved in the development of malnutrition and the loss of muscle mass in this group of patients [12]. Sarcopenia is also associated with vitamin D deficiency [13]. In addition, growth hormone (GH) resistance and abnormalities of the GH/IGF-1 (growth hormone/insulin-like growth factor-1) axis occurring in renal failure may impair protein synthesis and, as a result, reduce muscle mass [14]. An abnormal adipocytokine profile, particularly high leptin levels and hypogonadism with reduced plasma testosterone levels also contribute to the development of sarcopenia in patients with CKD [15].

Cardiovascular complications occur even in the early stages of CKD, intensifying with the progression of renal failure. Heart failure, which is one of the cardiovascular complications in CKD, affecting approximately 44% of haemodialysis patients, is another risk factor of sarcopenia [16]. The process of sarcopenia in CKD is intensified by multiple mechanisms of skeletal muscle mass loss, present also in heart failure, such as endothelial dysfunction, subclinical inflammation, hormonal disorders, elevated angiotensin II levels and increased reactive oxygen species (ROS) synthesis [17]. Sarcopenia is also associated with other cardiovascular complications, such as vascular damage, atherosclerosis, and poorer blood pressure control [18].

Recent studies have indicated that skeletal muscle homeostasis is regulated by transcription factors, such as muscle-specific microRNAs (miRNA). MiRNAs are single-stranded, non-coding RNA molecules composed of 21–25 nucleotides. MiRNAs recognise mRNA complementary sequences, interact with the 3' untranslated region (3'UTR) of the target mRNA, leading to the inhibition of translational processes or mRNA degradation at the post-transcriptional level [19]. It is now known that miRNAs are regulators of gene expression. Each miRNA can interact with different mRNAs, and each mRNA can be regulated by multiple miRNAs [20]. The expression of miRNAs can be altered by many pathological processes [21]. Many different miRNAs are expressed in different tissues and cells, but some are tissue-specific. MiRNAs are essential regulators of skeletal muscle development and homeostasis and affect the maintenance of muscle mass and normal muscle function. MiRNAs are involved in such processes as myoblast proliferation, muscle myogenesis and muscle cell differentiation. There is a group of muscle-specific miRNAs called myomiRs. The myomiRs group includes miR-1, miR-133, miR-206, miR-208, miR-499 and miR-486 [22]. Most myomiR family members are expressed in both the skeletal and heart muscles, with the exception of miR-206, which is skeletal muscle specific, and miR-208, which is expressed mainly in heart muscle [23]. Previous studies have shown that miRNAs play a critical role in skeletal muscle development and homeostasis; moreover, different miRNAs are involved in muscle dysfunction and muscle diseases, including sarcopenia [24, 25].

Classification of sarcopenia

Sarcopenia can be divided into primary and secondary forms. Primary sarcopenia is associated with the ageing process, while the secondary type may or may not occur in the elderly but develops in the course of numerous medical conditions and in individuals with low physical activity. Secondary sarcopenia may arise as a result of malignancies, inflammatory or hormonal disorders, organ failure, anorectic drug use and nutritional disorders, such as reduced food intake or gastrointestinal disease [26]. Since many of these disorders are present in CKD, it is very likely that patients with impaired renal function will

develop sarcopenia. Loss of muscle mass in secondary sarcopenia is more accelerated and intense than in the primary form of the disease [27]. Sarcopenia can also be acute or chronic. Sarcopenia lasting for less than 6 months is considered acute and is a result of a coexisting disease process or trauma. If sarcopenia persists for over 6 months, it can be diagnosed as a chronic condition.

Diagnosis of sarcopenia

Sarcopenia is diagnosed when reduced muscle strength and low muscle mass and/or impaired muscle quality occur at the same time. The 2018 European guidelines for the definition and diagnosis of sarcopenia confirm that decreased muscle strength is considered the most reliable tool for assessing muscle function, so sarcopenia is probable when low muscle strength is detected. A sarcopenia diagnosis is confirmed by the presence of low muscle strength together with low muscle quantity and/or quality. When these symptoms are accompanied by low physical performance sarcopenia is considered severe [7].

There are various methods to assess skeletal muscle strength and mass, muscle quality and physical performance. Skeletal muscle strength can be measured by handgrip strength or the five-repetition chair stand test. Measurement of hand grip strength requires the use of a calibrated dynamometer. Hand grip strength has been shown to correlate with skeletal muscle strength in other parts of the body and can serve as a substitute for more complex measurements of upper and lower limb muscle strength [28]. As this method is simple and does not require highly specialised equipment, it can be used in both hospitals and outpatient clinics. Another way of assessing skeletal muscle strength is the five-repetition chair stand test. It involves measuring the time needed to stand up from a sitting position five times without using the hands [29]. The cut-off points for the handgrip strength test is < 27 kg for men and < 16 kg for women, while for the five-repetition chair stand test it is > 15 s. [30].

There are several techniques to estimate muscle mass. The gold standards for measuring muscle mass are magnetic resonance imaging (MRI) and computed tomography (CT). However, the use of these methods is limited by the high cost, restricted access to the examinations and the need for specialised trained personnel. Furthermore, the cut-off points for the diagnosis of low skeletal muscle mass for CT and MRI are not well defined. Dual energy X ray absorptiometry (DXA) is more accessible than MRI and CT. It measures not only total muscle mass, but also appendicular skeletal muscle mass (ASM) [7]. Another method used to estimate muscle mass is bioelectrical impedance analysis (BIA). It is a simple and not very expensive method, the equipment is portable, so the patient does not have to be transported, and the method is also easy to use. The main disadvantage of BIA is that the method does not measure muscle mass directly, but only estimates total muscle mass or, using a number of available formulas, helps to estimate the skeletal muscle mass of the limbs. Since the muscle mass is related to body size, when quantifying ASM the absolute value of ASM can be indexed to height or weight: ASM/height2, ASM/body mass or ASM/BMI [31]. Abnormal ASM values are < 20 kg for men and < 15 kg for women, and abnormal indexed values are < 7 kg/m2 for men and < 5.5 kg/m2 for women [7].

A physical fitness assessment includes an evaluation of whole-body function, particularly mobility, which includes muscular fitness and central and peripheral nervous system function [7]. Methods used to assess physical fitness include: “Gait Speed Test”, “Short physical performance battery” (SPPB) test, “Timed-Up-and-Go” (TUG) test and “400-Metre Walk Test”. The Gait Speed Test is a simple and safe tool used for diagnosing sarcopenia and can predict the occurrence of adverse prognostic events, such as disability, cognitive impairment, falls and increased mortality [32]. The assessment of gait speed is also known as the “4 - Metre Walk Test”. Patients are asked to walk a distance of 4 metres at an individual pace. Walking speed is measured manually with a stopwatch or with an electronic device to measure the time needed to walk 4 metres [33]. The cut-off point for the walking speed test is a value ≤ 0.8 m/s, which allows the diagnosis of severe sarcopenia. Another method of measuring physical fitness is the SPPB test. It consists of three subtests: the ability to stand on one leg for 10 seconds, the time needed to walk 3 or 4 metres and the time needed to rise from a sitting to a standing position five times [34]. Patients with low SPPB usually need help in performing daily activities, have an increased risk of falls, reduced mobility, increased risk of hospitalisation and increased mortality [35]. Reduced mobility is diagnosed when a patient scores ≤ 8 on the SPPB test. The TUG test involves the patient being asked to stand up from a sitting position, walk 3 metres, turn around, return to the chair, and sit down again. The cut-off point for low physical performance in the TUG test is ≥ 20 s. [36]. The 400-Metre Walk Test measures the ability to walk independently and endurance. Participants are asked to complete 20 laps of 20 metres as fast as possible and are allowed up to two rest stops during the test. The cut-off point for the diagnosis of impaired fitness in the 400-Metre Walk Test is failure to complete the test or a distance walking time ≥ 6 minutes.

The European Study Group on Sarcopenia in Older People (EWGSOP2) has presented an updated algorithm for the diagnosis and assessment of the severity of sarcopenia, which is called Find-Assess-Confirm-Severity (F-A-C-S) [7]. The diagnostic process should begin with the patient completing the SARC-F questionnaire to confirm the possibility of sarcopenia (“Find” point). The SARC-F questionnaire was presented in Orlando in 2012 at the International Conference on the Diagnosis and Management of Sarcopenia [37]. The SARC-F questionnaire consists of five questions on strength (S), assistance with walking (A), rising from a chair (R), climbing stairs (C) and falls (F). A number of points that can be scored ranges from 0 to 2 for each point, from “None” to “very difficult”. The total number of points is 10, the number of points that predicts sarcopenia is ≥ 4. If the patient scores 4 or more on the SARC-F questionnaire or if sarcopenia is clinically suspected, the patient proceeds to the “Assess” point of the algorithm, during which muscle strength is measured by measuring hand grip

strength or the five-repetition chair stand test. Once reduced muscle strength is confirmed, the patient proceeds to the next point in the algorithm, "Confirm", which involves assessing muscle quantity or quality with the DXA, BIA, CT or MRI methods. The diagnosis of reduced muscle quantity or quality confirms sarcopenia. The final point in the algorithm is "Severity". Low physical performance assessed by the 'Gait Speed Assessment', the SPPB test, the "Timed-Up-and-Go" test or the "400-Metre Walk Test" enables diagnosing severe sarcopenia [7].

Although the awareness of possible sarcopenia development and its complications in CKD is growing among patients and healthcare professionals, it still requires improved diagnosis and management. Since sarcopenia in CKD is associated with increased morbidity and mortality, it is crucial to understand the exact mechanisms of loss of muscle mass and strength in patients with impaired renal function in order to prevent the development of sarcopenia, which would consequently enable patients to live longer and improve their quality of life. If sarcopenia is diagnosed early in CKD, then appropriate therapeutic processes and preventive measures could be introduced. Although scientists know a lot of mechanisms of sarcopenia in CKD, further research is still needed, and it is worth looking for new markers that could help in the diagnostic process of sarcopenia or that could predict the risk of developing reduced muscle mass and strength in CKD. As the number of patients with CKD is still increasing and the trend is set to continue in the future, it is highly advisable to look for causes of complications that increase morbidity and mortality in CKD with regard to possible future preventive or therapeutic measures.

Project: "The role of microRNAs as biomarkers of sarcopenia in chronic kidney disease patients".

Due to my interest in sarcopenia in patients with CKD, I submitted the application to the MINIATURA 7 competition organised by the National Science Centre for funding of the project "The role of microRNAs as biomarkers of sarcopenia in chronic kidney disease patients". On 20/09/2023, the application was accepted, and it received registration number 2023/07/X/NZ5/00637. The study will assess the genetic and non-genetic mechanisms of sarcopenia in patients with chronic kidney disease.

The research hypothesis is that changes in plasma concentrations of muscle-specific microRNAs – MyomiRs such as miR-1, miR-133, miR-206 and miR-499 are associated with the development of sarcopenia in patients with chronic kidney disease.

The study group will consist of 46 men aged 40 to 80 years with CKD and eGFR 15-29 ml/min/1.73 m2 (23 men with known sarcopenia and 23 men without sarcopenia). Patients will be age matched. The study will involve the patients from the Nephrology Outpatient Clinic of the Military Institute of Medicine - National Research Institute in Warsaw. The reason for including only men in the study is the observation that hypogonadism associated with reduced testosterone levels is one of the causes of sarcopenia in CKD. Furthermore, hypogonadism in CKD exacerbates cardiovascular complications. Inclusion criteria for the study will be a written consent to participate in the research project, age between 40 and 80 years and CKD stage G4 with eGFR 15-29 ml/min/1.73 m2. Exclusion criteria will be lack of consent to participate in the study, age below 40 and above 80 years, eGFR < 15 ml/min/1.73 m2 and eGFR ≥ 30 ml/min/1.73 m2, clinical signs of infection, metal elements in the body, physical exertion and excessive alcohol consumption the day before the examination.

The risk of sarcopenia will be assessed using the validated Polish version of the Mini Sarcopenia Risk Assessment Questionnaire (PL-MSRA-7) [38]. A total score ≤ 30 on the PL-MSRA-7 indicates a risk of sarcopenia. Muscle strength will be assessed by measuring hand grip strength using a calibrated dynamometer. Sarcopenia will be considered probable when the hand squeeze strength is < 27 kg. Skeletal muscle mass will be measured by bioelectrical impedance analysis (BIA) using a Body Composition Monitor (Fresenius Medical Care, Bad Homburg, Germany). The patients will remain in a supine position and electrodes will be placed in a tetrapolar configuration (on one hand and one foot). Skeletal muscle mass will be calculated, using the BIA equation by Janssen et al.: skeletal muscle mass (kg) = ([height2/BIA resistance × 0.401] + 3.825 - [age × 0.071]) + 5.102, where height is measured in centimetres, resistance is measured in ohms and age is measured in years [39]. Skeletal muscle mass will be presented as the index adjusted for height (kg/m2). Decreased skeletal muscle mass will be diagnosed if its index adjusted for height is < 7 kg/m2. Sarcopenia will be diagnosed when both hand tightness and skeletal muscle mass are below normal. Height and weight will be measured using a medical scale.

The eGFR will be calculated from the CKD EPI equation (2021): eGFRcr = 142 x min(Scr/κ,1)α x max(Scr/κ,1)-1.200 x 0.9938Age, where: Scr = standardised serum creatinine concentration in mg/dL, κ = 0.9, α = -0.302, min(Scr/κ, 1) indicates the lower of Scr/κ or 1, max(Scr/κ,1) indicates the higher of Scr/κ or 1, Age (years) [40].

Transthoracic echocardiography will be performed using a convex probe interfaced with a Logiq P6 ultrasound machine (GE Healthcare, Seoul, Korea). Echocardiographic measurements will be obtained on the basis of European Association of Cardiovascular Imaging guidelines.

Blood samples will be collected after a 12-hour overnight fasting period. Plasma concentrations of testosterone, creatinine, albumin, glucose, insulin, haemoglobin, total cholesterol will be tested at the Laboratory Diagnostics Department of the Military Institute of Medicine – National Research Institute. Plasma concentrations of microRNAs such as miR-1, miR-133, miR-206 and miR-499 will be measured at the Laboratory of Molecular Oncology and Innovative Therapies of the Military Institute of Medicine – National Research Institute using real-time PCR. Leptin, myostatin, IGF-1 and TNF-alpha will be measured by ELISA.

Descriptive statistics will be used in the groups of patients with and without known sarcopenia. In terms of continuous variables, the Student's t-test for paired data or the Wilcoxon test will be used for comparison between the study group and the control group, depending on the assumptions. Dichotomous variables will be compared, using the McNemary test and the Mantel-Heanszel analysis for matched data. Correlation analysis using the Pearson's or Spearman's correlation coefficient (depending on whether the assumptions are met) will be performed to investigate the relationship between the parameters studied in the group of patients diagnosed with sarcopenia. The threshold of statistical significance will be $p < 0.05$.

The results obtained will be compared between groups of patients with and without diagnosed sarcopenia. In addition, the results of the project will provide a basis for the preparation of more extensive and targeted research studies with a larger number of participants, including women in different stages of CKD, on new potential mechanisms of sarcopenia in CKD. Despite the extending range of knowledge of the causes of sarcopenia in CKD, there are still too few options for the prevention and management of muscle mass loss. So far, it is not fully understood why patients lose muscle mass with different intensities and why sarcopenia is present in some patients with the same eGFR value and not in others. The results of the study will perhaps let us better understand the causes of sarcopenia in CKD. In addition, the combination of cardiovascular and nephrological knowledge is very important for seeking the causes of sarcopenia, since the loss of muscle mass in CKD affects the progression of heart failure, and at the same time heart failure, which is a common cardiovascular complication in CKD, exacerbates sarcopenia.
Limitations of the present study include a relatively small sample size, the selection of patients of only one sex and only in the advanced stage of renal failure, and selection of only certain miRNAs. The simultaneous study design (cross-sectional study) will not allow us to follow the development of sarcopenia in patients who initially have normal muscle quantity and quality. In order to eliminate the above limitations on the basis of the results of the current study, it is going to be repeated on a larger sample including women, and a prospective cohort study is going to be conducted for approximately 3 years on patients in different, including less advanced, stages of renal failure. Such a study would include a 6-month evaluation of parameters targeting the potential role of miRNAs as modulators of nutritional status, muscle mass, muscle strength as well as progression of CKD. In the future, the miRNA panel is going to include cardiac tissue-specific miRNAs, which would allow the search for new associations between sarcopenia and cardiovascular complications in patients with CKD.

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FAILED LABOUR INDUCTION PREDICTORS FOR CAERSAREAN SECTION
NIEUDANA INDUKCJA PORODU. PREDYKTORY CIĘCIA CESARSKIEGO

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Abstract:

Introduction and objective. Every third labour is induced currently. The aim of the study was to evaluate the factors predicting a failed labour induction (IOL).

Material and methods: This was a retrospective cohort study of 214 labour inductions conducted at the Gynaecology and Obstetrics Ward of Solec Hospital in Warsaw from January to December 2019. The obtained data were statistically analysed using the SAS system.

Results: A failed induction of labour occurred in 28.97% of women undergoing the induction process. The risk factors associated with this failure and caesarean section (CS) delivery included primiparity (p = 0.0015), arterial hypertension during pregnancy (p = 0.0067), post-term pregnancy (p = 0.0067), and BMI of the patient >35 kg/m2 (p 3500 g 95% CI: 3448-3655), the use of dinoprostone in cervical pre-induction (p = 0.005) and the use of prostaglandins in IOL (p=0.003).

Conclusions: The strongest predictor for failed labour induction is primiparity.

Streszczenie:

Wprowadzenie i cel: Obecnie 30% porodów jest indukowanych. Celem badania było zbadanie czynników wpływających na nieudaną indukcję porodu.

Materiał i metody: Badaniem objęto retrospektywnie 214 indukcji porodu przeprowadzonych w Oddziale Ginekologiczno-Położniczym Szpitala Solec w Warszawie w okresie od stycznia do grudnia 2019. Uzyskane dane poddano analizie statystycznej przy użyciu systemu SAS.

Wyniki: Nieudana indukcja porodu wystąpiła u 28.97% pacjentek. Ryzyko nieudanej indukcji porodu jest powiązane z pierworództwem (p = 0,0015), nadciśnieniem tętniczym (p = 0,0067) i ciążą po terminie (p = 0,0067), BMI > 35 kg/m2 (p 3500 g (95% CI: 3448-3655), zastosowaniem dinoprostonu w preindukcji (p = 0,005) lub indukcji porodu prostaglandynami (p = 0,003).

Wnioski: Najsilniejszym predyktorem nieudanej indukcji porodu jest pierworództwo.

Keywords: caesarean section, labour induction, parity, postdates induction, dinoprostone.

Słowa kluczowe: cięcie cesarskie, indukcja porodu, rodność, indukcja po terminie, dinoproston.

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Introduction

The number of induced labours is increasing, which is associated with developments in perinatology. According to the UK data, in the year 2010 inductions accounted for approximately 20% of deliveries, while today the figure is 30–40% [1]. Labour induction has been known since ancient times. Hippocrates described mammary stimulation and mechanical dilation of the cervical canal as methods of inducing labour, while Soranos of Ephesus also mentioned amniotomy as an induction method. The most common indications for inducing labour before its spontaneous onset include post-term pregnancy, premature foetal membrane rupture after the 37 weeks' gestation, suspected high foetal weight or hypotrophy, abnormal foetal assessment results, pregnancy complicated by diabetes, hypertension or cholestasis.

Aim

This study was aimed at determining whether there are factors predisposing to failed labour induction and whether the indications for induction, parity, age, BMI, foetal weight and sex, a method of preinduction or induction used influence the course of labour induction.

Material and methods

We retrospectively analysed the course of labour induction in 214 patients qualified for this procedure in 2019 at the Department of Gynaecology and Obstetrics, Solec Hospital, Warsaw. The characteristics of the study group are presented in Table 1. The obtained data were statistically analysed using the SAS system.

Table 1. Characteristics of the study group

Gestational age	≥ 24 weeks
Most common indications for induction	Post-term pregnancy 35.98% PROM 19.15% GDM 17.28%
Patient's age	30.6 years (CI 95%: 29.972–31.234)
Primiparas	61.2% (131/214)
Delivery type	Natural delivery: 152 (71.03%) Caesarean section: 62 (28.97%)
Most common indications for surgical delivery	Threatened intrauterine foetal anoxia: 59.67% (37/62) Failure to progress: 20.96% (13/62)

Results

Successful labour induction depends on the patient's parity. The risk of caesarean section is the highest in primiparas. In the study group, primiparas accounted for 85.48% of failed inductions. In multiparas, the percentage of natural deliveries was 89.15%. The results were statistically significant ($p < 0.05$), see Table 2.

The study revealed no correlation between the patient's age and the course of labour induction. The percentage of caesarean sections is proportional to the percentage of primiparas in the age group, as shown in Table 3. Among primiparas, an association between maternal age and delivery type was observed, with the risk of failed labour induction increasing for women ≥ 30 years of age ($p < 0.05$).

Table 3. Age and parity versus delivery type

Age	Percentage of caesarean sections	Percentage of primiparas
18-19 years	100%	100%
20-24 years	26.30%	82%
25-29 years	32.40%	82%
30-34 years	30.00%	53%
35-39 years	20.68%	30%
40-44 years	10.00%	22%

The mean BMI in the study group was 29.707 kg/m2 (CI 95%: 29.174-30.239) and was significantly higher in the group of patients who had a caesarean section compared to inductions ending in natural delivery: 31.031 kg/m2 (CI 95%: 29.941–32.121) vs. 29.166 kg/m2 (CI 95%: 28.577–29.756). This is shown in Figure 1. Both in primiparas and multiparas, a significant effect of excessive weight gain on failed labour induction is evident ($p < 0.05$).

Figure 1. Delivery type depending on BMI index.

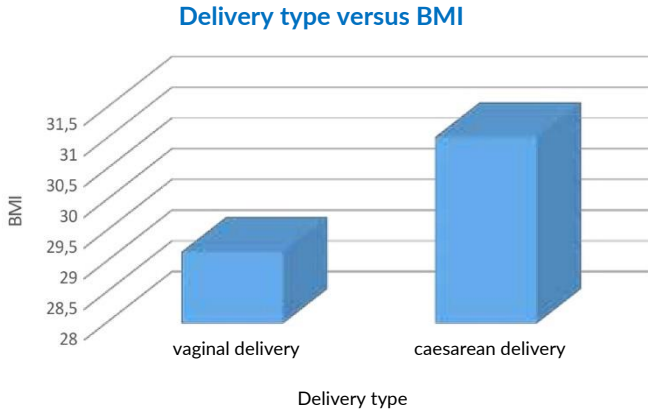


Table 2. Delivery type depending on parity.

Delivery type	Delivery number						
	1st delivery	2nd delivery	3rd delivery	4th delivery	5th delivery	6th delivery	Total
CD	53	6	1	1	1	0	62
	40.46%	10.91%	5.0%	25.0%	33.33%	0%	28.97%
VD	78	49	19	3	2	1	152
	59.54%	89.09%	95.0%	75.0%	66.67%	100%	71.03%
Total	131	55	20	4	3	1	214
	61.21%	27.70%	9.35%	1.87%	1.40%	0.47%	100%

Table 4. Delivery type versus indications for induction.

Delivery type	Indications for induction								
	Post-term pregnancy	PROM	GDM	PIH, NT	Decreased foetal movement	Large foetus	IUFD	Other	Total
CD	30	9	9	10	1	1	0	2	62
	38.96%	21.95%	24.32%	52.63%	12.50%	16.67%	0.0%	9.52%	28.97%
VD	47	32	28	9	7	5	5	19	152
	61.04%	78.05%	75.68%	47.37%	87.50%	83.33%	100.0%	90.48%	71.03%
Total	77	41	37	19	8	6	5	21	214
	35.98%	19.16%	17.29%	8.88%	3.74%	2.80%	2.34%	9.81%	100%

Indications for labour induction influence its course (p = 0.0067). In the study group, the highest risks of surgical delivery were associated with hypertension in the parturient (the caesarean section rate in this group was 52.6%) and with post-term pregnancy (the caesarean section rate was 38.96%). In contrast, in the case of other analysed indications, induction was successful in more than 75% of patients. Foetal weight influences the course of labour induction. The risk of caesarean section increases if the foetus weighs over 3500 g (95% CI: 3448-3655). In the study group, the birth weight was significantly higher in failed labour inductions than in natural deliveries - see Table 5.

Table 5. Birth weight versus delivery type.

Delivery type	Birth weight
Natural delivery	3403.158 (CI 95%: 3448.427–3655.121)
Caesarean section	3551.774 (CI 95%: 3300.909–3505.407)

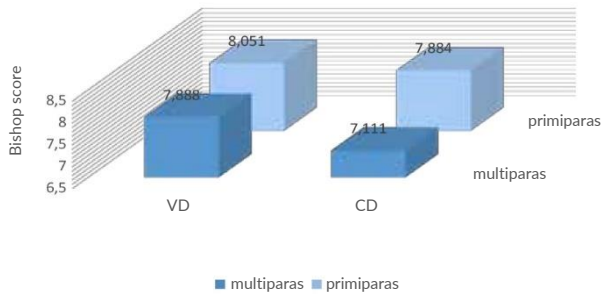
The study showed no effect of foetal sex on labour induction - see Table 6.

Table 6. Delivery type depending on foetal sex.

Sex	Total	Caesarean section	Natural delivery
Son born alive	118	34 (29%)	84 (71%)
Daughter born alive	91	28 (31%)	63 (69%)

The degree of maturity of the cervix influences the course of labour induction (p=0.0005). Multiparas gave birth naturally with a mean Bishop score of 7.888 and by caesarean section with a score of 7.111. In primiparas, on the other hand, the score was respectively: 8.051 in the case of vaginal delivery and 7.884 in the case of surgical delivery (Figure 2). If the cervix was mature and did not require preinduction, labour induction was successful in 80.6%.

Figure 2 Bishop score and delivery type depending on parity.



The method of preinduction used influences the course of labour induction. In the present study, the highest percentage of failed labour inductions was observed after the use of dinoprostone. The results are statistically significant (p=0.0005). See Table 7.

Table 7. Preinduction method versus delivery type.

Preinduction method	Delivery type	
	Natural delivery	Caesarean section
Foley catheter	62.5%	37.5%
dinoprostone	36.842%	63.157%
misoprostol	71.428%	28.571%
no pre-induction	80.645%	19.354%

The course of labour induction depends on the induction method used - see Table 8. In the presented study, the highest percentage of failed labour inductions was observed after the use of prostaglandins (p=0.003).

Table 8. Induction method versus delivery type.

Induction method	Natural delivery	Caesarean section
oxytocin	74.603%	25.396%
amniotomy	69.902%	30.097%
prostaglandins	46.153%	53.846%

In the present study, threatened foetal intrauterine asphyxia was the most common reason for surgical induction of labour. For this reason, 59.68% of caesarean sections were performed. The data are statistically significant (p < 0.0001) - see Table 9.

Table 9. Indications for caesarean section during labour induction.

Delivery type	Indications for caesarean section								
	None	Threatened anoxia	Failure to progress 1st stage	Failure to progress 2nd stage	Threatened infection	Foetal head high straight bit / Hyperextension	Threatened eclampsia	Other	Total
CD	0	37	7	6	5	4	2	1	62
	0.00	59.68%	11.29%	9.68%	8.06%	6.45%	3.23%	1.61%	28.97%
VD	148	3	0	1	0	0	0	0	152
	69.16%	1.40%	0.00%	0.47%	0.00%	0.00%	0.00%	0.00%	71.03%
Total	148	40	7	7	5	4	2	1	214
	69.16%	18.69%	3.27%	3.27%	2.34%	1.87%	0.93%	0.47%	100%

Based on the study, the risk of failed labour induction increases in primiparas (p = 0.0015), especially those over 30 years of age; it also increases with a patient's BMI > 35 kg/m2 (p < 0.05) and in patients induced due to hypertension (p = 0.0067) and post-term pregnancy (p = 0.0067). The risk of caesarean section is higher in the absence of maturity of the cervix (p = 0.0005), after the use of dinoprostone for preinduction (p = 0.005) or labour induction with prostaglandins (p = 0.003), and if the foetal weight is over 3500 g (95% CI: 3448-3655).

Discussion

In the analysis presented here, there was a strong association between failed labour induction and primiparity. Similar results were obtained by Marconi et al. and Mohammed et al., indicating that the parity is the most significant risk factor for caesarean section during labour induction [2, 3]. In their study, Dorwal et al. reported that the patient's parity was the main factor influencing the failure of labour induction (p < 0.001) [4]. In their study, Metrop et al. found a significant association of the parity, BMI and hypertension with the outcome of labour induction [5].

The age of the parturient influences the outcome of labour induction. Claramonte Nieto found a significant increase in the risk of caesarean section during labour induction in women ≥ 35 years of age, increasing with age and amounting to an OR of 1.79 (95% CI 1.50-2.14) for women aged 40-44 years and an OR of 3.95 (95% CI 2.66-5.98) for women aged ≥ 45 years, respectively [6]. Similar results were obtained by Marconi et al., who compared a delivery type in primiparas and multiparas. For primiparas, the risk of caesarean section increases progressively > 30 years of age and doubles at the age ≥ 40 years, whereas for multiparas, the risk only doubles for women aged ≥ 40 years compared to those giving birth aged 25-29 years [2]. In contrast, in their study Kwayke-Ackah et al. showed no effect of the age on the delivery type in primiparas [7].

The study shows an increase in caesarean section rates with increasing BMI regardless of the parity. According to Levine, the strongest prognostic adverse factor for successful labour induction is class III obesity /BMI ≥ 40/ [8]. In their study, Taoudi et al. showed that caesarean sections are performed four times more frequently in obese women than in normal-weight patients [9]. In contrast, Batinelli et al. did not associate the increased risk of caesarean section to patient's obesity [10]. In contrast, Menichini et al. found no difference in the rate of surgical deliveries depending on the obesity of a pregnant woman but noted a prolongation of the first stage of labour and total induction time at BMI ≥ 30 [11].

In our analysis, an association was found between failed labour induction and hypertension in pregnancy and ≥ 41 weeks' gestation, resulting in the highest caesarean section rates in these groups, of 52.63% and 38.96%, respectively. Mebratu et al. and Metrop et al. also point to hypertension

complicating pregnancy as a cause of failed labour induction [5, 12]. On the other hand, Tarimo et al. claim that independent factors for surgical induction of labour may include the first labour (RR = 1.46; 95% CI: 1.18-1.81) and post-term pregnancy (RR = 1.45; 95% CI: 1.09-1.93) [13]. McCoy et al. found a significantly increased risk of caesarean section in patients at ≥ 41 weeks' gestation compared to those at 37.0-40.6 weeks' gestation (46.8% vs. 26.0%, p < 0.001) [14]. Zhao et al. showed the highest rate of successful labour induction at 39 weeks' gestation, decreasing with later gestational age due to foetal distress symptoms [15].

The study showed the influence of foetal weight on the course of labour induction. In their study, Beshir et al. found weight < 3,500 g to be a predictor of a natural delivery during induction [16]. An association between failed labour induction and foetal weight > 3,500 g was also demonstrated by Tarimo et al. [13]. In contrast, Li et al. found no effect of foetal weight on the course of labour induction [17].

Analysis presented here demonstrated the relationship between maturity of the cervix and successful labour induction. Hosoya et al. found that labour induction may be successful with Bishop score > 6. [18]. Dorwal also showed a correlation between cervical maturity and the course of labour induction [4]. On the other hand, in their study Dîră et al. found no relationship between Bishop score and the delivery type until the end of the 41st week of gestation. After this time, they observed that the higher the Bishop score, the higher the chances of a natural delivery [19].

The most common indications for caesarean section in the present study were threatened intrauterine foetal asphyxia in 17.2% of inductions (59.68% of caesarean sections), followed by failure to progress in 6.07% (20.97% of caesarean sections) respectively. In the literature, the data are divergent: Senanayake et al. showed that the symptoms of foetal distress are an indication for surgical delivery in 58.3% of primiparas with induced labour and in 60.5% of multiparas, while the failure to progress was the reason for caesarean section in 25.9% of cases [20]. In contrast, Quach et al. in a study of a group of almost 3,000 women undergoing labour induction, more frequently observed a failure to progress (10.5%) as an indication for caesarean section compared to threatened intrauterine foetal asphyxia (7.6%) [21]. Also, Mayne et al. showed that the most common indication for caesarean section during induction was the failure to progress [22]. On the other hand, Zhao et al. found that among patients undergoing labour induction, the most common indication for caesarean section is foetal distress [15].

In the analysis presented here, preinduction of labour with dinoprostone most often resulted in surgical delivery, with a caesarean section rate of 63.16% (p=0.0005). The course of labour induced with misoprostol or dinoprostone was analysed by Jolivet et al. [23]. On the basis of her study, she concluded that the use of dinoprostone was associated with a significantly higher risk of caesarean section compared with misoprostol (aOR = 2.44; p = 0.003). In contrast, in a meta-analysis including 104 studies de Vaan et al. showed comparable rates of successful induction when using intracervical catheter with dinoprostone and a slightly increased risk of caesarean section after using catheter compared to misoprostol [24]. On the other hand, in their analysis Mlodawski et al. showed an increased risk of caesarean section and abnormal KTG recording for misoprostol compared to a cervical catheter [25]. Different results were presented by Blanc-Petitjean et al. with the highest rate of surgical deliveries after catheter use [26].

The course of labour induction depends on the method used. In the study presented here, the highest rate of surgical deliveries occurred after the use of prostaglandins. Similar results were obtained by Al-Hafez et al. The highest rate of caesarean sections was performed in the group of patients induced with prostaglandins compared to other methods, including oxytocin infusion and amniotomy (25.5% vs. 14.8%, AOR 1.80; 1.07–3.02) [27]. Kerr et al, on the other hand, showed a lower risk of surgical delivery after the use of misoprostol, compared to both dinoprostone (RR 0.84, 95% CI 0.78–0.90) and oxytocin (RR 0.67, 95% CI 0.50–0.90) [28]. In contrast, in their analysis Wei et al. observed a lower caesarean section rate after dinoprostone compared to oxytocin among patients with a Bishop score of 0-3. With a degree of maturity of the cervix of 4-6 on the Bishop score, the two methods are equivalent [29]. Zhang et al. compared misoprostol and oxytocin in labour induction, showing a lower caesarean section rate after misoprostol of 11.5% vs. 25.2% [30].

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MICROBIOME IN PANCREATIC FLUID – PRELIMINARY ANALYSIS OF PANCREATIC CYSTIC LESIONS

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Abstract:

Introduction and objective

One of the main precursory lesions for pancreatic carcinoma is a pancreatic cystic neoplasm. Differentiation between the various types of cysts is a clinical challenge. The microbiome colonizing the pancreatic cyst fluid is mostly unknown. The aim of the study was the microbiological assessment of pancreatic cysts compared with biochemical parameters and histopathological results.
Material and methods

30 patients with pancreatic cysts who undergoing surgery in 2022-2023 at the Department of General and Transplant Surgery, Medical University of Lodz, were enrolled in the study. Preoperative biochemical levels of blood parameters were analysed. Bacterial culture results were taken from the nasal vestibule, the skin of the groin, as well as from cyst fluid and bile (in case of cholecystectomy) and the histopathological reports were analysed.

Results

Mean age was 58.77±13.56 years. 10 patients (33.3%) had malignant lesions. 9 patients (30%) had positive cultures from cyst fluid. 6 patients (16.8%) had malignant conditions. *Enterobacter cloacae*, *Enterococcus faecium Staphylococcus spp* were found. In the malignant group, the patients were statistically significantly older (68.40±5.70 y vs. 53.95±13.86 y, p=0.004), tumour diameters were smaller (4.00±2.00 cm vs. 8.50±5.77 cm, p=0.003) and CA 19-9 level were higher (100.22±186.46 ng/ml vs. 12.35±16.08 ng/ml, p=0.045) than in the benign group.

Conclusions

The occurrence of specific types of bacteria in patients with malignant pancreatic cysts appears to be of significant clinical importance. Further studies are needed.

Keywords: pancreatic cystic neoplasm, microbiome, pancreatic cancer, bacterial culture.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive neoplasms. One of the main precursory lesions for PDAC are pancreatic cystic neoplasms (PCNs), including mucinous cystic neoplasm (MCN), intraductal papillary mucinous neoplasm (IPMN) and serous cystic neoplasm (SCN) [1, 2].

Due to the development of imaging techniques, the frequency of detecting pancreatic cystic tumours is increasing. It is estimated that pancreatic cystic tumours occur in 2% to 45% of the population [3]. Cystic lesions in the pancreas occur far more often than has been previously estimated [4].

Despite the novel diagnostic tools, differentiation between the various types of PCN is a significant clinical challenge [5]. The accuracy of identifying a specific type of pancreatic cystic tumour is between 40% and 95% for magnetic resonance imaging (MRI/MRCP) and between 40% and 81% for computer tomography (CT) [3]. Also, endoscopic ultrasonography (EUS) is not an optimal method to identify the type of pancreatic cystic tumour. Cytological analysis of the fluid from the cyst has 42% sensitivity and 99% specificity in differentiating mucinous and non-mucinous pancreatic cystic lesions [3].

As mentioned before, pancreatic cysts harbour the potential to develop into cancer. Currently, there are no optimal tools for this risk stratification, and identifying cysts that require complicated surgical treatment still remains a challenge. The risk of postoperative complications following pancreatic surgery is associated with a 30-40% morbidity rate and a 3-10% mortality rate [6]. Hence, the decision to operate should be clearly justified by the medical indicators, such as cancer diagnosis or a high risk of this cancer.

The microbiome colonizing of the pancreatic cyst fluid is mostly unknown. However, some of the microbiomes with potentially detrimental functions residing in the pancreatic cystic fluid may contribute to the neoplastic process [7]. A comprehensive understanding of this phenomenon for pancreatic cancer development in pancreatic cysts would be of great clinical significance.

Aim

The aim of the study was the microbiological assessment of pancreatic cysts in comparison with biochemical parameters and histopathological results.

Material and methods

The data were analysed retrospectively of 30 patients with pancreatic cysts, aged 27 to 76 years, who underwent surgery in 2022 to 2023 at the Department of General and Transplant Surgery, Medical University of Lodz. Informed signed consent for the operation and use of the data was obtained from all the patients. The bioethical commission of Medical University of Lodz approved this retrospective study (Number RNN/04/23/ KE dated 10th of January 2023)

Measured were the preoperative blood levels of haemoglobin, amylase, lipase, CRP, cancer markers (CA 19-9, CA 15-3, CEA, CA 125, AFP) and leukocytosis. Before surgery, cultures were also taken from the nasal vestibule and the skin of the groin.

During the surgery samples of pancreatic cyst fluid and bile (in case of cholecystectomy) were taken for microbiological analysis. These samples were taken for testing in a 5 ml syringe with a 5 mm needle (*ex vivo*). Bacterial cultures were performed in the bacteriology laboratory of the Barlicki Teaching Hospital in Lodz. Histopathological reports were also included and studied.

Statistical analysis was performed with the use of a commercially available statistical software package (Statistica 13.1 for Windows; StatSoft Poland Ltd.).

Continuous variables were expressed as mean ± SD, median, and minimum–maximum values. The normal distribution was verified with the Shapiro-Wilk test. The data was compared for statistical analysis using the Student's t-test to evaluate the differences between quantitative variables following a Gaussian distribution. Variables following a non-parametric distribution were compared with the Mann-Whitney test. Categorical data analysis was done using the Chi 2 test. Alpha < 0.05 was set as a threshold of statistical significance.

Microbiological procedures

Samples of bile and pancreas cyst fluid (PCF) were used for microbiological examinations. The inoculations were performed according to the EUCAST (European Committee on Antimicrobial Susceptibility Testing) guidelines (eucast.org). Tested specimens were inoculated onto a Columbia agar with a 5% sheep blood medium (bioM4rieux, Marcy l'Etoile, France) that supports the growth of a variety of bacteria, MacConkey agar with crystal violet (bioM4rieux, Marcy l'Etoile, France) which allows growth of only Gram-negative bacteria, and Sabouraud gentamicin chloramphenicol 2 agar (bioM4rieux, Marcy l'Etoile, France) which allows growth of fungi. The inoculations on Columbia agar and MacConkey agar were incubated at 35°C for up to 2 days, whereas the inoculations on Sabouraud agar were incubated at 35°C for up to 7 days. Bacterial and fungal species identification and susceptibility testing were performed using a VITEC®2 Compact (bioM4rieux, Inc. Hazelwood, MO, USA).

Results

A total of 30 adult patients (18 female and 12 male) were included in the study. Baseline variables are shown in Table 1.

Among the patients who had surgery, 11 (36.6%) underwent distal pancreatectomy with splenectomy, 3 (10%) underwent Whipple pancreatoduodenectomy, 5

Table 1. Baseline variables in the studied group.

Variable	Mean±SD	Median (IQR)	Min.	Max.
Age	58.77 ± 13.56	62.50 (47.00-68.00)	27.00	76.00
Size of tumour (cm)	7.00 ± 5.27	6.50 (3.00-10.00)	2.00	30.00
CA 19-9 (U/ml)	41.64 ± 112.85	7.90 (5.70-18.70)	0.80	567.10
CA 15-3 (U/ml)	42.32 ± 134.93	12.70 (6.10-16.70)	3.70	599.00
CA 125 (U/ml)	13.78 ± 14.35	8.80 (6.00-14.00)	4.60	65.60
CEA (ng/ml)	3.34 ± 7.25	1.25 (0.90-2.80)	0.40	35.10
AFP (ng/ml)	3.92 ± 2.92	2.65 (2.00-4.90)	0.90	10.10
Hb (g/dl)	13.26 ± 1.65	13.50 (12.60-14.00)	9.10	16.50
WBC (x103 /µl)	7.86 ± 3.75	6.80 (5.40-9.10)	3.60	20.10
CRP (mg/l)	15.89 ± 42.69	2.45 (1.30-6.70)	0.20	204.50
Amylase (IU/l)	80.04 ± 111.58	51.00 (35.00-94.00)	19.00	593.00
Lipase (U/l)	55.10 ± 62.52	29.00 (15.00-67.00)	4.00	277.00
Days of hospitalisation	12.27 ± 6.67	9.00 (8.00-17.00)	3.00	27.00

CA - cancer antigen, CEA - carcinoembryonic antigen, AFP - alpha fetoprotein, Hb - haemoglobin, WBC - white blood cell count, CRP - C-reactive protein, SD - standard deviation, IQR - interquartile range

16.6%) palliative surgery, 2 (6.6%) enucleation of the tumour, 4 (13.2%) operative percutaneous drainage and 5 (16.6%) anastomosis of the pancreatic cyst with the small intestine. Cholecystectomy was performed in 10 (33.3%) patients.

Mean age was 58.77 years (SD 13.56 years). The mean diameter of the tumour was 7.00±5.27 cm. In 5 patients (16.6%) the cyst was located in the head of the pancreas, in 11 patients (36.6%) in the corpus, and in 14 patients (46.6%) in the tail of the pancreas. In the postoperative examination, 10 patients (33.3%) had malignant lesions while the other 20 patients (66.7%) had benign cysts (Table 2).

Three patients (10%) had a negative culture taken from the nasal vestibule. In the rest of the participants, 24 had *Staphylococcus epidermidis*, three had *Staphylococcus aureus MSSA* and two had *Corynebacterium pseudodiphteriticum*.

Table 2. Histopathological results.

Type of tumour	Number of patients	Malignant
Pseudocyst	9	No
Inflammatory tumour	1	No
Choledochal cyst	1	No
Cystic pancreatic adenocarcinoma	4	Yes
IPMN without dysplasia	4	No
IPMN with neuroendocrine tumour G1	1	Yes
IPMN with moderate grade dysplasia	1	Yes
IPMN with high grade dysplasia	2	Yes
IPMN with carcinoma	1	Yes
Cystic neuroendocrine tumour G1	1	Yes
MCN without dysplasia	3	No
MCN with low grade dysplasia	1	No
SCN	1	No

IPMN - intraductal papillary mucinous neoplasm, G1 - grade 1, MCN - mucinous cystic neoplasm, SCN - serous cystic neoplasm

In the skin of the groin, three cultures were negative, in twenty-four cases *Staphylococcus epidermidis* was detected, in three cases *Staphylococcus aureus* and in one case *Corynebacterium pseudodiphteriticum*.

Four patients out of the ten undergoing cholecystectomy had a positive culture: in three cases *Escherichia coli*, in one *Klebsiella pneumoniae*, in one *Enterobacter cloacae* and in one *Enterococcus faecium VRE* (*Vancomycin-Resistant Enterococcus* resistant to ampicillin, imipenem, levofloxacin).

Nine patients had a positive culture from the cyst fluid: one *Corynebacterium*, one *Klebsiella pneumoniae*, one *Staphylococcus aureus*, one *Staphylococcus epidermidis*, one *Enterobacter cloacea*, one *Enterococcus faecalis*, one *Escherichia coli*, one *Enterococcus faecium VRE*, one *Staphylococcus capitis* and one *Staphylococcus haemolyticus*.

Patients were divided into the benign and malignant cyst groups according to the postoperative histopathological result and into positive and negative culture groups according to bile and pancreatic cyst fluid culture result. In the group having a benign cyst the tumour diameter was larger than in the malignant group (8.50±5.77 cm vs. 4.00±2.00 cm, p=0.003). The difference was statistically significant. In the malignant group the patients were older than in the benign group (68.40±5.70 y vs. 53.95±13.86 y, p=0.004). CA 19-9 level was higher in the malignant group than in the benign group (100.22±186.46 U/ml vs. 12.35±16.08 U/ml, p=0.045),
which was statistically significant. In the negative culture group, the AFP level was statistically significantly higher than in the positive culture group (4.56±2.99 ng/ml vs. 1.68±0.84 ng/ml, p=0.038).

Discussion

In the current study, it was established that in 9 out of the 30 (30%) patients the PCF samples harboured a microbiome. It is especially worth noting that 6 of these patients had malignant conditions (Table 3).

Table 3. Microbiome and tumours.

	Microbiome found in PCF (Pancreatic Cystic Fluid)	Neoplasm (Benign/ Malignant)
1	Corynebacterium	Benign
2	Klebsiella pneumoniae	Benign
3	Enterobacter cloacae resistant to amoxicillin, clavulanic acid, and cefuroxime axetil	**Malignant**
4	Enterococcus faecalis susceptible to ampicillin, gentamicin HC, teicoplanin, vancomycin, and linezolid, Escherichia coli resistant to amoxicillin and clavulanic acid mic 16	**Malignant**
5	Staphylococcus epidermidis resistant to erythromycin and clindamycin	**Malignant**
6	Staphylococcus capitis not resistant	**Malignant**
7	Enterococcus faecium HLAR linezolid mic 2	Benign
8	Staphylococcus aureus	**Malignant**
9	Staphylococcus haemolyticus tetracycline mic 2, tigecycline mic 0.25, and vancomycin mic 2	**Malignant**

mic - minimum inhibitory concentration

A total of 10 patients out of 30 had malignant conditions, and in 4 out of the 10 patients no microbiota was found in their PCF.

In a previous study [7], *Bacillus*, *spp. Fusobacterium*, *Acinetobacter spp.*, *Anaerococcus spp.*, *Staphylococcus spp.*, *Escherichia spp.*, *Faecal bacterium*, and *Shigella* (among others) were confirmed in the PCF. Patients with both malignant and benign cysts (IPMN, pseudocysts, MCM, and SCA) participated in this study. Likewise, *Staphylococcus spp*, *Escherichia spp.*, and *Faecal bacterium* were found in the group of patients in this study.

So far, the human gut microbiome was suggested to be an important environmental factor linked to the development of different intestinal and extra-intestinal malignancies [8-10]. In the stomach, *Helicobacter pylori* can initiate a cascade of molecular events finally leading to cancer. In the colon, *Fusobacteria nucleatum* has been linked to the mucosal dysplasia [10].

Furthermore, *Fusobacterium nucleatum* was found in pancreatic cyst fluid [7, 11] and was associated with the transformation of LGD (low-grade dysplasia) IPMN to HGD (high-grade dysplasia). *F. nucleatum* is a gram-negative, anaerobic oral bacteria that commonly resides in saliva. Equally, we found the presence of a well-known group of bacteria, *Staphylococcus*, in the fluid of pancreatic cysts with a malignant potential.

Only few studies worldwide have demonstrated that bacteria in the pancreatic fluid can render cancer chemotherapy less efficient since it can metabolize anticancer drugs [12, 13]. In a previous study on mice, the pancreatic cancer became resistant to gemcitabine [14], a commonly used drug in many countries for the treatment of PDAC. Various bacteria, including, *Enterobacter cloacae*, *Klebsiella pneumonia*, and *Escherichia Coli*, responsible for this resistance, were found in the examined pancreatic microbiome. These studies highlight the significance and importance of further analysis of the microbiome in pancreatic lesions.

Conclusion

In our one-centre retrospective study, the confirmed presence of specific types of bacteria in patients with malignant pancreatic cysts appears to be of significant clinical importance. Further studies to assess pancreatic cysts microbiomes and its influence on cancerogenesis are needed.

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DIAGNOSTIC AND THERAPEUTIC DIFFICULTIES IN AN ELDERLY PATIENT WITH RHEUMATOID ARTHRITIS, SEPSIS AND LISTERIA MONOCYTOGENES MENINGITITIS

Trudności diagnostyczne i terapeutyczne u starszego chorego z reumatoidalnym zapaleniem stawów, sepsą oraz zapaleniem opon mózgowo-rdzeniowych o etiologii *Listeria monocytogenes*

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Abstract: *Listeria monocytogenes* is a gram-positive, intracellular bacterium of the *Corynobacteriaceae* family, rod-shaped, relatively anaerobic, and ubiquitous in the environment. *Listeria monocytogenes* is the bacterium that causes a disease called listeriosis that may take place under the form of mild, self-limiting infections or severe, life-threatening ones. In this article, we present the case of an 81-year-old patient with impaired consciousness, admitted to the Department of Nephrology with suspected urosepsis. The patient was treated with immunosuppressant (methotrexate) due to rheumatoid arthritis. He did not present meningeal symptoms, had a high fever, and his clinical status during admission was unclear. *Listeria monocytogenes* was identified in both blood and cerebrospinal fluid cultures. Despite intensive antibiotic therapy, the patient's condition failed to improve. Due to circulatory and respiratory failure, he required mechanical respiratory support and continuous 33-day care in the Clinical Intensive Care Unit and, after extubation, further rehabilitation and treatment in the Nursing and Treatment Institution (ZOL). The presented case of the patient shows the diagnostic and therapeutic difficulties of a *Listeria monocytogenes* infection in an elderly person treated with immunosuppressive therapy.

Streszczenie: *Listeria monocytogenes* to Gram-dodatnia wewnątrzkomórkowa bakteria z rodziny *Corynobacteriaceae* o kształcie pałeczki, względnie beztlenowa, powszechnie występująca w środowisku. *Listeria monocytogenes* jest bakterią wywołującą chorobę zwaną listeriozą i mogącą przebiegać od łagodnych infekcji ulegających samoograniczeniu, do ciężko przebiegających zakażeń zagrażających życiu. Przedstawiamy przypadek 81-letniego pacjenta z zaburzeniami świadomości przyjętego do Kliniki Nefrologii z podejrzeniem urosepsy. Chory leczony był immunosupresyjnie metotreksatem z powodu reumatoidalnego zapalenia stawów. Pacjent nie prezentował objawów oponowych, wysoko gorączkował, a obraz kliniczny w chwili przyjęcia był niejasny. Zarówno w wykonanych posiewach krwi, jak i płynu mózgowo-rdzeniowego zidentyfikowano *Listerię monocytogenes*. Pomimo prowadzonej intensywnej antybiotykoterapii stan pacjenta nie poprawiał się. Z powodu niewydolności krążeniowo-oddechowej wymagał wspomagania mechanicznego czynności oddechowej i kontynuacji opieki przez 33 dni w Klinicznym Oddziale Intensywnej Terapii, a po ekstubacji – dalszej rehabilitacji i leczenia w Zakładzie Opiekuńczo-Leczniczym (ZOL). Przytoczony przypadek chorego pokazuje trudności diagnostyczne i terapeutyczne jakie stanowi zakażenie *Listerią monocytogenes* u osoby w starszym wieku leczonej immunosupresyjnie.

Keywords: sepsis, immunosuppression, listeriosis, Listeria monocytogenes, meningitis.

Słowa kluczowe: sepsa, immunosupresja, listerioza, Listeria monocytogenes, zapalenie opon mózgowo-rdzeniowych.

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Introduction

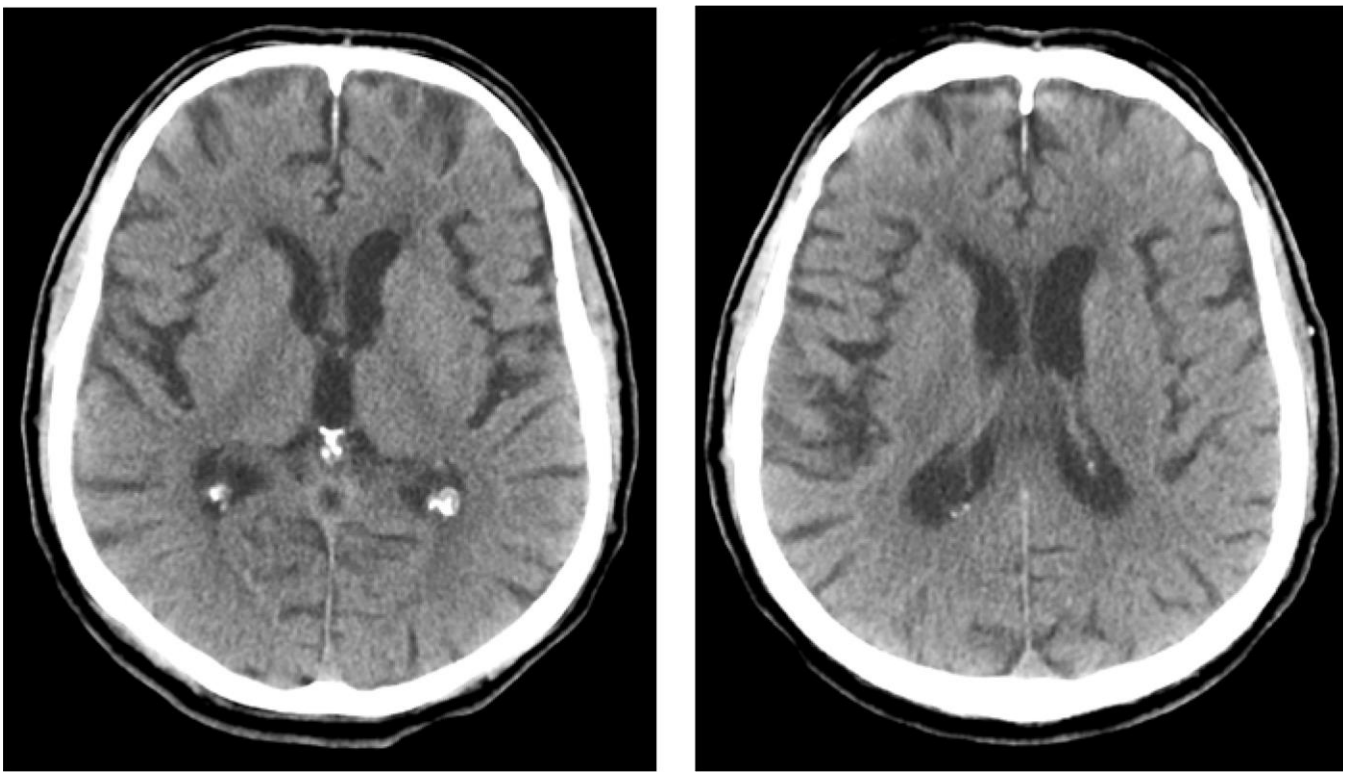
Listeriosis is a rare infectious disease caused by *Listeria monocytogenes*. Its natural environmental niche is soil, from which it is transmitted to plants and animals. Agricultural activities play an important role in the circulation of the bacteria in the environment [1]. Listeria colonizes the gastrointestinal tract, turning some animals and about 5% of the human population into asymptomatic carriers. Infection usually takes place via the gastrointestinal route

by the ingestion of contaminated food and, less commonly, through damaged skin, respiratory mucous membranes, conjunctiva, placenta, or the birth canal during childbirth [2]. The most commonly contaminated products include unpasteurized milk, cheese, smoked fish, eggs, pork, frozen foods, raw fruits and vegetables, and delicatessen products. The size of the infectious dose depends on the age, gender (over the age of 65, men are more likely to suffer from the disease), the health of the host and the type of food contaminated with *L. Monocytogenes* [3]. In healthy individuals, the symptoms mimic a flu-like infection, with additional joint pain, drowsiness, vomiting and moderate diarrhoea [1, 2]. The severe course of the infection usually affects those with immune systems impaired due to illness, pregnancy, and often as a result of taking immunosuppressive drugs. It may lead to sepsis, neuroinfections and, in some cases, to the formation of microabscesses in the brain. Infection may also affect the eye, skin, bones, joints, heart muscle, endocardium, lymph nodes, peritoneum, liver (inflammation, abscesses) [2, 4, 5]. Symptoms of the disease can appear as early as 2 days and as late as over 2 months after the start of the infection [2].

Case study

An 81-year-old patient with chronic kidney disease (CKD), type 2 diabetes treated with oral medications, rheumatoid arthritis (no documentation, the family was informed about ongoing treatment with methotrexate), was brought to the ED by the Emergency Medical Team due to consciousness disturbance. The patient had not left his room after a night's sleep and had been found on the floor, in a severe general condition, unconscious; it was not clear how long he had remained in this condition. Tests performed showed: elevated inflammatory markers (leukocytosis 24.9 x 10^9/l with neutrophil smear, CRP: 23.5 mg/dL, procalcitonin (PCT) level 2.91 ng/mL), impaired renal function (creatinine: 3.0 mg/dL), rhabdomyolysis markers (CK: 4385), INR 2, and a urinalysis which revealed leukocyturia. A computed tomography (CT) scan of the head showed no signs of intracranial haemorrhage; the examination revealed focal hypodense lesions in the white matter and periventricular diffuse hypodense areas. The ventricular system was asymmetrical, not displaced, dilated. The patient was consulted by a neurologist; no meningeal or focal neurological signs were found. The patient was admitted to the Department of Nephrology with suspected urosepsis. On admission, the patient was circulatorily and respiratorily stable, but with limited verbal and logical contact. He had a fever of almost 39°C. Broad-spectrum antibiotics, meropenem and ciprofloxacin were immediately administered. On the day of admission, the patient had his first epileptic seizure, his condition deteriorated, and fever persisted. Metronidazole was added to the treatment for the prophylaxis of aspiration pneumonia. A lumbar puncture was performed with a collection of cerebrospinal fluid for general examination. It revealed the presence of protein (167.6 mg/dL), elevated cytosis (70/uL - mononuclear cells 57.1%, multinuclear cells 42.9%), glucose within normal limits (66 mg/dL). Cerebrospinal fluid and blood cultures contained *Listeria monocytogenes*. A specialist in infectious diseases was consulted in relation to the patient, and ampicillin was added to meropenem. Despite the ongoing epilepsy treatment, seizures and apnoea were observed. The patient was intubated, ventilator respiratory support was applied, a norepinephrine infusion was started, and the patient was transferred to the Intensive Care Unit for further treatment.

Figure 1, 2 CT scan of the patient's head on admission.



As a result of treatment, the inflammatory parameters decreased, and control blood cultures were found to be sterile.

Despite the resolution of the features of infection, verbal and logical contact did not return. After several months of hospitalization, the patient, breathing efficiently with a tracheostomy, cardiovascularly stable and fed through a PEG, was transferred to the Nursing and Treatment Institution (ZOL) for further care and nursing.

Discussion

In recent years, there has been a systematic increase in *Listeria monocytogenes* infections in Poland [3]. Sepsis and meningitis are the most common forms of listeriosis [6]. Meningitis or meningoencephalitis accounts for as much as 70–97% of infections caused by Listeria in humans. The ability of this bacterium to cause both encephalitis and acute meningitis distinguishes it from other pathogens responsible for meningitis (such as *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae*), while it shows some similarity in this regard to the pathogenicity of *Mycobacterium tuberculosis* [7]. In their study, involving 30 patients with immunodeficiency or over the age of 50 with meningitis of *L. Monocytogenes* aetiology, Brouwer et al. showed that only 43% (13 of the 30 patients studied) of the patients with positive CSF cultures exhibited the classic triad of symptoms: fever, neck stiffness, and impaired consciousness. On the other hand, a CSF examination revealed the presence of *L. monocytogenes* in only 24% of patients, a significantly lower proportion compared to neuroinfections caused by other pathogens (80% of patients) [8]. The above studies are confirmed by the described case: the patient did not present meningeal symptoms, which delayed the diagnostic process.

The mechanisms of simultaneous meningitis and encephalitis can be twofold: the infection may spread by crossing the blood-brain barrier or by further spread of central nervous system infection [7]. The mortality rate in listeriosis meningitis is 30–40% [9]. Neurological complications occur in about 15% of those cured [9]. Brain abscesses (about 10%) are another, somewhat less common complication of neurolisteriosis. They are usually located in the subcortical regions, thalamus, pons, and medulla [7]. Encephalitis and brainstem encephalitis manifest themselves as progressive brainstem dysfunction. The initial stage manifestations (the first few days) of the infection may take the form of headaches, deterioration of well-being, nausea, and vomiting, then, the next stage involves cranial nerve damage and cerebellar symptoms, paresis, sensory disturbances, and meningeal symptoms. Surprisingly, brainstem infection occurs mainly in patients without predisposing factors [7]. Central nervous system lesions are frequently accompanied by behavioural disorders and epileptic seizures [2]. The antibiotic therapy with intravenous ampicillin or amoxicillin is the treatment of choice. Alternatively, sulfamethaxazole (in patients allergic to penicillins), vancomycin, meropenem, linezolid, and rifampicin are administered [5, 10]. Most strains are resistant to cephalosporins and fosfomycin, but there are also strains resistant to: ampicillin, vancomycin, gentamicin, clindamycin, tetracycline, macrolides, ciprofloxacin and others [5]. In patients with impaired cellular immunity, vancomycin is used with ceftriaxone and ampicillin [6]. The patient developed the infection due to severe medical conditions that can lead to opportunistic infections. The patient was an elderly person, treated for RA with methotrexate, and had type 2 diabetes.

Listeria infections are reportable in Poland [4]. In 2018, 131 infections were registered (99.2% required hospitalization), while a few years earlier (2010) there were far fewer of them, at only 64 [11].

Conclusion

It is difficult to diagnose neuroinfections in elderly patients in the department of internal medicine due to consciousness disorders in the course of various diseases, including infectious and metabolic diseases (e.g. encephalopathy in sepsis). Such symptoms as delirium or coma without neurological deficits may precede the diagnosis of sepsis by 1-2 days, and are not due to direct CNS infection, but are the result of multiple mechanisms, including: the influence of inflammatory cytokines, cerebral microdamage, microcirculatory disturbances, cerebral circulation, neurotransmission, etc. [9]. The discussed case shows that there is a need to consider rare aetiological agents, such as *Listeria monocytogenes*, in the differential diagnosis of infections presenting central nervous system symptoms, especially in patients with immunodeficiency or at an old age.

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A RARE CASE OF HERPES ZOSTER OPHTHALMICUS WITH THE ONSET PRESENTING AS A HEADACHE

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Abstract: The article presents a rare case of herpes zoster ophthalmicus with a headache as a first symptom, and discusses the clinical presentation, diagnosis and treatment in the context of clinical experience and the published literature.

Keywords: herpes zoster virus ophthalmicus, varicella-zoster virus ophthalmicus.

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Introduction

Herpes Zoster Ophthalmicus (HZO) is an eye infection caused by a localised reactivation of latent Varicella-Zoster Virus (VZV), also known as Human Herpesvirus 3 (HHV-3), present in the sensory ganglion and extending along the ophthalmic branch of the fifth cranial (trigeminal) nerve [1]. HZO develops in approximately 10% to 25% of all treated cases of herpes zoster infection, but affects 50% of all cases when the antiviral treatment is not readily available [2, 3]. The first exposure to the virus causes the primary infection, which is chickenpox and occurring mostly in children [4]. Afterwards, VZV is maintained in the latent state by VZV-specific T cell-mediated immunity and is reactivated under favourable conditions of decreased immunity due to infection, age, treatment with immunosuppressants, or inflammation [5]. After reactivation, VZV is highly contagious, and may be transmitted via aerosols or by direct contact with infected tissues [1, 2, 4].

Prodromal symptoms are usually present, including pain or tingling in the forehead, fever, headache, malaise and chills. The initial and characteristic symptom is unilateral hyperesthesia or paraesthesia of the skin within the affected area. This area is then covered by the rash, which evolves through the macular, papular, vesicular, and pustular stages before it scabs over [3]. Other common HZO symptoms include painful and severe eyelids and corneal oedema, ocular pain, conjunctival, episcleral, and circumcorneal conjunctival hyperaemia (ciliary flush) and photophobia [6]. HZO may affect all eye tissues and structures, causing keratitis, scleritis, uveitis, trabeculitis, choroiditis, acute retinal necrosis, optic neuritis, nerve palsies, and cavernous sinus thrombosis [3].

Clinical diagnosis of HZO is based on history and the findings from physical and slit-lamp examinations. In rare cases, viral cultures, polymerase chain reaction (PCR), and antibody testing, are required for diagnosis. Other tests, such as tonometry and corneal esthesiometry, may also be needed to assess the risk of complications [6].

Treatment is based on topical and if needed systemic antiviral agents, such as acyclovir, valacyclovir, and famciclovir. Mydriatics and topical corticosteroids are also in use [2].

Below is presented a case of patient with HZO with an unusual initial presentation.

Case report

A 77-year-old generally healthy man attended the Emergency Department (ED) late at night with an unspecific, generalised headache and mild pain in his right eye which persisted for 2 days. He denied a history of any recent injury or accident. He had lost his left eye as a result of a childhood injury, and had an ocular prosthesis in the left orbit.

On an ocular examination, the best corrected visual acuity (BCVA) in the right eye was 20/25, the intraocular pressure (IOP) was 19 mmHg with full visual field and normal eye movements, not limited by pain. In the slit lamp biomicroscopy, the bulbar conjunctiva was pale, the cornea was transparent, smooth and clean. The anterior chamber was quiet. The pupil was mildly dilated, with normal pupillary reflex. The lens showed a degree of opacity and was otherwise normal. The fundus exam revealed an orange-pink optic disc with distinct, smooth margins and a

cup to disc ratio of 0.9, vasculature adequate for age, attached retina and absent foveal reflex.

The unremarkable ocular examination prompted a neurological consultation and another ophthalmic examination to ascertain any new signs and symptoms occurring overnight. The patient left the ED in the morning, pain free, but he returned 3 days later with palpebral oedema and erythematous vesicular rash on the right side of his forehead and right eyelids, but without visual impairment. He was initially prescribed oral acyclovir 800 mg p.o. 5 times a day and instructed to clean the skin lesions with skin disinfectant and apply ichthammol ointment twice a day. He was also admitted as an inpatient to the dermatology ward due to facial involvement with fluid-filled vesicles typical of HZO. As the laboratory tests revealed a serum level of C-reactive protein (CRP) of 3.0 mg/dl (the upper normal limit is 0.8) and procalcitonin (PCT) of 0.21 ng/mL, oral acyclovir was substituted with intravenous injection at 10 mg/kg and oral doxycycline 200 mg once a day. Another 3 days later, in another ophthalmic examination, the palpebral oedema was still visible, alongside blepharostenosis, with fully preserved eye movements. Topical medications were added, including ofloxacin eye drops, vitamin A eye ointment and sulfathiazole ointment for external use.

On day 9 following the initial visit, corneal epithelial defects were identified on slit lamp biomicroscopy without other abnormalities. On day 12. following the initial visit, the man was discharged home on oral acyclovir 800 mg to be taken 5 times a day for the next 12 days and ofloxacin eye drops as well as vitamin A eye ointment to be applied 4 times a day. Detailed recommendations were provided regarding the skin care regimen to be followed twice a day, including cleaning all skin lesions with skin disinfectant and applying ichthammol ointment. An emollient cream was recommended for the face and head skin, alongside the recommendation to use sun protection, ensure proper hydration and nutrition. Follow-up ophthalmology and neurology appointments were also scheduled.

The eye examination on day 19, following the initial ED visit, was largely unremarkable, except for mild corneal oedema visible in the slit lamp biomicroscopy. Topical treatment was modified to corneal dehydration eye drops 4 times a day and hydrocortisone eye drops twice a day. Additionally, the neurologist diagnosed the patient with postherpetic neuralgia, prescribing a combination of tramadol (37.5 mg) and paracetamol (325 mg) PRN, as well as gabapentin (400 mg once a day) for pain relief. The most recent ophthalmology follow-up appointment only yielded the diagnosis of blepharitis, so dexpanthenol-containing eye drops were prescribed to be used 3 to 4 times per day.

Discussion

The typical course of HZO seen in most cases of latent virus reactivation in the trigeminal ganglia causes flulike symptoms of fatigue, malaise and low-grade fever, which can precede the onset of a skin rash by up to a week. In some cases, however, HZO may start with a headache (generalised or cluster), without the above prodromal symptoms. This was the case with our patient, and a few similar cases have been published to date, concerning children and adults [7, 8].
While not uncommon itself, HZO has some detrimental consequences, which makes it a potentially dangerous infection. If detected late, it may lead to chronic ocular inflammation, a disabling pain as the infection spreads along the ophthalmic branch of the nerve and even vision loss [6]. In the presented case, our key objective was to prevent vision loss, as the man's only eye was affected, so the treatment decisions were made accordingly.

The aim of treatment in HZO is three-fold and includes managing the acute viral infection, controlling the acute pain, and preventing postherpetic neuralgia [5]. The standard antiviral treatment, involving oral acyclovir administered at a dose of 800 mg five times a day, should be continued for 7 to 10 days [2]. Intravenous acyclovir is recommended, especially in immunocompromised patients [9]. In the reported case the decision to switch from oral to intravenous acyclovir was guided by the need to protect the only eye of the patient and it, indeed, prevented potentially damaging ocular manifestations. If the treatment is commenced within the first 72 hours following the onset of symptoms, it may accelerate the rash resolution, reduce pain, limit the spread of the virus, lead to a milder postherpetic neuralgia, or prevent it, as well as decrease the risk of dendritic and stromal keratitis, and anterior uveitis [5]. In some cases, antibiotics are administered to prevent secondary bacterial infection. This was true in the above case – topical ofloxacin and oral doxycycline were used, considering the patient's age and the fact that it was his only eye. Topical and systemic corticosteroids may be used in cases with a favourable risk to benefit ratio [6]. Their effect is two-fold, as not only do they help to control inflammatory response to VZV infection, but additionally become a part of the pain management strategy. In line with that, the above patient was treated with hydrocortisone eye drops to help manage his ocular pain.

Pain in HZO, both acute and chronic, can be really debilitating, affecting the quality of life to a degree comparable to myocardial infarction, major depression, or type 2 diabetes mellitus [10]. Acute pain is managed with local agents. However, topical anaesthetics should not be prescribed due to their corneal toxicity [2]. Oral analgesics may also be needed. The described patient experienced the pain of headache as his first (and main symptom), followed by neuralgia. Pain management was, therefore, used accordingly and neurology referral was made early.

Neurology follow-up plays an important role, due to possible postherpetic neuralgia which affects approximately 7% of all patients with HZO [5]. It involves constant or intermittent pain in the distribution of the affected dermatome, which may last for months or years, generally improving with time [3]. It is seen more often in older patients and those with pronounced prodromal symptoms, which means that the male discussed above met only one of those criteria, as he did not report the usual

prodromal non-specific symptoms of a developing infection. In some cases, HZO may lead to cranial nerve palsies, typically involving the third, fourth, and sixth cranial nerve [5, 11]. Treatment involves topical capsaicin cream, analgesics, tricyclic antidepressants and, sometimes, anticonvulsants [11]. Treatment of our patient reflected those principles as well.

It is generally believed that the age and immune status predispose people to develop HZO and its sequelae, as well as affecting their severity [12]. However, the paper by Campos et al. [7], who reported HZO followed by postherpetic neuralgia and two severe flare-ups, in an immunocompetent 8-year-old girl, appears to demonstrate that it is not always the case. Similarly, the research suggests that the prevalence of HZO in females is higher than in males [13]. Our patient is a male, and while he falls into the age category where shingles would be normally included in differential diagnosis granted the typical presentation, he did not have any significant underlying diseases making him unusual for his age group. This suggests the need for vigilance to identify cases with more 'atypical' presentations.

Conclusions

Each suspicion of HZO, in primary care or elsewhere, should prompt an urgent ophthalmology referral, as the involvement of an ophthalmologist is crucial. Physicians need to be vigilant, as the presentations may vary on onset. Rapid treatment commencement may help to avoid vision-threatening and neurological sequelae. Patients with HZO require interdisciplinary care and regular follow-up appointments.

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CASE REPORT

PNEUMATOCELE IN A COVID-19 PATIENT
PNEUMATOCELE U PACJENTA Z COVID-19

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Abstract: A patient with coronavirus disease 2019 (COVID-19), treated in a temporary hospital, presented symptoms of sudden respiratory failure, which in imaging studies indicated pneumothorax as the cause. The thoracic surgical intervention involving drainage of the pleural cavity initially brought the desired effect, but only for a short time. In the following days, new pneumothorax chambers requiring drainage were formed, due to pneumatocele as it was discovered on a CT scan. Drainage of life-threatening pneumatocelular pneumothorax is a minimally invasive and sufficient treatment procedure in COVID-19, and computed tomography should be a standard for symptoms of respiratory failure in already drained patients.

Streszczenie: Pacjent z chorobą koronawirusową 2019 (COVID-19) w szpitalu tymczasowym zaprezentował objawy nagłej niewydolności oddechowej, co w badaniach obrazowych wskazywało na odmę opłucnową jako przyczynę. Interwencja torakochirurgiczna, polegająca na drenażu jamy opłucnej, początkowo przyniosła pożądany efekt, ale tylko na krótki czas. W kolejnych dniach powstały nowe komory odmy opłucnowej wymagające drenażu, jak się okazało w tomografii komputerowej, z powodu pneumatocele. Drenaż zagrażającej życiu odmy opłucnowej jest minimalnie inwazyjną i wystarczającą procedurą leczenia COVID-19, a tomografia komputerowa powinna być standardem w przypadku objawów niewydolności oddechowej u już zdrenowanych pacjentów.

Keywords: thoracic surgery, covid-19, pneumothorax, pneumatocele.

Słowa kluczowe: torakochirurgia, covid-19, odma opłucnowa, pneumatocele.

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Introduction

Since the beginning of the pandemic, the SARS-CoV-2 virus infection has been an interdisciplinary challenge. Many papers, including case reports, have been published outlining the continuously updated guidelines for the diagnosis, treatment, and control of the *coronavirus disease 2019* (COVID-19). When a thoracic surgical procedure was necessary, there was no single treatment regimen, and only case reports were published [1].

Pneumatocele are air chambers that can form *de novo* during pneumonia and predispose the individual to the formation of pneumothorax chambers [2]. Their origin is not fully known, and some authors claim that they result from necrosis of the airway wall [3]. Retrospective studies show that a spontaneous pneumothorax occurs in 1% of hospitalised COVID-19 patients and in about 2% of COVID-19 patients in the Intensive Care Unit (ICU) [4, 5].

Only a few case reports have been found worldwide in non-intubated patients who, despite not receiving continuous positive airway pressure (CPAP) treatment, developed a spontaneous pneumothorax. Yet in such cases, the pneumothorax resolved after conservative treatment or drainage, and the patient left the hospital within several days [1, 6, 7].

The case referred to in our paper differs significantly from those described to date, as it highlights the non-standard

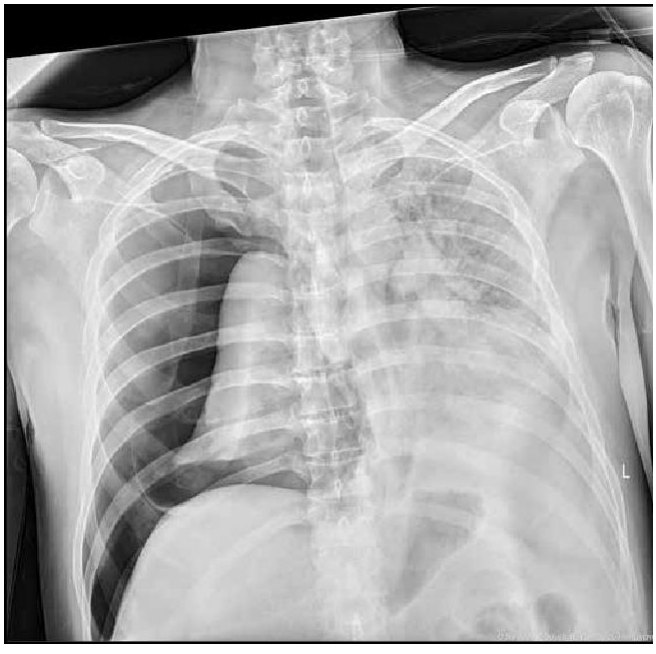
course of the disease and indicates the dynamics of COVID-19 management.

Case study

A 45-year-old patient, unvaccinated against COVID-19, presented to the Hospital Emergency Department on account of worsening dyspnoea in the course of SARS-CoV-2 infection confirmed by an antigen test two days before. His symptoms included cough, sore throat, and fever up to 38.5° Celsius persisting for 10 days. There was a history of hypertension treated with valsartan and bisoprolol, and overweight Body Mass Index (BMI) of 28.63 kg/m^2 (abdominal obesity). On admission he was in average condition, with preserved verbal-logical contact, pulse oximetry saturation without oxygen therapy was 80%, respiratory rate 20 breaths/min, blood pressure 129/87 mmHg, and heart rate 97 beats/min. Laboratory tests revealed: slightly elevated inflammatory markers without leukocytosis, neurocytosis, lymphopenia and eosinophilia. Liver parameters, coagulogram and fibrin degradation products were within normal value ranges. A contrast-enhanced chest CT scan showed ground-glass opacity and 65% of the lung parenchyma affected by the disease process (COVID scale 16/25). No signs of pulmonary embolism were detected. After passive oxygen therapy, saturation was 88%. Medicinal treatment was implemented: Remdesivir, Ceftriaxone, and Dexamethasone; then, due to no clinical improvement, the patient was started on Tazobactam and Piperacyline, Ciprofloxacin and Baricitinib. The pharmacotherapy complied with the guidelines in force at the time. Antithrombotic prophylaxis was administered throughout the hospitalisation.

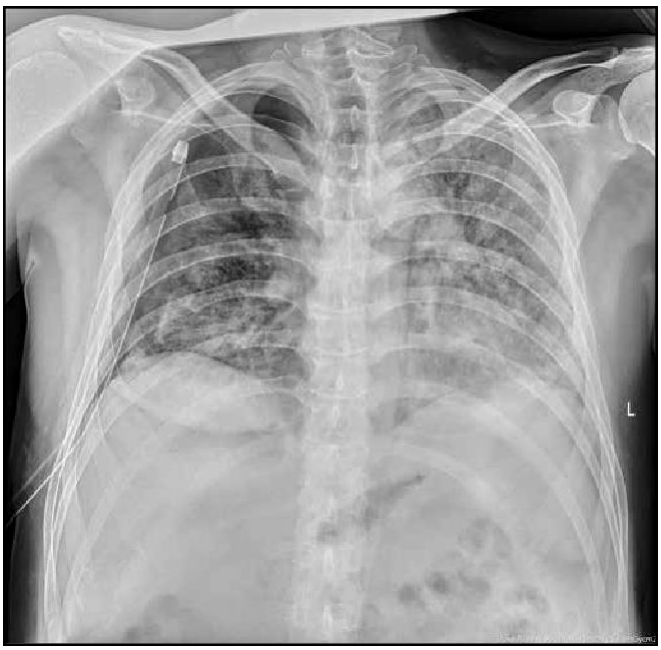
On the first day of treatment, the patient experienced a saturation drop to 80% with average clinical conditions. The patient reported dyspnoea and weakness. With a respiratory rate of 15 breaths/min, treatment with high flow nasal oxygen therapy (HFNOT) with a flow rate of 60 l/min was implemented and a satisfactory saturation from pulse oximetry of 94% was achieved. After 14 days, oxygen therapy was changed to a simple mask.

Figure 1. X-ray before drain insertion.



On the day of discharge, the 25th day of treatment, the patient reported girdle pain on the right side of the chest and dyspnoea. Significantly diminished vesicular sound was detected on auscultation over the right lung. The respiratory rate was up to 40 breaths/min and the saturation was 80%. Laboratory tests revealed B-type natriuretic peptide (NT-proBNP) 1227 pmol/L [68–112 pmol/L]. An urgent chest X-ray revealed an 80-mm-wide pneumothorax. After drainage of the right pleural cavity, a clinical improvement was achieved, and a normal vesicular sound was heard over the right lung on auscultation. The saturation was 96%, while the respiratory rate dropped to 20 breaths/min.

Figure 2 X-ray after drain insertion.

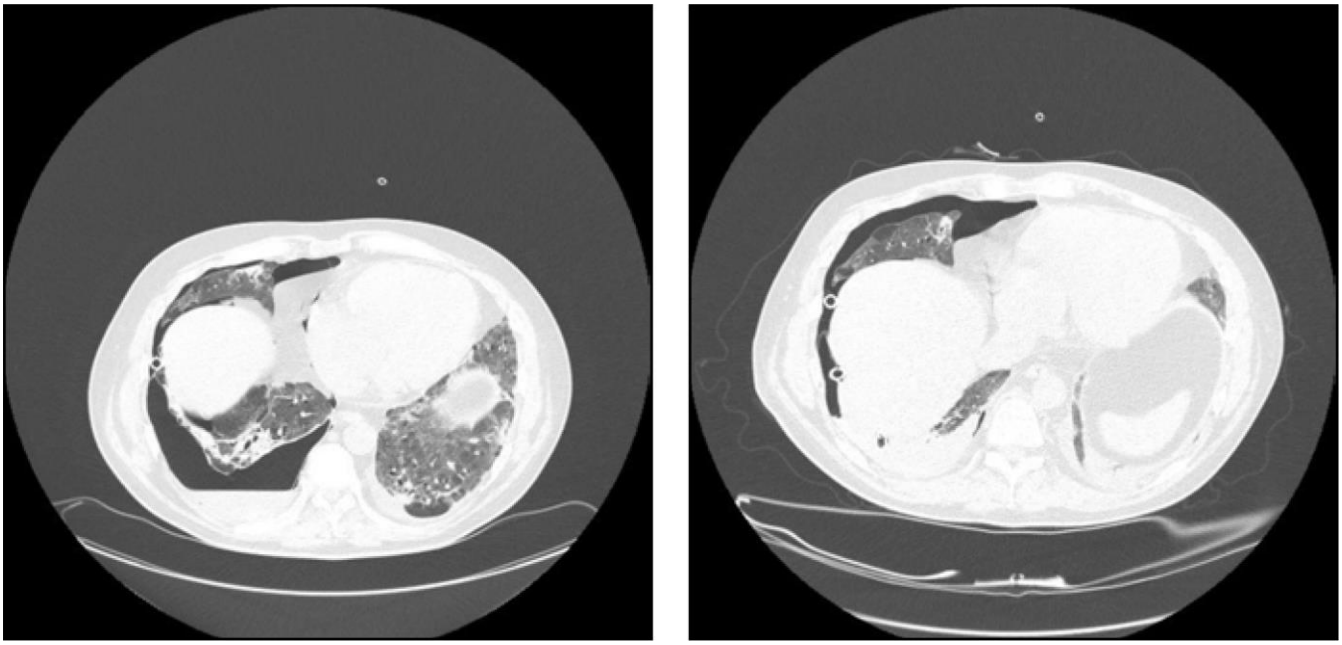


During follow-up, the condition worsened again with desaturation down to 80%. A chest CT scan showed a pneumothorax chamber that was not covered by the range of the chest tube placed 3 days before, as well as numerous smaller air chambers. A second drain was placed in the right pleural cavity in the posterior axillary line and clinical improvement was achieved, with a pulse oximetry saturation of 95%.

Nine days after the first drain insertion, the patient's condition was improved enough that a decision was made to remove both drains.

Four days later, a physical examination revealed diminished vesicular sound over the right lung in the posterior axillary line, with a relatively good clinical condition with no other physical abnormalities. A chest CT scan revealed a 100-

Figure 3 CT scan of the patient's chest.



(A) Visible drain and a posterolateral pneumothorax chamber, pneumatocele forming. B) Status post insertion of a second drain into the pleural cavity, multiple pneumatoceles visible.

mm-wide pneumothorax chamber. A decision was made to transport the patient to a referral centre with thoracic surgery facilities, where another chest drain was inserted on the right side.

After 14 days of observation at the reference centre, the patient was discharged in good general condition with a Heimlich valve (a one-way valve to prevent the return of contents with an attached bag). During a follow-up visit at the surgical outpatient clinic, no signs of a pneumothorax were visible in the chest X-ray and the one-way valve was removed.

The patient remains under the care of the outpatient clinic.

Conclusions

The described situation took place in a temporary "covid" hospital, where the patients were taken care of by doctors of various specialisations and a surgeon was not always present. Daily auscultation of the patient, analysis of the patient's condition and respiratory functions by doctors regardless of the medical specialisations, quickly and easily led to establishing the diagnosis of a pneumothorax, even before performing imaging examinations. The case report suggests that in the absence of the patient's progress after drainage of the pleural cavity, the presence of pneumatocele could be suspected. A performed CT scan clarified the cause of the initial treatment failure. Pneumatocele can be a major challenge when treating a patient infected with SARS-CoV-2 and should be suspected in patients with COVID-19 when a pneumothorax develops.

Discussion

In this case report, the newly forming multiple pneumatocele predisposed the patient to the formation of relatively large pneumothorax chambers that required surgical interventions, which could not be managed with consecutive drains. The pneumothorax chambers significantly affected the patient's clinical condition. Some authors claim that pneumatocele form when invasive oxygen therapy is used; however, this trend has not been observed in our centre [6, 8-10]. Conservative treatment brings good results in patients who do not present symptoms of respiratory failure, while our patient required emergency intervention [8, 10]. Thoracoscopic surgical treatment is not a standard procedure and is applied to a small number of patients [7]. Minimally invasive solutions should be sought, and drainage of the pleural cavity seems to be such an option, as evidenced by the above case report.

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CASE REPORT

A GIANT ANEURYSM OF THE MIDDLE CEREBRAL ARTERY TREATED BY EFFECTIVE EMBOLIZATION

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Abstract: A giant aneurysm (GA) of the middle cerebral artery (MCA) is rare and accounts for approximately 0.5-4.8% of intracranial artery aneurysms. Early diagnosis of a brain GA is critical. Classic digital subtraction angiography (DSA), with the option of three-dimensional rotational angiography, remains the "gold standard" in the diagnosis of intracranial aneurysms, including GAs. The primary goal of brain GA treatment is to permanently exclude the aneurysm from the circulation system while preserving the flow in the candelabra. The secondary goal is to stop the growth of the aneurysm and reduce any 'mass effect' symptoms it causes. Despite new endovascular techniques and advances in microsurgery, the treatment of GAs of the MCA is still a therapeutic challenge. There are only a few reports in the literature describing cases of patients diagnosed with a GA of the MCA and evaluating various treatment methods. In this article, we present the case of a 78-year-old patient with a GA of the right MCA, who underwent effective embolization of the active part of the aneurysm.

Keywords: embolization, case report, endovascular treatment, middle cerebral artery, giant aneurysm.

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Introduction

Intracranial artery aneurysms are the most common type of cerebral vascular malformations [1]. They occur in 2.8% (95% CI, 2.0-3.9%) of the human population and 85% of cases are located in the anterior part of the arterial circle of Willis [2-4].

Proven risk factors for the occurrence and rupture of intracranial aneurysms include age, female gender, smoking, alcoholism, hypertension, hyperlipidemia, hyperglycemia, family history of polycystic kidney disease or subarachnoid haemorrhage (SAH), as well as the presence of aneurysms in at least two relatives [5-6]. Other risk factors for the development of aneurysms include connective tissue disorders, such as Ehlers-Danlos syndrome, head injury, infection or birth defects. In addition, it has been shown that the presence and intensity of the inflammatory process may be more important in the process of aneurysm rupture than its size and location [7].

Symptoms of aneurysms may suggest the presence of a brain tumour, resulting from the mass effect (headaches and dizziness, seizures, nausea and vomiting, visual disturbances, or symptoms of focal damage to the central nervous system (CNS) i.e. cranial nerve palsy, hemiparesis, dysphagia or aphasia), especially with a large or giant aneurysm (GA) [8].

A GA of the middle cerebral artery (MCA) with a diameter greater than 2.5 cm is rare and accounts for approximately 0.5-4.8% of all diagnoses [9-13]. They can develop de novo in defective areas of the internal elastic lamina or evolve from smaller aneurysms under constant hemodynamic stress [14]. Most of them are the saccular type. The pathogenesis of intracranial aneurysms is influenced by a number of risk factors, including genetic variables as proven by a higher frequency of aneurysms in some hereditary diseases, including polycystic kidney disease and familial aggregation [15]. Familial aneurysms account for 5.1% in the population of giant aneurysms [16]. The study by Khurana et al. showed that all patients with large ruptured aneurysm were heterozygous for the endothelial nitric oxide synthase (eNOS) [17]. However, a study conducted by Huttunen et al. showed no correlation between aneurysm size and rupture age, suggesting that aneurysm size is mainly a consequence of hemodynamic stress [18].

Early diagnosis of a brain GA is critical. In a brain computed tomography (CT) scan, a GA appears as a well-circumscribed, circular or lobular, slightly hyperdense lesion, often manifesting a "mass effect" [14]. A CT in the vascular option with the use of contrast (angio-CT) is the most frequently performed examination in the diagnosis of intracranial aneurysms. However, classic digital subtraction angiography (DSA) with the option of three-dimensional

rotational angiography remains the “gold standard” in the diagnosis of intracranial aneurysms [19].

The primary goal of brain GA treatment is to permanently exclude the aneurysm from the circulation while preserving the flow in the candelabra. The secondary goal is to stop the growth of the aneurysm and reduce the ‘mass effect’ symptoms it causes.

Despite new endovascular techniques and advances in microsurgery, the treatment of a GA of the MCA is still a therapeutic challenge, which is additionally often complicated by technical difficulties, such as the fusiform shape, thrombi in the aneurysm sac, atherosclerosis and calcification of the arterial walls, the presence of candelabra or the involvement of the M1 segment [20-21].

In this article, we present the case of a 78-year-old patient with a GA of the right MCA, who underwent effective embolization of the active part of the aneurysm.

Case report

The 78-year-old patient was admitted urgently to the Neurological Clinic of the Military Institute of Medicine - National Research Institute (MIM-NRI) in July 2022 due to speech disorders, impaired coordination and balance, psychomotor retardation and periodic problems with concentration and memory. Symptoms started about a year earlier and gradually worsened. The ambulatory performed a CT examination of the brain, which showed a partially hyperdense, focal lesion in the middle cranial fossa size of 59 x 54 x 55 mm, containing annular calcifications. It infiltrated the sphenoid bone and the left temporal bone, and caused a “mass effect” [Fig. 1 A]. The patient was under the constant care of the Surgical Clinic due to an aneurysm dilatation of the abdominal aorta to 45 mm over a length of 6 cm below the origin of the renal arteries. The past medical history also included hypertension, hyperlipidemia, prostatic hyperplasia, status after surgical treatment of glaucoma and cataracts (2021), and status after surgical treatment of the cervical spine (1997).

The neurological examination on admission showed central paresis of the facial nerve on the left side (the patient could not precisely determine the time of onset of the symptom), slight dysarthria and insecurity as part of the gait. A magnetic resonance imaging (MRI) examination of the brain, performed during hospitalization, revealed a GA of the right MCA in the middle cranial fossa, size 63x50mm in the transverse dimensions and 54 mm in the longitudinal dimension, causing a “mass effect” with swelling of the brain tissue of up to 25 mm wide [Fig. 1 B-F]. In addition, multifocal vascular brain injury had been described. After a consultation with an interventional radiologist, a brain DSA was performed including a 3D examination of the right ICA. Its result confirmed the presence of the GA of the right MCA [Fig. 2 A]. The aneurysm was completely filled with thrombi and calcifications, with an active aneurysm neck, the size of which was 5.8 x 3.8 mm. The right MCA and its candelabras were lifted up and profiled by the mass of the aneurysm. The patient was consulted by an ophthalmologist - no oedema of the optic discs was found during the examination of the fundus. He did not require antiplatelet therapy before the procedure, because the implantation of a brain stent was not planned. After cardiological consultation and modification of antihypertensive treatment on 7 July 2022 the embolization of the active part of the right MCA segment M1/2 aneurysm with the use of cerebral embolization spirals was performed in the Interventional Radiology Laboratory of the MIM-NRI [Fig. 2 B-C]. The course of the procedure was without complications. After embolization, the patient was recommended to control blood pressure and take statins. The patient was consulted by neurosurgeon and qualified for surgical treatment: resection of the aneurysm by craniotomy.

During hospitalization, the patient was treated with anti-edematous drugs (dexamethasone and mannitol). Due to the EEG recording with single sharp waves with a slow one in the right temporal region, he received also an anti-epileptic treatment (sodium valproate). In good general condition, the patient was discharged home with the recommendation to take antiepileptic treatment and perform blood pressure 24-hour monitoring before the planned neurosurgical procedure.

In October 2022. the patient was admitted to the Neurosurgical Clinic of the MIM-NRI. On admission, the patient was in good neurological condition; Glasgow Coma Scale (GCS) score of 15 points, with a discrete central paresis of the left facial nerve observed. Due to the sustained significant improvement in the patient’s functioning and the fact that the active part of the aneurysm was properly embolized, as well as because of the high risk of the surgical treatment, the surgery was finally abandoned. The follow-up cerebral arteriography was recommended in about 6 months. In November 2022, the patient underwent a follow-up visit at the Neurological Clinic of the MIM-NRI. During the visit, the patient’s condition and mood were good, he did not report any new ailments; however, a discreet central paresis of the left facial nerve persisted. The follow-up MRI examination with contrast was recommended, as well as angio-MR, in which embolization coils were visualized in the neck of the aneurysm. There was no flow signal or contrast within the aneurysm [Fig 3 D-F]. No significant dynamics in the size of the aneurysm sac was observed. In May 2023, the patient was admitted to the Neurosurgical Clinic of the MIM-NRI for follow-up DSA. On admission, the patient was in good neurological condition, and a discrete central paresis of the left facial nerve was still present. From a puncture of the right radial artery under local anaesthesia, a selective angiography of the right cerebral hemisphere was performed, revealing an image comparable to the postoperative examination in July 2022. This confirmed that the good effect of the treatment was maintained. Due to the correct embolization of the active part of the aneurysm, lack of progression of changes in the radiological image and stable clinical condition of the patient, conservative treatment and regular neurological/neurosurgical follow-up visits were recommended.

Figure 1. Baseline imaging examinations. (A) The brain CT scan from 27 June 2022 showed the presence of a pathological mass in the middle cranial fossa of the right brain hemisphere. MRI examination performed on 29 June 2022 revealed a GA with size of 63 x 54 x 50.1 mm with a layered thrombus. (B) Sequence Ax T2 FLAIR, (C) +C ax3DT1, (D) Obl.3D SWAN, (E) Obl. sag T2 Prope, (F) Obl.cor.T2 Prope. (B) MRI showing lesion morphology, (C) nature of vascularization, (D) presence of haemoglobin deposits, (E, F) size and location.

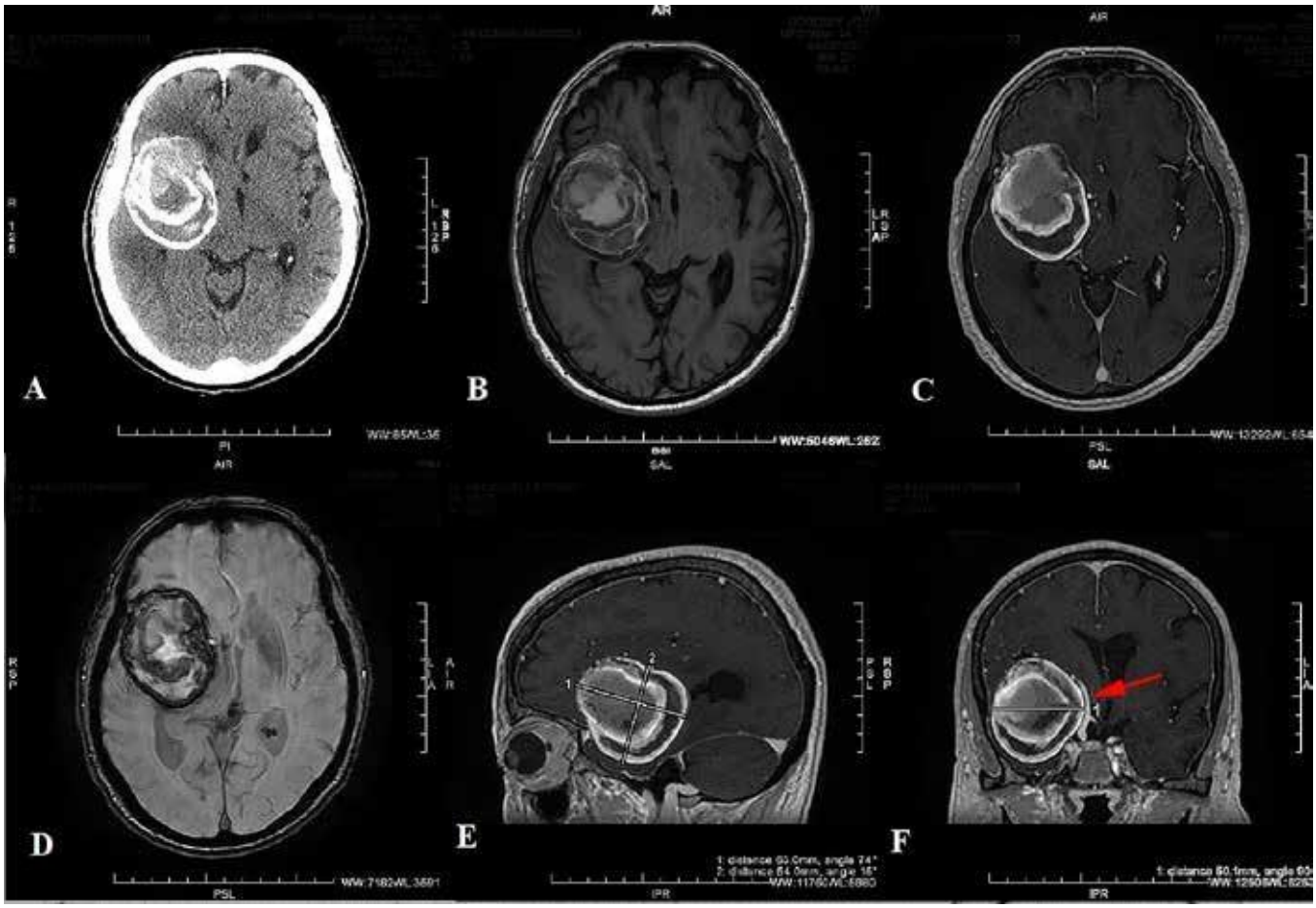


Figure 2 Classic digital subtraction angiography examination. A) The A-P projection shows the 'mass effect' of the GA in the form of ICA and MCA modelling on the GA bag. (B) Administration of a contrast agent through a microcatheter to the active part of the aneurysm. (C) Condition after coil embolization of the active part of the aneurysm.

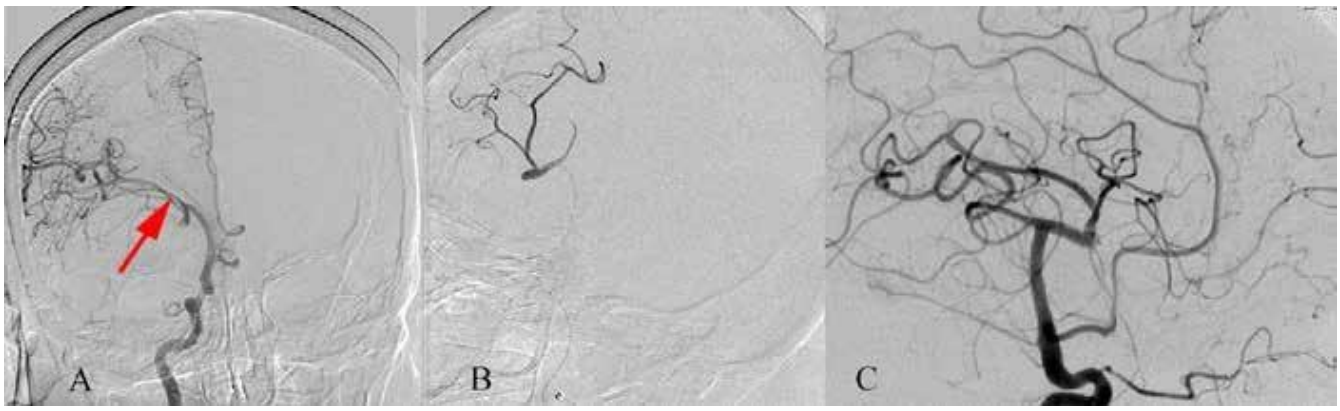
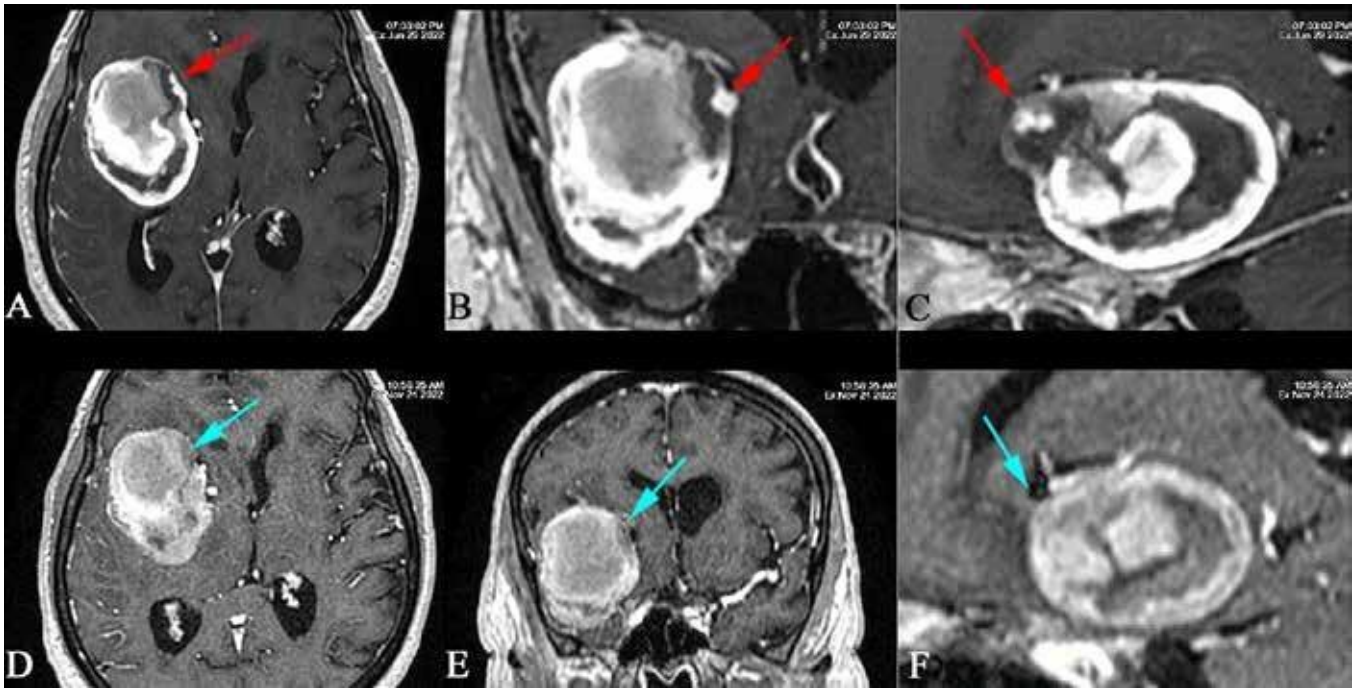


Figure 3 MRI examination with intravenous contrast agent, T1-weighted sequences in axial (A, B), coronalis (B, D) and sagittalis (C, F) projections. GA replenishment site from the RMCA side in the MRI from 29 June 2022 is marked with red arrows (A, B, C). The follow up MRI examination performed on 24 November2022 showed effective embolization of the active part of GA, marked with blue arrows (D, E, F).



Discussion

The dominant clinical symptoms in patients with GAs (i.e. headaches, seizures and features of focal CNS damage) are related to the mass effect [22]. In addition, the large size of the GAs, their irregular shape, heterogeneous enhancement and oedema of the brain tissue visible around the lesion, may often be misinterpreted as a brain tumour in imaging tests, such as CT or MRI.

Untreated intracranial GAs have a 5-year mortality rate > 80% due to the high risk of subarachnoid haemorrhage and the progressive mass effect [14]. The aim of the treatment of intracranial aneurysms is to exclude them from the circulation and protect the patient against recurrent haemorrhage, i.e. the consequences of intracranial bleeding. Currently, there are two methods of treatment available, surgery and endovascular treatment, which can be performed together or separately [8].

Endovascular treatment requires appropriate equipment: an angiograph, as well as catheters and microcatheters of very small dimensions. Endovascular aneurysm embolization procedures are performed with the use of X-rays and iodine contrast agents. This method consists of inserting an appropriate set of microcoils inside the aneurysm sac and filling it with special coils or dedicated devices to exclude the aneurysm from the cerebral circulation. Currently, stents are used to redirect the blood and reduce blood flow to the aneurysm. There are also methods of combining both coils and stents simultaneously in the procedure. In case of the use of brain stents, the patient should take double antiplatelet therapy (clopidogrel+ acetylsalicylic acid or brilique + acetylsalicylic acid) to prevent clotting in the implanted stent. In our case, there was no such need, because only embolization coils were used. After excluding the aneurysm from the circulation, anticoagulation can be used in the case of cardiac indications, e.g. atrial fibrillation. The results from the research conducted by Hanada et al. suggest that in patients requiring oral anticoagulants, direct oral anticoagulant (DOACs) may be more beneficial than vitamin K antagonists (VKA) for preventing stroke occurrences after endovascular treatment [23].

Considering their large size, localization and morphology (absence of aneurysm neck and dependent distal vessels), GAs pose a technical challenge and still cause great difficulties during endovascular procedures. These are aneurysms with the highest rate of recanalization, which often require repeated treatment, frequently incomplete and complicated, both during and after the procedure [24]. In addition, although cerebral arteries are relatively constant in their anatomy, there are individual differences that should be kept in mind before treatment.

There are only a few reports in the literature describing cases of patients diagnosed with GAs of MCA and evaluating various treatment methods. Sadik et al. described a fusiform, partially thrombotic MCA aneurysm of more than 8 cm in size, in a patient who died after an exploratory craniotomy [25]. Drake noted that among 9 cases of GA neurosurgical treatment published in the years 1965-1977 by various authors, 4 patients (44%) died [26].

In recent reports, in which microsurgical treatment was preferred, postoperative complications occurred in 23.3%-60% of patients [9, 11]. In a study by Pilipenko et al., aneurysm clipping was the most common therapeutic intervention, followed by bypass surgery and endovascular treatment [27]. Neurological deterioration in the perioperative period was observed in 50.9% of patients, and mortality was 1.8%. Complete closure of the aneurysm was achieved in 78.2%, of patients while the long-term outcome was favourable in 76.9%. Mortality including long-term follow-up was 9.4%. Recurrent GAs MCA after surgery was observed in 3.6% of patients. The most common complication was acute ischemic stroke (AIS) (80% of cases). Park et al. also showed, that AIS was the most common complication associated with the neurosurgical treatment of GAs MCA [9]. In their study, aneurysm clipping was the most common therapeutic method, followed by vascular bypass and endovascular treatment. A total of 60% of patients experienced one or more procedural and/or SAH-related complications. According to various authors, AIS in the postoperative period after GAs MCA treatment occurred in 14–25% of cases [9, 12, 28-29].

After surgical treatment, the size of GA may be stable or increase over time. Therefore, each growing residual aneurysm should be considered an indication for a second intervention [9, 30].

Prior to initiating therapeutic management, it should be individually tailored to each clinical case, taking into account the risk factors for adverse outcomes. The decision on the choice of treatment should be preceded by an analysis of clinical condition, the results of imaging examinations and the experience of the treating team. In the case of the patient described in this article, the probability of an adverse outcome of the neurosurgical procedure outweighed the long-term risk of aneurysm rupture. In addition, the patient's good clinical condition and advanced age were the main reasons for abandoning surgery in favour of the endovascular treatment.

As mentioned earlier, the patient was under the constant care of the Surgical Clinic due to an aneurysm dilatation of the abdominal aorta. A study conducted by Rouchaud et al. showed that the prevalence of associated intracranial aneurysms in patients with abdominal aortic aneurysms was 11.8% (128/1081) [31]. There was a slight association between abdominal aortic aneurysm size and the prevalence of intracranial aneurysms. There was no significant association between the locations of aortic and intracranial aneurysms. Similarly, a study by Erben et al. showed that the co-prevalence of intracranial aneurysms among patients with abdominal aortic aneurysms was more than three times the rate seen in patients without abdominal aortic aneurysms [32]. In addition, Kurtelius et al. found that the prevalence of aortic aneurysms is increased significantly in patients with fusiform intracranial aneurysms and slightly in patients with saccular intracranial aneurysms [33]. The authors recommend screening patients with fusiform intracranial aneurysms for aortic aneurysms. However, based on our observations, the percentage of such cases is small. According to the opinion of vascular surgeons of the MIM-NRI, screening for CNS aneurysm is not normally performed in patients with a history of aortic aneurysm. In the case of the coexistence of aneurysms in different locations, then periodic imaging tests,
e.g. angio-CT or Doppler ultrasound, should be performed.

Based on previous reports from the medical literature, case reports of the occurrence and treatment of GA still belong to casuistry. Currently, the main challenges requiring further research are the introduction of new precise diagnostic methods for the assessment of collateral flow and the long-term evaluation of both endovascular treatment results and combination methods. The careful follow-up of patients in the long term after surgery and control angiographic examinations are very important. The relative rarity of GA MCA necessitates multicenter studies and published case reports. Such work could increase the reliability of the collected data and improve the patients' outcomes.

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CASE REPORT

GENERALIZED HAEMOPHILUS INFLUENZAE INFECTION AS AN EXAMPLE OF THE NEED TO EXPAND DIAGNOSTIC PROCEDURES RELATED TO INCREASED EMIGRATION AND THE MEDICAL CARE OF A FOREIGNER

Przypadek zakażenia uogólnionego o etiologii *Haemophilus Infulenzae* jako przykład konieczności rozszerzenia podejścia diagnostycznego w świetle wzmożonej emigracji i opieki nad pacjentem z zagranicy

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Abstract:
Sepsis (also known as a bloodstream infection or generalized infection) is a life-threatening condition. Currently, thanks to the widespread use of vaccinations, the occurrence of generalized infections, including those caused by *Haemophilus influenzae*, is becoming increasingly rare. However, due to the outbreak of the armed conflict in Ukraine, an increasing percentage of unvaccinated Ukrainian children, and their migration, then the increase in the number of cases with this aetiology can be expected. This article covers a clinical case of a 15-month-old Ukrainian boy with symptoms of respiratory tract infection. The child was vaccinated according to the Ukrainian vaccination schedule, and during the diagnostic process, sepsis caused by *Haemophilus influenzae* was detected. Early diagnosis and the use of a broad-spectrum antibiotic therapy contributed to the therapeutic success and the prevention of severe complications associated with sepsis.

Streszczenie: Posocznica (sepsa, zakażenie uogólnione) jest schorzeniem zagrażającym życiu. Aktualnie dzięki powszechności szczepień ochronnych obserwuje się coraz rzadsze występowanie uogólnionych zakażeń w Polsce, w tym wywołanych przez *Haemophilus influezae*. W związku z wybuchem konfliktu zbrojnego w Ukrainie, zwiększaniem się odsetka niezaszczepionych dzieci ukraińskich oraz ich migracją, należy jednak spodziewać się wzrostu liczby zachorowań o tej etiologii. W poniższym artykule przedstawiono przypadek kliniczny 15-miesięcznego chłopca narodowości ukraińskiej z objawami infekcji dróg oddechowych, szczepionego zgodnie z ukraińskim kalendarzem szczepień, u którego w toku postępowania diagnostycznego wykryto posocznicę o etiologii *Haemophilus influenzae*. Wczesne postawienie rozpoznania oraz zastosowanie szerokospektralnej antybiotykoterapii przyczyniły się do osiągnięcia sukcesu terapeutycznego i uniknięcia ciężkich powikłań związanych z przebyciem posocznicy.

Keywords: sepsis, vaccination, Haemophilus influenzae.

Słowa kluczowe: posocznica, szczepienie, Haemophilus influenzae.

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Introduction

Sepsis (bloodstream infection) is defined as Systemic Inflammatory Response Syndrome (SIRS) following bacteriologically confirmed or probable infection.

The most common sepsis-causing pathogens include coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, *Escherichia coli* as well as, much less common due to the use of population vaccination: *Neisseria meningitidis*, *Haemophilus influenzae and Streptococcus pneumoniae* [1].

A meta-analysis of epidemiological studies on paediatric sepsis showed that the global annual incidence of sepsis is 48/100,000 children, and of severe sepsis is 22/100,000. The mortality rate among children is 1–5% for sepsis and 9–20% for severe sepsis [2].

In 2007, vaccination against *H. influenzae* for children aged 1 and 2 years were introduced to the Polish Preventive Vaccination Plan, and since than the incidence of an invasive disease of this aetiology has decreased [3, 4]. It is confirmed by the report of the National Reference Centre for the Diagnostics of Bacterial Infections of the Central Nervous System (KOROUN), according to which a total of 90 cases of an invasive disease caused by *H. influenzae* were registered in 2022 [4].

This paper presents a case of a 15-month-old Ukrainian boy with generalised infection caused by Gram-negative *Haemophilus influenzae* with no reliable confirmation of vaccination.

Case study

A 15-month-old Ukrainian boy was admitted to the department because of a fever that was up to 38.8°C, lasting for 3 days, accompanied by a cough and a runny nose. The available documentation showed that he had been vaccinated according to the Ukrainian vaccination schedule, including against *Haemophilus influenzae*.

On admission, the boy was in a grave condition. A physical examination revealed excessive nasal discharge, palpable single small cervical lymph nodes, a reddened throat, and swollen tonsils. Auscultation revealed harsh vesicular sound over the lung fields, single wheezes, prolonged expiratory phase, the chest percussion revealed lowered borders of the lungs, while signs of dyspnoea were also observed: SpO2 86%, intercostal and subcostal retractions. Due to the epidemiological situation at the time, antigen tests for influenza, COVID-19 and RSV were performed; their results were negative.

The tests performed after admission showed high inflammatory markers (CRP 10.9 mg/dL, PCT 33.61 ng/mL) and elevated aspartate aminotransferase and lactate dehydrogenase levels (AST 84 U/L, LDH 1015 U/L). Markers for renal functions were normal. There were no signs of myocarditis (Table 1). The ECG was normal for the age. A catheterized urine sample showed leukocyturia of 30.2/µL (the normal range being up to 13.2/µL) with leukocyte clusters of 5.3/µL. Urine culture was found to be sterile.

Chest X-ray showed increased density of parenchyma in the inferior and superior fields of the right lung, perihilar density in the superior field of the left lung and in the retrocardiac area, as well as enlargement of the hilar regions typical of the lymph nodes (Figure). Abdominal ultrasound revealed no parenchymal organ abnormalities.

Figure The patient's chest X-ray, AP position (source: Military Institute of Medicine – National Research Institute).

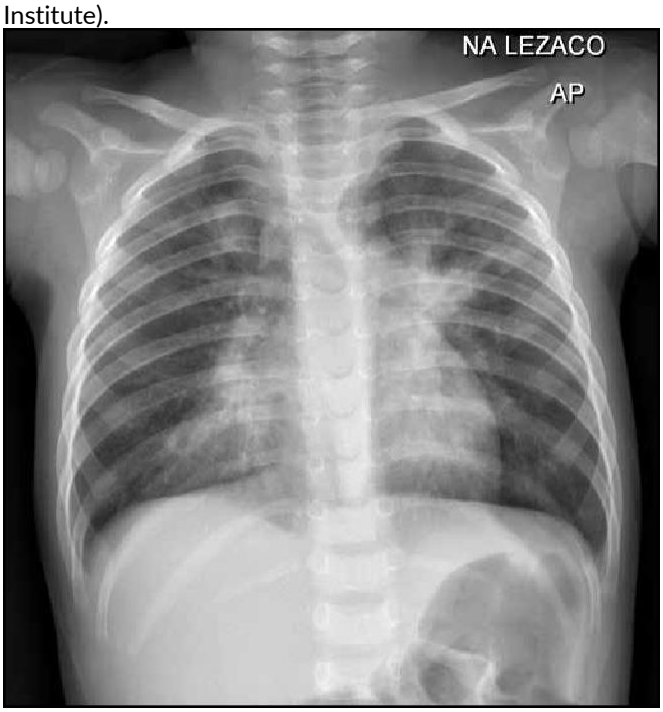

Table 1. Results of the patient's blood tests during hospitalisation.

Parameter	Value on admission	Value after 10 days of treatment	Standard for age
WBC [x10 ^{9}/L]	9.78	9.67	6.0–17.5
Neu [x10 ^{3}/µL]	7.75	2.98	1.5–8.0
CRP [mg/dL]	10.9	0.5	< 0.8
PCT [ng/mL]	33.61	0.20	≤ 0.046
ESR [mm]	31	-	8
AST [U/L]	84	-	60
LDH [U/L]	1015	351	370
Troponin [ng/L]	11.4	-	< 14.0
NT-proBNP [pg/mL]	423.1	-	31–675
CK [U/L]	113	-	38–171
CK- MB [U/L]	36	-	0–25

Due to the boy's grave general condition and septic inflammatory markers, after collecting blood cultures, broad-spectrum antibiotics were included in the treatment: ceftriaxone at a dose of 100 mg/kg body weight in 1 daily dose and amikacin at a dose of 15 mg/kg body weight in two split doses.

On the second day of hospitalisation, the boy developed neck stiffness, a positive lower Brudzinski's sign, a positive Kernig's sign and a general increase in muscle tone. An ophthalmologic examination ruled out oedema of the optic nerve disc. Cerebrospinal fluid was collected; its morphology and general examination showed no abnormalities (Table 2). A culture grew *Staphylococcus auricularis* (most likely a contamination of the sample). On the fifth day of hospitalisation, a blood culture result was obtained, from which grew *Haemophilus influenzae* sensitive to the applied treatment (Table 3).

Table 2. Cerebrospinal fluid examination results.

Parameter	Patient's result	Standard for age
Colour	colourless	colourless
Turbidity	clear	clear
Cytosis [/uL]	5	≤ 5
Protein [mg/dL]	16.3	15–45
Glucose [mg/dL]	81	40–80
Sodium [mmol/L]	134	130–150
Potassium [mmol/L]	2.5	2.8–4.1
Chlorides [mmol/L]	114	> 117

Table 3. Antibiogram and sensitivity of H. influenzae to specific antibiotics.

Antibiogram	Mechanism of resistance
Ampicillin	Sensitive MIC: 0.50
Ciprofloxacin	Sensitive MIC: 0.016
Meropenem	Sensitive MIC: 0.25
Trimethoprim / Sulfamethoxazole	Resistant MIC: 32
Cefotaxime	Sensitive MIC: 0.023

During the following days of hospitalisation, the child's condition gradually improved. The physical examination showed the normalisation of muscle tone and resolution of the signs of dyspnoea (treatment included prednisolone at a dose of 1 mg/kg body weight for 3 days). After 10 days, normalisation of the laboratory parameters in the blood tests was observed.

At the end of the 11th day of antibiotic therapy, due to the good general condition, the boy was discharged home.

Discussion

Sepsis is a life-threatening condition, so a quick establishment of a correct diagnosis and early administration of treatment significantly affects the prognosis [5, 6].

The basic principle in the treatment of sepsis is targeted antibiotic therapy. Since in the initial phase of the disease the aetiologic agent is generally unknown, empirical aggressive antibiotic therapy with the broadest possible spectrum antimicrobial effect must be administered with subsequent possible modification of treatment after obtaining culture results [6].

Thanks to the early introduction of empirical antimicrobial treatment with ceftriaxone and amikacin on the first day of hospitalisation, the described case of sepsis with *H. influenzae* aetiology ended in a therapeutic success. A differential diagnosis included such diseases as sepsis caused by other bacteria, viral sepsis, meningitis and encephalitis, or intracranial haemorrhage.

When discussing the above case, we need to consider the current health care system in Ukraine and the attitude of Ukrainian society towards vaccination.

In 2006, two monovalent conjugated *Haemophilus influenzae* type b (Hib) vaccines (Hiberix; GlaxoSmithKline, Middlesex, United Kingdom and ActHib; Sanofi Pasteur) were introduced in Ukraine. In 2007-2008, the government additionally purchased the DTaP-Hib quadrivalent conjugated vaccine (TetraHib; Sanofi Pasteur) for routine use in infants [7].

Although vaccines covered by the national preventive vaccination plan in Ukraine are provided free of charge to outpatient clinics and hospitals; unfortunately, even before the outbreak of the armed conflict, vaccination rates in the country were among the lowest in Europe [8].

Public attitudes, widespread aversion to vaccination, the spread of misinformation about vaccines on social media, the lack of public trust in the Ukrainian authorities, and problems with the supply of vaccines continuously contribute to the low vaccination uptake in Ukraine [8, 9]. The Russian military invasion may also significantly impact the problem– according to UNICEF, about 40% of partially vaccinated or unvaccinated children live in the countries affected by various types of conflict [9].

According to WHO, vaccination coverage in Ukraine is steadily falling below the target thresholds required to reach herd immunity [8]. The percentage of Ukrainian children after a full course of Hib vaccination dropped dramatically from 83% in 2013 to 39% in 2017 [9]. An additional problem is unreliable entries in medical records in a society distrustful of vaccination.

Considering the above data, vigilance should be exercised when diagnosing Ukrainian children, even if they have a document confirming vaccination against *Haemophilus influenzae*.

Conclusions

When diagnosing a foreign patient, it is necessary to consider the aetiology of infection that does not fit the current epidemiological situation in Poland. Management of sepsis in paediatric patients requires monitoring of the patient's condition and careful analysis of tests due to the

large and rapid variability of vital signs. Thanks to early establishment of a correct diagnosis and comprehensive diagnostic procedures, intensive treatment may be administered. Appropriate therapeutic management, following the current standards, allows for effective treatment of sepsis and a significant reduction in the frequency of complications.

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XXVII INTERNATIONAL CONGRESS OF THE POLISH CARDIAC SOCIETY – CARDIONEPHROLOGICAL ASPECTS OF THE CONFERENCE

XXVII Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego – aspekty kardionefrologiczne konferencji

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Abstract: This year's International Congress of the Polish Cardiac Society took place in Poznań on September 28-30, 2023. During the congress, several sessions were dedicated to cardiovascular complications in patients with chronic kidney disease. The current possibilities were presented for the prevention and treatment of cardiovascular diseases in this group of patients.

Streszczenie: Tegoroczny Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego odbył się w Poznaniu w dniach 28-30 września 2023 r. Podczas kongresu kilka sesji poświęcono powikłaniom sercowo-naczyniowym u pacjentów z przewlekłą chorobą nerek oraz przedstawiono aktualne możliwości prewencji i leczenia chorób sercowo-naczyniowych w tej grupie pacjentów.

Keywords: chronic kidney disease, cardiovascular complications, congress.

Słowa kluczowe: przewlekła choroba nerek, powikłania sercowo-naczyniowe, kongres.

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The XXVII International Congress of the Polish Society of Cardiology took place in Poznań on 28-30 September 2023. Among the dozens of sessions on current issues related to conservative and interventional cardiology, prevention, pathomechanisms and the treatment of cardiovascular diseases and new therapeutic approaches, some lectures concerned cardiovascular complications in patients with chronic kidney disease (CKD). Since the main causes of morbidity and mortality in patients with CKD are such cardiovascular complications as hypertension, heart failure, and atherosclerosis and its consequences: coronary artery disease, cerebral artery disease and peripheral artery disease, it is extremely important to understand the mechanisms leading to the development of these complications. The awareness and knowledge that cardiovascular complications in patients with CKD may develop in the first stages of renal failure, and then progress rapidly, especially in patients undergoing renal replacement therapy, should result in a more thorough cardiological analysis of a patient with impaired renal function at every stage, including in the early stages of CKD. The above is also true for the converse situation: patients with cardiovascular diseases should undergo a renal function evaluation for plasma creatinine concentration, eGFR and UACR. Due to the extension of life expectancy across the world, including Poland, the number of patients with CKD is gradually growing, which is why the cooperation between a cardiologist and a nephrologist is becoming so important in the comprehensive care of the patient. A prompt cardiology or nephrology consultation is not always possible or available in all centres, so there is a growing need for the physician to understand the pathomechanisms of cardiovascular complications in patients with CKD and the modern diagnostic and therapeutic options for these complications.

About cardiac amyloidosis

Prof. Malgorzata Kurpesa MD, PhD (1st Clinic and Department of Cardiology of the Medical University of Łódź) presented the topic of amyloidosis, a disease which is quite frequently diagnosed in nephrology departments, and which may also affect the heart. Amyloidosis is characterised by the extracellular deposition of an insoluble protein with a fibrillar structure, which leads to the development of organ failure. The heart is most commonly affected by light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR), both hereditary (ATTRv), as well as a wild type (ATTRwt). Amyloidosis with cardiac involvement is classified as a restrictive cardiomyopathy that can lead to the development of heart failure, thromboembolic complications, aortic valve stenosis, and cardiac

arrhythmias, both supraventricular (such as atrial fibrillation) and ventricular. The diagnosis is based on imaging exams and/or biopsies, but the suspicion of cardiac amyloidosis may be raised even on the basis of a resting ECG. During Prof. Kurpesa's lecture, she presented the ECG changes that may accompany cardiac amyloidosis, facilitating and accelerating the diagnostic process. The most common ECG pathology in patients with cardiac amyloidosis, which is observed in 60% of cases, is low QRS complex voltages (LQRSV) in the limb leads, defined as a QRS complex amplitude ≤ 5 mm. LQRSV reflects the severity of amyloidosis in the heart and is associated with an unfavourable prognosis. She presented the ECG recordings of patients with cardiac amyloidosis, with characteristic low QRS complex voltages in the limb leads, with normal voltages of QRS complexes in the precordial leads. Other pathologies in ECG recordings that may occur in patients with cardiac amyloidosis include poor R-wave progression in the precordial leads and left atrial abnormalities. A very important part of the presentation involved pathomechanisms of the brady- and tachyarrhythmias in the course of amyloidosis. Bradyarrhythmias may be caused by denervation of sympathetic fibres by amyloid deposits and thickening of the myocardium due to amyloid deposition in cardiac tissue, resulting in impaired flow of electrical impulses. It seems very interesting that numerous amyloid precursor proteins can be cytotoxic and increase oxidative stress and cell apoptosis in the myocardium, thus also leading to bradyarrhythmias, including sinus node dysfunction. Tachyarrhythmias also originate from left ventricular hypertrophy due to amyloid deposits and myocardial fibrosis. Atrial fibrillation in the course of cardiac amyloidosis is a common arrhythmia. It is caused by amyloid deposits, the development of restrictive cardiomyopathy and the impairment of left ventricular filling, with consequent enlargement of the atrial cavities. Ventricular arrhythmias are also common in patients with cardiac amyloidosis, ranging from single extra ventricular beats to ventricular tachycardia and ventricular fibrillation.

Cardiorenal complications

Fabry disease is a rare disorder that affect the heart and kidneys. Prof. Marek Jastrzębski MD, PhD (1st Department of Cardiology and Interventional Electrocardiology, Jagiellonian University, Krakow) delivered an interesting lecture on electrocardiographic changes in the course of Fabry disease. Fabry disease is caused by a deficiency in alpha-galactosidase A, which results in the accumulation of glycosphinglipids in tissues, including the heart and kidney tissue. This leads to the development of failure in both these organs, so although the disease affects about 1 in 40,000 live births, it should not be forgotten in the context of common cardiac and renal complications. From the nephrological perspective, manifestations of Fabry disease include proteinuria, which over time leads to the development of nephrotic syndrome. At resting ECG, patients with Fabry disease frequently present atrioventricular blocks resulting from atrioventricular junction damage, shortening of the PQ interval, and widening of the QRS complex. Shortening of the PQ interval and widening of the QRS complex may initially raise the suspicion of preexcitation syndrome. The exact cause of the shortening of the PQ interval in Fabry disease is not known, but it is thought that glycosphingolipid deposits in the myocardium can conduct impulses from the atrium to the ventricles more rapidly. In addition to the shortening of the PQ interval and widening of the QRS complex, high QRS complex voltages and repolarization abnormalities can also be observed on the ECG in patients with Fabry disease.

Another disease presented at the congress, which can progress with both cardiac and renal damage, is sarcoidosis. Sarcoidosis is a granulomatous disorder of unknown aetiology, characterized by the accumulation of lymphocytes and macrophages at sites of disease activity, which then transform into epithelioid cells and form noncaseating granulomas. The production of 1,25(OH)2D3 by macrophages results in hypercalcemia and hypercalciuria, which can lead to the development of nephrolithiasis and renal failure. A lecture on the cardiac complications of sarcoidosis was given by Michalina Krych MD (Department of Congenital Heart Defects, National Institute of Cardiology, National Research Institute, Warsaw). Cardiac involvement in the course of sarcoidosis can affect up to 20% of diagnosed patients and is the most common cause of sudden death in this group. In the course of sarcoidosis with cardiac involvement, the ECG frequently reveal atrioventricular blocks, ventricular arrhythmias, both single extra ventricular beats and ventricular tachycardias. The morphology of the QRS complex in cardiac sarcoidosis varies, with RBBB being more common, LBBB being less common, while fragmentation of the QRS complex is also observed. The presence of an epsilon wave in the ECG in patients with cardiac sarcoidosis may raise the suspicion of arrhythmogenic right ventricular cardiomyopathy (AVRC). Occasionally, those patients with suspected AVRC turn out to suffer from sarcoidosis with cardiac involvement, which is ultimately diagnosed on the basis of histopathological imaging of a cardiac tissue biopsy. ST-T interval changes that may be typical of sarcoidosis include inverted T-waves, prolonged T-peak to T-end interval and changes typical of myocardial ischemia.

Kidney and hypertension

One session of the congress was devoted to the topic of renal denervation in the treatment of hypertension. During the session, Prof. Andrzej Januszewicz MD, PhD (Department of Hypertension, Cardinal Stefan Wyszynski Institute of Cardiology – National Research Institute, Warsaw) presented a lecture on resistant hypertension. The prevalence of resistant hypertension is estimated at 10–20% among hypertensive patients, especially in the population suffering from CKD. The diagnosis of true resistant hypertension is based on the presence of blood pressure values above 140/90 mmHg despite taking hypotensive medications from three groups: Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin II Receptor Blocker (ARB), calcium antagonist and diuretics. Abnormal blood pressure control must be confirmed by a 24-hour blood pressure measurement using Automatic

Blood Pressure Monitoring (ABPM) or during home measurements. It is necessary to rule out the secondary causes of hypertension as well as, which was emphasized several times during the lecture, the patients' non-compliance with medical advice.

Risk factors for true resistant hypertension include age over 70, female gender, black race, excessive sodium and alcohol intake, smoking, obesity, CKD, diabetes, and obstructive sleep apnoea. What is very important and worth remembering is the presence of resistant hypertension in almost 45% of patients with moderate and severe forms of obstructive sleep apnoea. In CKD, particularly in its advanced stages, sodium and fluid retention play an important role in the development of resistant hypertension. Damage to the vascular endothelium caused by an increase in plasma concentration of inflammatory cytokines in obesity, diabetes and CKD leads to endothelial dysfunction, increased arterial stiffness and impaired vasodilatory function, thereby increasing arterial pressure. Untreated resistant hypertension results in the development of such cardiovascular complications as coronary artery disease, peripheral artery disease and an increased risk of stroke. In addition, this group of patients is more likely to suffer from left ventricular hypertrophy and heart failure, such cardiac arrhythmias as atrial fibrillation, kidney damage, albuminuria, and the development of CKD. Individuals with resistant hypertension more often have a depressed mood, experience a poorer quality of life and impaired quality of work. Januszewicz highlighted the role of spironolactone, which reduces arterial stiffness, chlortalidone and clonidine in the treatment of true resistant hypertension. He also presented promising results from a trial on the aldosterone syntheses inhibitor, baxdrostat, and the Precision trial with the endothelin receptor antagonist, aprocitentan.

New indications for renal denervation were presented by Prof. Wojciech Wojakowski MD, PhD (Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice). Renal denervation can be considered in patients with CKD stage G1-G3b with eGFR > 40 mL/ min/1.73 m2, after unsuccessful treatment intensification: adding spironolactone (contraindicated in patients with eGFR < 30 mL/min/1.73 m2), beta-blocker, alpha-1-blocker or a drug with a central mechanism of action. Currently, there are no studies that compare pharmacological treatment of hypertension with renal artery denervation. Renal denervation is a moderately effective method, corresponding to the addition of a single hypotensive drug. There are three techniques of renal denervation: radio frequency-based denervation, ultrasound denervation and chemical denervation, of which radio frequency-based denervation and ultrasound denervation are the most effective. The observed effect of radio frequency-based denervation is permanent. To date, the ineffectiveness of renal artery denervation has been due to the failure to perform nerve ablation of additional renal arteries that have not been denervated before. A difficulty in assessing the effectiveness of renal artery denervation after the procedure results mainly from the lack of clinical markers of denervation effectiveness immediately after the procedure. Renal denervation is an irreversible procedure. Although a phenomenon of reinnervation has been observed, autonomic fibres are subject to reinnervation at a lower rate and at a slower pace than vasomotor fibres. Renal denervation is considered a safe method, with a low perioperative risk. The main complications of renal denervation include increased natriuresis, renal artery stenosis (occurring in less than 1% of cases) and a slight eGFR decrease.

The micro is the macro

As multiple sessions were held simultaneously during the congress, it was impossible to attend all of them, hence it is difficult to judge which lectures were the most interesting. However, there is no doubt in my opinion that one of the most important topics is coronary microcirculation; the session devoted to this issue was titled: “The micro is the macro! a few words about coronary circulation”. The session was held by: Prof. Piotr Hoffman MD, PhD (Department of Congenital Heart Diseases, Cardinal Stefan Wyszynski Institute of Cardiology – National Research Institute, Warsaw), Prof. Jacek Legutko MD, PhD (Clinical Department of Interventional Cardiology, Institute of Cardiology, Jagiellonian University, Krakow), Prof. Marcin Grabowski MD, PhD (Department of Cardiology, University Clinical Centre, Medical University of Warsaw), Prof. Piotr Rozentryt MD, PhD (Department of Chronic Diseases and Civilization Threats, Medical University of Silesia in Katowice, Department of Cardiology, Silesian Centre for Heart Diseases in Zabrze), Prof. Miłosz Jaguszewski MD, PhD (Invasive Cardiology Laboratory, Department of Cardiac Intensive Care and Pulmonary Circulation, University Clinical Centre, Gdańsk, 1st Department of Cardiology, Medical University of Gdańsk). This issue is important not only for cardiologists, but it should also be well-known to nephrologists, since the main cause of morbidity and mortality in patients with CKD are cardiovascular complications, which involve coronary microcirculation, with a chest pain being commonly reported by patients in nephrology departments.

The coronary arteries consist of epicardial coronary arteries and the microcirculatory network, with intramural arterioles less than 100 μm in diameter being the main regulator of myocardial oxygen supply. The most common cause of myocardial ischemia is atherosclerosis of the coronary arteries. However, myocardial ischemia can also occur with normal epicardial coronary arteries. It may happen as a result of a spasm of the epicardial arteries or the presence of myocardial bridges, which compress the epicardial artery and make it constrict, which under resting conditions may not produce symptoms, but during exertion or emotional stress, i.e. in situations of increased oxygen demand of the heart muscle, can cause chest pain. The microcirculatory pathomechanisms resulting in myocardial ischemia include microvascular spasm, endothelial dysfunction, arteriolar remodelling and decreased arteriolar density. Microcirculatory vasomotion disorders may result from excessive microvascular spasm (vasospastic endotype) or from vasodilation disorders (vasodilation endotype). Coronary microcirculatory disorders progress

with age, are exacerbated in patients with sedentary lifestyles and in smokers, and progress in conditions typically associated with an increased inflammatory process, such as obesity, hypertension, atherosclerosis, diabetes mellitus, CKD, and systemic inflammatory and autoimmune diseases. Microvascular angina increases the risk of stroke, myocardial infarction, and death. A diagnosis of microvascular angina is established on the basis of the presence of signs of myocardial ischemia (angina pain), the demonstration of myocardial ischemia (imaging with functional assessment) as well as the exclusion of significant stenosis in the epicardial arteries (coronarography, angio-CT) and a demonstration of coronary microcirculation dysfunction (microvascular contraction after acetylcholine, ST segment changes on ECG and coronary microvascular resistance). The treatment of microvascular angina depends on its endotype, but weight reduction and lifestyle changes are always emphasized. Patients with vasospastic disorders receive calcium channel antagonists and long-acting nitrates, while those with vasodilation disorders are treated with beta-blockers, ACE inhibitors and statins. Metabolic drugs used in microvascular angina include ranolazine, nicorandil and trimetazidine. The session also highlighted the cardioprotective effects of sodium glucose cotransporter 2 (SGLT2) inhibitors, which reduce plasma volume and peripheral vascular resistance, thereby lowering preload and afterload. The lecturers also analysed beneficial effects of SGLT2 inhibitors on cardiac wall remodelling by reducing inflammatory processes and fibrosis. These beneficial cardioprotective effects of SGLT2 inhibitors may also reduce angina symptoms. The session also included the presentation of the paper "*Physiological roles of hydrogen sulfide in mammalian cells, tissues, and organs"* (Physiol. Rev. 2023, 103, 31-276. doi: 10.1152/physrev.00028.2021) devoted to the beneficial role of hydrogen sulfide in the cardiovascular system, the effects of its excess and deficiency.

Cardiovascular problems and dialysis

One session of the congress dealt with cardiac problems in pre-dialysis and dialysis patients. During the session, the following lecturers delivered their speeches: Prof. Ilona Kurnatowska MD, PhD (Department of Internal Medicine and Transplant Nephrology, Medical University, Łódź), Prof. Krzysztof Rzeczuch MD, PhD (Institute of Heart Diseases, Medical University, Wrocław), Prof. Grzegorz Gajos (Department of Coronary Artery Disease and Heart Failure, Jagiellonian University, Krakow), and Prof. Magdalena Krajewska (Department of Nephrology and Transplantation Medicine, Medical University, Wrocław). Deterioration of renal function already in the early stages of CKD leads to faster development of cardiovascular complications, which increase with the progression of renal failure. This leads to a growth in the number of cardiovascular events, hospitalisations, and deaths. Since life expectancy is rising, the number of people with CKD is gradually growing.

One of the problems for a cardiologist consulting a patient with end-stage renal failure is the qualification for kidney transplantation surgery. It should be remembered that not all patients with end-stage renal failure require a cardiology consultation. If a patient with CKD qualified for a kidney transplantation has a normal echocardiogram, with no changes in resting ECG and chest x-ray, is less than 50 years old, has been on dialysis for less than 2 years, has no diabetes, no addictions, and does not present symptoms of ischemic heart disease and does not report cardiac arrhythmias, then a cardiology consultation before kidney transplantation is not necessary. However, considering the rate of progression of cardiovascular complications in patients with CKD, there are few patients who do not require a cardiology consultation before kidney transplantation.

Cardiac arrhythmias pose a significant problem in patients with end-stage renal failure. As many as 32% of dialysis patients may experience atrial fibrillation, other observed disorders include bradyarrhythmias and ventricular arrhythmias. Cardiac arrhythmias can be exacerbated by the dialysis procedure itself, which is associated with the rapid removal of excess potassium, with low calcium concentrations in the dialysis fluid, with too intense ultrafiltration or with post-dialysis alkalosis.

The build-up of calcification in dialysis patients makes aortic valve calcium deposits twice as common in this group of patients and leads to aortic stenosis twice as quickly as in the general population. Due to coronary calcification, patients with CKD more often require the management of calcified lesions during percutaneous coronary interventions (PCI), with such specialist tools as rotational or orbital atherectomy, cutting balloons, the lithotripsy procedure, and lasers, while, in many cases, several tools must be used. Despite increasingly advanced therapeutic options for treating coronary calcifications, it should be remembered that PCI procedures in calcified arteries are more likely to be ineffective and cause complications in the form of vessel perforation. Increased calcification of vessels and valves in dialysis patients is caused by disorders of the calcium-phosphate metabolism, but also by the use of vitamin K antagonists, which intensify calcification.

The administration of contrast during imaging studies in pre-dialysis or dialysis patients with preserved renal function is also a significant problem. According to the recommendations of the Polish Society of Nephrology, prophylaxis of contrast-induced kidney injury should consist in the proper hydration of the patient. Oral hydration is preferred, while intravenous administration of fluids is recommended only in high-risk patients. Loop diuretics, mannitol, nonsteroidal anti-inflammatory drugs, ACEIs, ARBs, metformin, aminoglycosides and other nephrotoxic drugs should be avoided prior to the contrast-enhancement examination. There are no data on the efficacy of theophylline, fenoldopam or high doses of statins in the prevention of acute contrast-induced kidney injury. Prophylactic haemodialysis or hemofiltration to remove the contrast agent should also be waived; instead, attention should be paid to the possibility of volume overload of the patient after contrast administration.

Simultaneous cardiac and renal disorders

On the last day of the congress, one of the sessions was devoted to the simultaneous occurrence of heart failure and renal disease, and this problem was presented by Prof. Krzysztof Pawlaczyk MD, PhD (Department of Nephrology, Transplantation and Internal Medicine, Medical University, Poznań), Prof. Ewa Straburzynska-Migaj MD, PhD (1st Department of Cardiology, Medical University, Poznań), Prof. Przemysław Leszek MD, PhD (Department of Heart Failure and Transplantation Medicine, Cardinal Stefan Wyszynski Institute of Cardiology – National Research Institute, Warsaw) and Prof. Jan Biegus MD, PhD (Department of Cardiac Intensive Care, Institute of Heart Diseases, Wrocław). During the session, the lecturers presented the division and pathomechanism of cardio-renal and reno-cardiac syndromes, noting that, most likely, in the near future, specialists will distinguish another, sixth type of cardio-renal syndrome caused by diabetes.

Heart failure is associated with an increased risk of CKD, while CKD increases the risk of heart failure with both a preserved and reduced left ventricular ejection fraction. During this session, it was also noted that CKD is an independent risk factor for the development of cardiovascular disease and occurs in almost half of the patients with heart failure, regardless of the ejection fraction. According to the 2021 ESC Guidelines on cardiovascular disease prevention, patients with CKD from stage G3b onward face a high or very high 10-year cardiovascular risk of death. The risk assessment emphasizes the role of the urine albumin-creatinine ratio (UACR), which is used to estimate the degree of glomerular filtration barrier damage, and which is technically very simple. Both decreased eGFR and increased albuminuria are independently associated with the increased risk of cardiovascular death. The drugs used in heart failure and in CKD are renin-angiotensin-aldosterone system (RAAS) blockers and SGLT2 inhibitors. SGLT2 inhibitors and ACEIs or ARBs have a synergistic action, lowering glomerular pressure and reducing albuminuria.

The session outlined the cardiac and renal mechanisms of action of SGLT2 inhibitors, such as increasing glucosuria and natriuresis, reducing volume status, decreasing sympathetic nervous system activation, reducing left ventricular hypertrophy, improving myocardial remodelling and contractility, as well as decreasing glomerular pressure and reducing albuminuria, as mentioned above. SGLT2 inhibitors reduce glomerular pressure by enhancing the contraction of the afferent arterioles and most likely the diastole of the efferent arteriole. Since SGLT2 inhibitors have nephroprotective effects and slow the progression of kidney disease, the expected worsening of eGFR after starting treatment with agents from this group should not be a reason for their withdrawal. The session also outlined the mechanisms of action of ARNI drugs, such as sacubitril/valsartan. Sacubitril inhibits the enzyme neprilysin, which inactivates natriuretic peptides, while valsartan blocks the action of angiotensin II. Neprilysin inhibition causes increased urinary sodium excretion and increased diuresis, inhibition of renin and aldosterone release, decreased sympathetic nervous system activity, inhibition of fibrosis and adverse myocardial remodelling, decreased vascular resistance and arterial stiffness. The renal effects of ARNI drugs are associated with higher levels of circulating natriuretic peptides, improved renal blood flow, and increased glomerular filtration rate. These drugs also affect podocyte function; in addition, their use allow for reduction of the diuretic dose. The most commonly used diuretics in patients with CKD and heart failure are loop diuretics. It should be noted that thiazide diuretics and mineral corticoid receptor blockers, which are often recommended for heart failure, should not be used in patients with an eGFR below 30 mL/min/1.73 m2. During the session, the speakers presented finerenone, a novel, non-steroidal and selective mineralocorticoid receptor antagonist, which had been added to the group of the nephroprotective drugs alongside RAAS inhibitors and SGLT2 inhibitors. Preclinical data and the results of the Fidelio-DKD trial confirmed that finerenone is a molecule with high selectivity for the mineralocorticoid receptor, does not penetrate the central nervous system, does not cause gynaecomastia, is associated with a lower risk of hyperkalemia, and is equally distributed between the heart and kidneys. According to the latest ESC 2023 guidelines, finerenone is recommended in patients with type 2 diabetes and CKD to reduce the risk of hospitalization on account of heart failure. In patients with diabetes, finerenone reduces the incidence of cardiovascular episodes and renal failure as an adjunct to ACEi or ARB when eGFR > 60 mL/min/1.73 m2 and UACR ≥ 300 mg/g or when eGFR is 25-60 mL/min/1.73 m2 and UACR ≥ 30 mg/g.

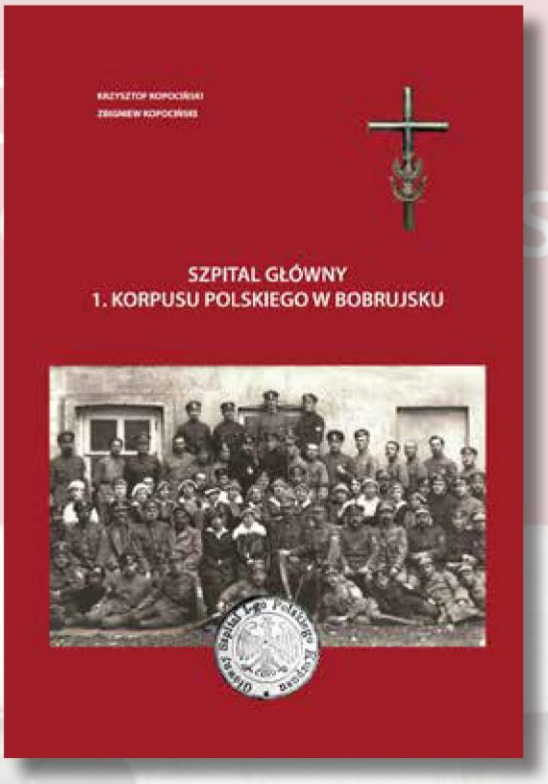
During the congress, numerous aspects of current issues in the field of cardionephrology were comprehensively presented. The fact that cardiovascular complications begin in the early stages of renal failure, progress with a decrease in eGFR and are the main cause of morbidity and mortality in CKD was repeatedly emphasized. In view of the increasing number of individuals with CKD, it is very important to combine the knowledge of cardiology and nephrology in order to prevent, slow down development and properly treat cardiovascular complications in this group of patients, thereby prolonging their life and improving its quality. Congress participants discussed the difficulties and therapeutic differences in the treatment of cardiovascular complications in CKD patients. Thanks to the opportunity of asking questions to experts and engaging in discussions, everyone had a chance to clarify any doubts they may have had and broaden their knowledge.

Figures XXVII International Congress of the Polish Society of Cardiology.

“Central Hospital of the 1st Polish Corps in Bobruisk”

“The publication was issued on the 105th anniversary of the Bobruisk Central Hospital, the largest health care facility of the 1st Polish Corps of Gen. J. Dowbor-Muśnicki. The passage of many years and the unfavourable political climate during the inter-war period, especially after the May 1926 putsch, and in the period of the Polish People's Republic, were not conducive to a reliable and objective presentation of Dowborczycy’s achievements. No historian has analysed the work of the Bobruisk General Hospital before, so our monograph fills an existing research gap. [...]

In the surrounding rampant violence and anarchy, resulting from the four years of World War I and then the savage Bolshevik Revolution, the Bobruisk General Hospital was in 1918 an island of normality, decency, and humanity. While saving lives and the health of Polish soldiers, as well as the representatives of other nations, including prisoners of war, the staff continued the most honourable traditions of the Polish military health service from the times of the Kościuszko or November Uprisings, adding new pages of glorious history concerning military sanitary centres. This monograph is a tribute to all the staff members of the general health care institutions of the 1st Polish Corps, especially the Bobruisk Central Hospital, who in extremely difficult conditions, risking their own health and lives, saved hundreds of other lives and prevented the outbreak of a massive epidemic of infectious diseases among the soldiers of the 1st Polish Corps, according to the authors of the monograph.



The authors are the brothers **Krzysztof Kopociński MD, PhD** and **Zbigniew Kopociński MD, PhD**, who are physicians, specialists in eye diseases as well as medical historians. They are graduates of the Faculty of Medicine of the General Bolesław Szarecki Memorial Military School of Medicine in Łódź. The authors and co-authors of more than a hundred scientific and popular science publications, including eight monographs, such as “105 Szpital Wojskowy w Żarach. Duma Ziemi Lubuskiej [105th Military Hospital in Żary. The pride of the Land of Lubusz]” (2014), “Lekarze szpitala wojskowego w Żarach [Medical practitioners from the military hospital in Żary]” (2014), “Szpital wojskowy w Równem w latach 1919-1939 [Military Hospital in Równe in 1919-1939]” (2020), “Horkałużycka Golgota służby zdrowia 2. Armii Wojska Polskiego [Horka-Lusatia Golgotha of the health care service of the 2nd Polish Army]” (2021), Szpital Główny 1. Korpusu Polskiego w Bobrujsku [Central Hospital of the 1st Polish Corps in Bobruisk” (2023).

They came up with the idea and requested that the 105th Military Hospital in Żary has a distinctive name, “Borderland”, which materialised with a decision of the Minister of Defence in October 2014 concerning borderland activists. Krzysztof is a president of the Tarnopolanie’s Club in Żary and was also a member of the Board of the Society of the Lovers of Lviv and the South-Eastern Borderlands. Zbigniew is a president of the Żary branch of the Association for the Remembrance of the Victims of Genocide committed by Ukrainian Nationalists.

They are the initiators and designers of many borderland memorials, including a plaque to commemorate Polish military physicians from the 3rd District Hospital in Grodno and the 9th District Hospital in Brest-on-the-Bug killed in the Katyn Massacre (2007), planting the Oak of Remembrance and unveiling of a plaque in tribute to Lt. Col. Kazimierz Maciejewski MD, killed by the NKVD in Żary (2011), a plaque in tribute to the Righteous in the Ukraine in Żary (2015), a plaque in tribute to the Warsaw Doctors-Insurgents from the 105th Borderline Military Hospital in Żary (2015), the Volyn Cross at the Communal Cemetery in Żary (2016), a plaque in tribute to Prof. Bolesław Jałowy in Żary (2018), naming a city park in Wrocław after Maj. Prof. Lesław Węgrzynowski (2019).

For their activities they have received the “Buzdygan 2016”, a prestigious award of the military community, given annually to persons of particular merit to the Polish Army. In 2017, the World Congress of Kresowianie presented them with the “Praemium Honoris Cresovianae” award for their outstanding contributions to the restoration of the national memory of the Polish Borderlands.

6th Scientific Congress of the Polish Society of Medical Biology

The 6th Scientific Congress of the Polish Society of Medical Biology will be held on September 19-21, 2024 at the Airport Hotel Okęcie, 24 Komitet Obrony Robotników St. in Warsaw.

It will be a regular meeting of scientists and clinicians engaged in the general problems of Medical Biology. The participants will have the opportunity to listen to lectures by prominent representatives of this scientific discipline and exchange views with them. It will also be an opportunity to present the work and establish new professional and social contracts.

The Board of the Polish Society of Medical Biology has entrusted the organization of the Congress to the Military Institute of Medicine – National Research Institute and the University of Warsaw. As always, you are welcome to participate in the congress.

Kindest regards,
Chairman of the Scientific Committee of the Conference
Prof. Ewa Bulska and Prof. Bolesław Kalicki

The conference agenda includes:

- The keynote lecture of the 6th Congress of the Polish Society of Medical Biology will be delivered by Prof. Ian E. Alexander (BMedSci, MBBS, PhD), Professor of Paediatrics and Molecular Medicine and Director of Laboratory Research and Senior Scientist at Westmead Children's Hospital (Sydney, AU). He is also Head of the Gene Therapy Research Facility, a joint initiative of the Children's Medical Research Institute (CMRI) and The Sydney Children's Hospitals Network (SCHN), Professor of Paediatrics and Molecular Medicine at the University of Sydney, and Honorary Consultant in Clinical Genetics at Westmead Hospital.
- Plenary lectures by invited guests (30 min)
- Oral reports (10 min)
- Poster sessions (poster size 70–100 cm). Poster sessions will be held throughout the day; VARIA poster session: Thursday, Young Scientist poster session: Friday.
- Sessions of Young Scientists (academicians under 35 years of age): oral reports (10 min) or a poster.

Congress organizers:
Polish Society of Medical Biology,
Military Institute of Medicine – National Research Institute,
University of Warsaw
All details are available on the congress website:
https://wimcon.wim.mil.pl/VI-Zjazd-Naukowy-PTBM/