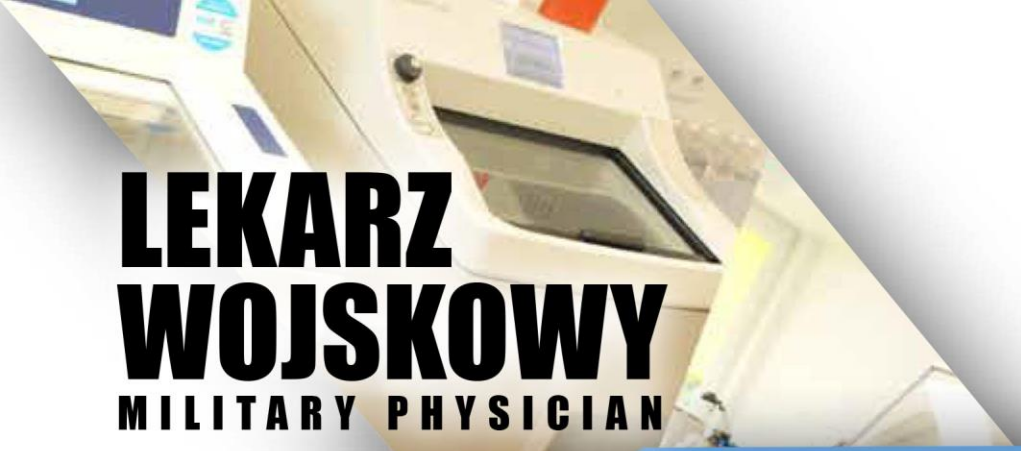
LEKARZ WOJSKOWY
MILITARY PHYSICIAN



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- Treatment of thyroid orbitopathy (Graves Orbitopathy) based on EUGOGO 2021 guidelines, with a focus on the Polish reality
- A brain abscess caused by Nocardia abscessus
- Selective embolization of thyroid arteries as an alternative treatment to amiodarone-induced hyperthyroidism
- Theoretical principles of Colour Doppler Imaging in ophthalmic ultrasound (part I)

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Informacje dla autorów

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

1. "Military Physician" publishes original (experimental and clinical) articles, reviews, reports on military issues, deontological papers, interesting case reports, articles on the history of medicine, descriptions of rationalisation results, posthumous memoirs, letters to the editor, book reviews, article (reviews) summaries from international journals particularly on the military health service, reports on meetings and scientific conferences, and announcements of events.
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   6) ensure a professional publishing process;
   7) ensure confidentiality and security of personal data processing in accordance with applicable regulations (including GDPR).

Letter from the Editor-in-Chief

Welcome!

As the summer holiday is now over, it is now time for the third issue of the 100th volume of “Military Physician”. In presenting it, I would like to highlight the work on ultrasound in ophthalmology, “Theoretical principles of Colour Doppler Imaging in ophthalmic ultrasound (part I).” Another particularly noteworthy work is “Treatment of thyroid orbitopathy (Graves Orbitopathy) based on EUGOGO 2021 guidelines, with a focus on the Polish reality.” In this issue, we also explore the potential of the Department of Pathology of the Military Institute of Medicine.

As a reminder, I would like to ask the authors of short-listed papers to review the received version of the paper quickly and thoroughly before printing – this will speed up the publishing process and help avoid minor errors.

The Editorial Team are continuously improving our website, and their efforts will soon result in the launch of a newsletter and the option to subscribe to “Military Physician”, providing you with easier access to all our content. Please feel free to visit our website at https://lekarzwojskowy.wim.mil.pl/.

Autumn is traditionally the season for conferences and the presentation of scientific achievements. However, it is also a great time to prepare new interesting and original publications. I encourage you to submit your papers, as only in this way can we increase the value of our journal, leading to the even wider prevalence and ultimately increasing the scientometric value of the articles published.

Here is the latest issue of “Military Physician” and I wish you an inspiring read.

Prof. Bolesław Kalicki, MD, PhD

ERRATUM

“Military Physician” 2/2022 vol. 100

Page	Published	Correct
112	**Justyna Pyrko[1]** 1. *Department of General, Oncological, Metabolic and Thoracic Surgery, Military Institute of Medicine, Central Clinical Hospital of the Ministry of National Defence, Poland*	**Justyna Pyrko[1], Arkadiusz Chmieliński[1], Andrzej Kwiatkowski[1], Artur Maliborski[2]** 1. *Department of General, Oncological, Metabolic and Thoracic Surgery, Military Institute of Medicine, Central Clinical Hospital of the Ministry of National Defence, Poland* 2. *Department of Medical Radiology, Central Clinical Hospital of the Ministry of Interior and Administration, Military Institute of Medicine, Poland*

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MILITARY PHYSICIAN

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CONTENTS

BARRET'S OESOPHAGUS – ENDOSCOPIC METHODS OF TREATMENT

Przełyk Barretta – endoskopowe metody leczenia

Piotr Królikowski[1], Piotr Gietka[1], Katarzyna Królikowska[2], Maciej Gonciarz[1]

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Abstract: Barrett's esophagus (BE) is a chronic gastrointestinal disease associated with a transformation of the esophageal squamous epithelium to cylindrical epithelium. The pathology occurs secondarily to chronic gastroesophageal reflux. This process affects up to 5% of the general population and is the only known precursor to oesophageal adeno-carcinoma. Advanced endoscopic imaging techniques with appropriately collected biopsy material play a critical role in establishing the diagnosis. Treatment involves endoscopic techniques consisting of local removal or destruction of metaplastic, dysplastic or neoplastic transformations, as presented in this paper.

Streszczenie: Przełyk Barretta (BO) to przewlekła choroba układu pokarmowego, która jest związana z przekształceniem nabłonka wielowarstwowego przełyku do typu walcowatego. Patologia występuje wtórnie do przewlekłego refluksu żołądkowo-przełykowego. Proces ten dotyka nawet 5% ludności z populacji ogólnej i jest jedynym znanym prekursorem gruczolakoraka przełyku. W rozpoznaniu najistotniejszą rolę odgrywają badania endoskopowe z użyciem zaawansowanych technik obrazowania wraz z odpowiednio pobranym materiałem biopsyjnym. W leczeniu wykorzystuje się techniki endoskopowe polegające na miejscowym usunięciu lub zniszczeniu zmienionej metaplastycznie, dysplastycznie lub nowotworowo tkanki, co zostanie przedstawione w poniższej pracy.

Key words: treatment, endoscopy, supervision, dysplasia, Barrett's oesophagus.

Słowa kluczowe: leczenie, endoskopia, nadzór, dysplazja, przełyk Barretta.

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Introduction

In 1906, Wilder Tileston, a pathologist from Boston, described three cases of a peptic ulcer of the oesophagus, demonstrating that the mucous membrane around the ulcer corresponded to that normally found in the stomach. Moreover, he believed that the condition for the formation of this type of ulceration is an insufficiency of the cardia. [1] For over 40 years afterwards, these observations did not meet with much interest. Only in 1950 did the Australian-born surgeon, Norman Rupert Barrett, working at St. Thomas' Hospital in London, describe the case of a patient with ulcers lined by columnar epithelium in the distal oesophagus. As it was assumed that columnar epithelium could only be found in the stomach, Barrett postulated that it was a segment of the stomach that had been tethered within the thorax by a congenital anomaly, the so-called short oesophagus. Three years later, Allison and Johnstone described seven patients with reflux oesophagitis in whom gastric mucous membrane was found in the area of the inflammatory lesions. The authors rejected the thesis that the observed changes could be explained by the displacement of the stomach to the thorax. Barrett himself agreed with them, and proposed the name "lower oesophagus lined by columnar epithelium". Since then, the eponym "Barrett's oesophagus" has been commonly used [2, 3].

Definition

The definition of Barrett's oesophagus (BEO) has been subject to various modifications, primarily due to the presence or absence of intestinal metaplasia in the endoscopic biopsy specimens. The term "metaplasia" has not been clearly defined either. Following Virchow, it was understood as normal tissue in an abnormal location. This phenomenon may be observed not only in the oesophagus, but also in the stomach, gall bladder, and other organs [3]. In the case of the oesophagus, intestinal metaplasia is a condition in which the squamous epithelium in the distal segment of the oesophagus is replaced by a columnar epithelium containing goblet cells. As the metaplastic tissue is composed of many different types of differentiated cells, and can be a precursor of cancerous lesions, it is considered pathological [4]. The American Gastroenterological

Association of Gastroenterology (AGA), American College of Gastroenterology (ACG), European Society of Gastrointestinal Endoscopy (ESGE) and Benign Barrett's and Cancer Taskforce Consensus Group (BOB CAT) consider intestinal metaplasia to be a necessary condition for the diagnosis of BEO. According to other gastroenterological associations, such as the British Society of Gastroenterology (BSG) and Asia-Pacific Working Group (APWG), intestinal metaplasia is not a necessary prerequisite for the diagnosis. However, the BOB CAT consensus emphasises that the presence of intestinal metaplasia should be stated in the diagnosis [5].

Epidemiology

The principal cause of BEO is gastro-oesophageal reflux disease (GORD) persisting for over 5 years. According to various studies, the disease is found in approximately 10-20% of European and American populations [6]. Other risk factors include age over 50 years, male sex, tobacco smoking and central obesity. The possible contribution of factors such as family history, type 2 diabetes, sleep apnoea or drinking coffee is increasing [7, 8, 9, 10]. Due to methodological limitations, it is difficult to determine the exact prevalence of BEO in the general population. It is estimated to be approximately 2% [11]. In the USA, in the adult population, the rate is estimated to be 5.6% [12].

Endoscopic presentation

In the endoscopic examination, following the ACG 2016 guidelines [10, 12], the requisite for a BEO diagnosis is the presence of mucosal lesion extending over 1 cm above the gastro-oesophageal junction. In order not to miss intestinal metaplasia, at least 8 biopsies should be obtained for histopathological analysis. It is not recommended to collect biopsy specimens from the unchanged gastro-oesophageal junction – the Z-line or the area less than 1 cm above the Z-line. In the latter case, the results of assessments of the same specimen conducted by a few pathomorphologists may differ too much to be conclusive. To describe the endoscopic changes visible in a Barrett's segment, it is recommended to use the uniform, international system, known as the Prague classification [13]. It uses two characteristics to describe the BEO extent. The C value (circumferential extent) measures the length of the salmon-coloured mucosa involving the entire circumference of the oesophagus (when only tongues in the Z-line are observed, the C value is 0), and the M value (maximal extent) measures the total length of the BEO, i.e. the circumferential extent (not always present) and the length of the tongues (Figures 1, 2).

Chromoendoscopy

The *in vivo* mucosal staining techniques occurring during an endoscopic study (chromoendoscopy) are used to increase the detection of altered mucosal epithelium, compared to an endoscopic study without the use of such techniques. The method involves distribution of a dye on the surface of the mucosa, and as the dye is absorbed by the metaplastic epithelium, the changed mucosa is highlighted. In gastrointestinal chromoendoscopy the following dyes are used: methylene blue, toluidine blue, cresyl violet, crystal violet, Congo red, Lugol's solution and acetic acid. In the last case, the mucosa turns white, but after a few minutes the BEO changes the colour to red, as does the gastric mucosa. Acetic acid staining ensures a significantly higher detection of BEO, compared to other dyes. With the use of this technique, a targeted biopsy provides a similar rate of histopathological confirmation of BEO to a standard four-quadrant biopsy using the Seattle protocol. It involves a biopsy of four quadrants of the oesophagus at 2 cm intervals from the BEO segment without signs of dysplasia, and at 1 cm intervals in the case of dysplasia, as well as collecting a

Figure 1.

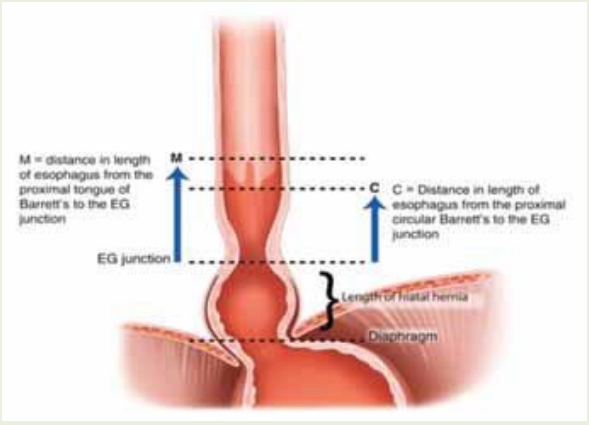
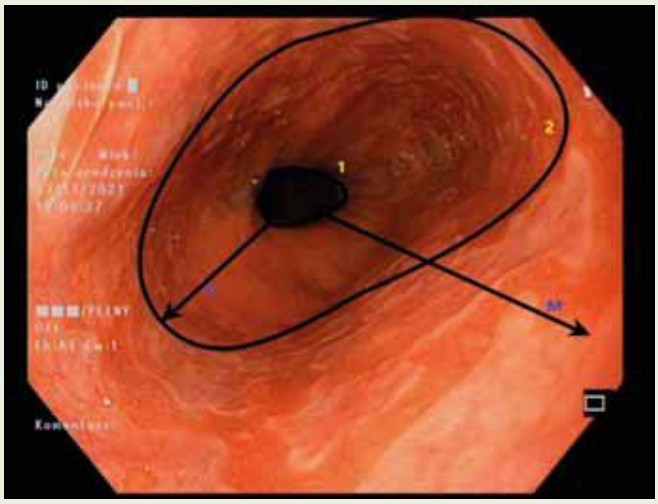


Figure 2.



No. 1 marks the physiological location of the gastro-oesophageal junction (Z-line), the line between the lower limit of the oesophageal palisade vessels and the upper limit of the gastric folds. No. 2 marks the pathological position of the Z-line in the endoscopic study of a patient with Barrett's oesophagus. The C feature in the Prague classification indicates a displacement of the Z-line above its natural position. The M feature in the above classification indicates the maximal extent of the tongues or islands of Barrett's oesophagus that are located above the gastro-oesophageal junction. In the example in Figure 2, the BO extent according to the Prague classification was assessed as C3M5 (own material of the Department of Gastroenterology and Internal Diseases, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine).

specimen from any suspected lesions [14].

Table 1. Comparison of BEO surveillance according to the British Society of Gastroenterology (BSG), the American College of Gastroenterology (ACG) and the International Consensus (BOBCAT) [14,10,5].

Degree of dysplasia	BSG	ACG	BOBCAT
No dysplasia	• BEO <3 cm, without IM: repeat gastroscopy. If no IM is found, discharge from surveillance • BEO <3 cm with IM: gastroscopy every 3-5 years, • BEO ≥3 cm: gastroscopy every 2-3 years • lifestyle modification	• gastroscopy with biopsy every 3-5 years • lifestyle modification	• routine surveillance is not recommended, but if initiated, it should be targeted at the patients at risk of cancer, and it should be based on age, gender, obesity, BEO extent and duration, intensity and frequency of symptoms, nicotinism • no surveillance if life expectancy is <5 years
Unspecified dysplasia:	• optimisation of PPI therapy and endoscopic control within 6 months,	• optimisation of PPI therapy and endoscopic control (no time criterion)	• optimisation of PPI therapy and endoscopic control within 12 months.
LGD	• flat lesions: optimisation of PPI therapy and endoscopic control within 6 months. If LGD in control endoscopy, refer the patient for RFA therapy. If the treatment was not started, gastroscopic control after 6 months • in nodular lesions: EMR and RFA as additive therapy or gastroscopy at 6-month intervals	• flat lesions: optimisation of PPI therapy and endoscopic control (no time criterion). If LGD in control endoscopy, refer the patient for RFA therapy. If the treatment was not started, gastroscopic control after 12 months • nodular lesions: EMR and RFA as additive therapy or gastroscopy at 6-month intervals	• flat lesions: optimisation of PPI therapy and endoscopic control within 6-12 months. If LGD in control endoscopy, refer the patient for RFA therapy • nodular lesions: EMR • if HGD or IMC is found, RFA recommended as additive therapy
HGD or T1a IMC	• flat lesions: RFA • nodular lesions: EMR + subsequent RFA as additive therapy	• flat lesions: RFA • nodular lesions: EMR + subsequent RFA as additive therapy	• flat lesions: RFA • nodular lesions: EMR + subsequent RFA as additive therapy,
Adenocarcinoma	• T1b sm1: oesophagectomy, EMR+RFA in patients who do not qualify for a surgical procedure, and a low risk of tumour • ≥T1b sm2: oesophagectomy	• T1b sm1: oesophagectomy. EMR+RFA in patients who do not qualify for a surgical procedure, and a low risk of tumour • ≥T1b sm2: oesophagectomy	• T1b sm1: oesophagectomy, EMR+RFA in patients who do not qualify for a surgical procedure, and a low risk of tumour • ≥T1b sm2: oesophagectomy

*LGD: low-grade dysplasia, HGD: high-grade dysplasia, IMC: intramucosal carcinoma, BEO: Barrett's oesophagus, RFA: radio frequency ablation, EMR: endoscopic mucosal resection. *It is worth noting that the above societies suggest assessment of the histopathological material conducted by two independent pathomorphologists if at least indefinite or low dysplasia is observed in the biopsy specimens.*

Virtual chromoendoscopy

Recently, virtual endoscopic techniques: NBI (Narrow Band Imaging), i-scan, FICE (Fuji Intelligent Colour Enhancement) and CLE (Confocal Laser Endoscopy) are used increasingly. NBI uses light wavelengths of 415 nm (blue) and 540 nm (green). The areas of more intensive colour indicate increased vascularisation, suggestive of pathological changes. The i-scan technique uses a narrow light band and digital image processing, while FICE is based on a similar principle as NBI, but it uses *ad hoc* computer algorithms. CLE combines traditional videoendoscopy and confocal microscopy, which allows for the assessment of the mucosa with an accuracy comparable to a histopathological examination. Before the test, a fluorescent contrast medium, most often fluorescein, is administered intravenously, and following its quick distribution to tissues, it is activated by a laser beam, providing high-resolution images (Confocal Laser Endomicroscopy). In clinical practice, also in our centre, NBI and i-scan are the most frequently used techniques.

Classic endoscopic examination of the upper gastrointestinal tract remains the unachievable gold standard of BEO diagnostics. However, alternative techniques for the diagnostics of the disease are being researched. They include Cytosponge, confocal laser endomicroscopy and breath analysis. The last method may be an attractive screening technique for oesophageal cancer, as it is non-invasive, and may be conducted as part of primary health care [15]. One report presents a volatile organic compounds (VOCs) panel that may be used in this technique [16, 17]. A study by Chang et al. used a nasal device (Aeonose, The eNose Company, Zutphen,

Netherlands) including sensors covered by metal oxides that react with a broad range of volatile organic compounds changing the conductivity in the sensor, which may be presented in a form of a diagram [17]. Despite the use of new diagnostic techniques, a histopathological examination remains the gold standard in the detection of BEO and its complications.

The pathogenesis of Barrett's oesophagus has not been fully explained. Transdifferentiation is a potential contributing mechanism. It involves the conversion of one type of differentiated cells into another type of differentiated cells. The process may involve two stages: first, cellular rejuvenation (dedifferentiation) takes place and then, as a result, the cells can divide and differentiate into another cell type. Sometimes the process of transdifferentiation may not involve dedifferentiation. The alternative path is transcommittment, in which a number of precursor cells or stem cells may undergo molecular transformations, resulting in abnormal differentiation. This process is most likely caused by environmental change due to GERD [18]. It has been demonstrated that the glands in the metaplastic epithelium in BEO may correspond not only to intestinal glands but also to the glands from the pyloric part of the stomach. It has been hypothesised that intestinalisation occurs with time [19, 20]. These observations additionally illustrate the challenges with a clear definition of BEO.

Barrett's oesophagus as a risk factor for oesophageal cancer

Barrett's oesophagus is the only known precursor of oesophageal adenocarcinoma. The first observations indicating a potential for BEO progression to cancer come from endoscopic studies conducted in the 1970s [3]. The intermediate stages involve low-grade and high-grade dysplasia. The risk of oesophageal cancer in patients with BEO is 11 times higher than in the general population, while the annual risk in this population is estimated at 0.11% [9]. Metaanalyses of numerous published studies indicate that progression of BE to oesophageal cancer is observed in 2.2% to 6.3% per 1000 patients per year [3]. A retrospective study involving 460 patients with BEO, diagnosed in the years 1992-2013 in John Hopkins Hospital (USA), demonstrated that in 120 patients the changes progressed to high-grade dysplasia, and in 62 patients to oesophageal cancer [9]. The risk factors for dysplasia and cancer of the oesophagus include advanced age, length of Barrett's oesophagus, central obesity, tobacco smoking, and not using non-steroidal anti-inflammatory drugs, protein pump inhibitors and statins. The annual risk of low-grade dysplasia progressing to cancer is estimated to be approximately 0.7%, whereas in the case of high-grade dysplasia, the estimated risk is approximately 7% [10]. The recent intensive research on biomarkers of increased risk for oesophageal cancer is promising. Particularly interesting are the studies on genetic disorders that can be detected at the early stages of the development of lesions; however, at the present stage, they have no application in clinical practice.

Pharmacological treatment

The BEO therapy is based on proton pump inhibitors (PPI) in standard doses (i.e. esomeprazole 20 mg/day; lansomeprazole 30 mg/day; omeprazole 20 mg/day and pantoprazole 40 mg/day), which have the greatest effect on modelling the course of the disease [21]. No data is available on the chemopreventive effect of PPIs on the development of BEO ~~O~~. Some studies suggest a beneficial effect of 300 mg/day of acetylsalicylic acid and/or non-steroidal anti-inflammatory drugs and statins in combination with PPI. At present, there is insufficient evidence to recommend such management. Antioxidants are also sometimes used, e.g. melatonin, which demonstrates a protective effect on the oesophageal mucosa, protecting it from endogenous (hydrochloric acid, pepsin) and exogenous (alcohol, NSAIDs) toxic factors. Melatonin supplementation is safe, and its mechanism of action, apart from eliminating free radicals, is also associated with its immunomodulating and pro-apoptotic properties [22].

Endoscopic treatment methods

The development of surgical endoscopy provided safe and minimally invasive techniques for the treatment of BEO, associated with a relatively low risk of complications. They primarily consist of intraoperative resection and ablation of focal lesions. These procedures require sufficient experience, as well as proper patient selection and preparation. Endoscopic methods of treatment of BEO include endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), radio frequency ablation (RFA), cryotherapy, argon plasma coagulation (APC), multipolar electrocoagulation (MPEC), photodynamic therapy (PDT), Nd:YAG laser therapy and KTP laser therapy. In patients who do not respond to pharmacotherapy and/or endoscopic treatment, oesophagectomy is recommended.

• Endoscopic mucosal resection

Endoscopic mucosal resection (EMR) is a therapeutic procedure involving the separation of the submucosal membrane and the muscle membrane, and the removal of the dysplastic epithelium. EMR is associated with a low risk of perforation, due to a loose adhesion between the two layers [23]. EMR is effective in the treatment of BEO segments of up to 15 mm. At present, the most effective and relatively the safest are the method's variants using a cap and rubber bands, although local bleedings, perforations and strictures due to scarring may occur. Bleeding is observed in 0-46% of cases, and it most often occurs during the procedure. The risk of perforation is estimated at 5% (it is the highest during the procedure), whereas the risk of strictures has a broad range, from 2% to 88%, proportionately to the extent of the area treated, and it is the highest in the case of BEO involving >75% of the oesophageal circumference [23, 24].

• Endoscopic submucosal dissection

Endoscopic submucosal dissection (ESD) is a technique introduced in Japan for the removal or early neoplastic lesions in the stomach. Due to its universal character, the procedure is now performed in patients with preneoplastic

and neoplastic lesions of the stomach, oesophagus, large intestine and duodenum. After preparation and marking of the resection area, the resected area is separated from the muscle layer using the endoscopic tools dedicated to this method. This technique enables the *en bloc* resection of even extensive lesions, with high precision, which is reflected in the level of radicality of the procedure [25]. The risk of bleeding is similar to that of mucosal resection, whereas the risk of perforation is higher. In most cases, the latter may be treated endoscopically with clips [26].

• Radio frequency ablation

Radio frequency ablation (RFA) is the endoscopic method most often used in the treatment of BEO. In this technique, an alternating current of 300-500 kHz passes through a balloon-based electrode and generates a lot of heat, which results in thermal damage to the surrounding tissues to a depth of 500-1000 µm. The scope of the procedure depends on the placing of the electrodes on the balloons: 360° – the angle for the treatment of circumferential lesions, and 90° and 60° – for focal lesions. To eradicate BEO, typically 2-4 procedures within 3-6 months are required [27], and the assessed effectiveness of RFA is 98%. The most common adverse event, observed usually up to 3-4 days after the procedure, is a pain in the thorax. Oesophageal strictures are found in approximately 8% of patients, and they may be effectively treated with endoscopic dilation. Bleedings and perforations occur very rarely [28]. Considering the above, RFA is currently considered the method of choice. Despite the presented benefits, it is not commonly available in Poland. This is probably due to the fact that specialist equipment is required, and the procedure is associated with high costs.

• Argon plasma coagulation

Argon plasma coagulation (APC) is a non-contact endoscopic technique, commonly used to eliminate vascular lesions. APC uses the conduction of high-frequency current by an ionised gas, argon in this case. As the gas is ionised by the current, it creates plasma in which electric arcs are formed, producing high temperatures. This, in turn, results in thermal tissue damage. The depth of the electric arc may be regulated by changes in the amperage, gas flow and/or gas pressure. Due to the thermal damage, in approximately 5-10% of patients, this method may lead to strictures and tissue scarring. To reduce this rate, hybrid APC may be used, involving submucosal injection of fluids, e.g. sodium chloride. Other complications of APC include discomfort in the upper abdomen and thorax, dysphagia and odynophagia. Perforations and bleeding are rarely observed [29]. Critics of the method point out the discrepancies in the assessment of its effectiveness, from 50% to 80% [30]. Moreover, in approximately 9% of patients, despite a complete eradication of BEO~~,~~ so-called "gland burning" was observed. It is associated with the risk of preservation of the dysplastic cells which may demonstrate a malignant progression to ECA [31]. The advantages of the method include its broad availability and cost-effectiveness.

• Multipolar electrocoagulation

Multipolar electrocoagulation (MPC) is another method using thermal ablation. It involves using an electric current, passing through a catheter introduced through the endoscope's working channel to the abnormal tissue. This technique is used especially in patients with flat BEO lesions, without raised lesions [32]. Randomised studies demonstrate a higher MPC effectiveness than APC, 75% vs. 63%, respectively. Pain and dysphagia are the most common peri- and post-operative complications of MPC. The risk of bleeding and perforation is minimal.

• Cryotherapy

Cryotherapy is also a thermal ablation technique. The abnormal tissue is destroyed by freezing, followed by thawing, and the cycle is repeated a few times in several minutes. The procedure should be repeated every few months, in order to achieve complete therapeutic success. Cryotherapy uses liquefied gases, such as nitrogen, nitrous oxide or carbon dioxide. Their application in the form of an aerosol (non-contact method) results in the interruption of cellular membranes and the formation of microclots in small blood vessels, which induces apoptosis. A modification of the "cryospray" technique is contact therapy with the use of cryoballoon. The extent, and especially the depth of the frozen area, depends on the duration of exposure, which affects the number of complications, including retrosternal pain, stricture requiring dilation treatment and dysphagia. Perforation is rarely observed. At present, a few types of cryotherapy systems are used, and they enable the application of temperatures from -78° C to -196° C [33]. Cryotherapy is effective, safe, and relatively inexpensive. Its main indications include treatment of the surfaces of the ~~o~~esophageal strictures and/or irregular surfaces. Due to a deep thermal penetration, it is also used in the treatment of extensive lesions and ECA [34]. Cryotherapy, especially with the use of a cryoballoon, demonstrates an effectiveness comparable to that of RFA, approximately 88-90% [35]. It may be applied when RFA is ineffective (second-line treatment), reducing dysplasia in 75% of patients and intestinal metaplasia in nearly 50% of patients [36].

• Photodynamic therapy

Photodynamic therapy (PDT) is one of the oldest tools for the ablation treatment of BEO. The procedure involves the application of a photosensitiser on the metaplastic oesophageal endothelium. Next, the photosensitiser is activated by the light of a specific wavelength. Photosensitisers included dye derivatives, such as hematoporphyrins, rhodamines, chlorophylls and phthalocyanines. In some countries, 5-aminolevulinic acid is administered orally on the day of the procedure, but its use may be associated with hypersensitivity and pain symptoms. Photosensitisers may also be administered intravenously in the form of porfimer sodium or photofrin [37]. The decisions regarding further PDT sessions are taken following a follow-up histopathological assessment of the specimens from the PDT application sites. As in APC, the "gland burning" effect may be observed, which is associated, as mentioned before, with the potential

preservation of the metaplastic cells. The risk of strictures after the procedure is high, increasing the costs of treatment. In addition, tissue hypersensitivity to photosensitisers may develop, and persist for up to 6 weeks following the procedure. Sometimes nausea and vomiting occur, as well as transient dysphagia. The effectiveness of PDT is relatively low. In a randomised study involving 68 patients, the effectiveness of eradication was 50%, compared to 97% in patients treated with APC [29]. In a metaanalysis by V. Thoguluva Chandrasekar et al., the effectiveness of eradication in patients with LGD and HGD was 92.2% and 77.5%, respectively, and 44.1% in the patients with intramucosal carcinoma [38]. The advantages of this method include deep tissue penetration by the light band, associated with a high potential for the reduction of ECA development in patients with dysplasia, as well as the simplicity of the technique [32]. New and more effective treatment methods are beginning to replace PDT.

• Laser methods – Nd:YAG and KTP laser

The laser methods, such as a neodymium-doped yttrium aluminium garnet (Nd:YAG) and potassium titanyl phosphate (KTP) laser, are also thermal methods. They are not as common as the other presented thermal techniques. These methods use crystals that, under the influence of laser radiation of the proper wavelength (532 nm), damage tissues. The penetration depth is relatively small, which makes the method safe regarding the potential risk of perforation. They are used in combination, or separately. The laser methods appear to be relatively safe and effective. Gossner et al., having used a laser technique in 10 patients with short-segment BEO, did not report any adverse events, and the eradication effectiveness after 15 months was 80% [39].

Conclusions

Oesophageal adenocarcinoma is a significant health problem, and its incidence is increasing. Therefore, it is important to find methods for early detection not only of cancer but also of pre-cancer conditions that may be treated effectively. Regarding the latter, endoscopic methods and proper management of patients with BEO are considered to be of great importance. Numerous studies indicate that a combination of resection and ablation methods is the most effective. Based on everyday clinical practice, despite the common availability of guidelines, they still are not followed in the surveillance of patients with BEO. The main goal of this article is to promote the management of patients with BEO approved by international scientific societies.

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REVIEW ARTICLE

TREATMENT OF THYROID ORBITOPATHY (GRAVES ORBITOPATHY) BASED ON EUGOGO 2021 GUIDELINES, WITH A FOCUS ON THE POLISH REALITY

Leczenie orbitopatii tarczycowej (gravesa) na podstawie wytycznych eugogo 2021 z uwzględnieniem warunków polskich

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Abstract: The European guidelines for medical management of Graves' orbitopathy (GO) were updated in 2021, introducing modifications to previous treatment methods. It has also opened the way for new pharmacotherapeutics, which can be an alternative to standard treatments. Although some products are difficult to obtain in Poland, the paper presents all the recommended therapeutic options, focusing on the practical aspect of diagnosis and treatment. According to the current state of knowledge, the most beneficial therapeutic option in case of moderate-to-severe GO is weekly glucocorticoid (GC) pulse therapy (4.5 g methylprednisolone per 12-week cycle) together with daily oral intake of mycophenolate. An equal option is the use of high-dose GCs (7.5 g of methylprednisolone per 12-week treatment cycle, compared to the 4.5 g previously recommended). Second-line treatment proposals have also been updated. Treatment regimes of sight-threatening GO has not changed significantly.

Streszczenie: Europejskie wytyczne leczenia orbitopatii tarczycowej zostały zaktualizowane w 2021 r., wprowadzając modyfikacje dotychczas stosowanego leczenia. Otworzyły również drogę nowym terapeutykom mogącym służyć jako alternatywa standardowego postępowania. Mimo ograniczonej dostępności niektórych preparatów na terytorium Polski w artykule przedstawiono wszystkie zalecane opcje terapeutyczne, skupiając się na praktycznym aspekcie diagnostyki i leczenia. W przypadku orbitopatii tarczycowej, umiarkowanej do ciężkiej, najkorzystniejszą opcją terapeutyczną, zgodnie z obecnym stanem wiedzy, jest zastosowanie cotygodniowych pulsów z glikokortykotsteroidów (4,5 g metylprednizolonu na cykl 12-tygodniowy) wraz z codziennym, doustnym przyjmowaniem mykofenolanu. Równorzędną opcją jest stosowanie wyższych dawek GKS (7,5 g metylprednizolonu na 12-tygodniowy cykl leczenia w porównaniu do dotychczas zalecanych 4,5 g). Zaktualizowano również propozycje leczenia drugiego rzutu. Schemat leczenia orbitopatii, która zagraża utratą wzroku, nie uległ istotnym zmianom.

Key words: Graves orbitopathy, orbitopathy, hyperthyroidism, thyroid orbitopathy, mycophenolane.

Słowa kluczowe: orbitopatia Gravesa, orbitopatia, nadczynność tarczycy, orbitopatia tarczycowa, mykofenolan.

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Introduction

The European guidelines for the management of Graves' orbitopathy (GO) were updated in 2021, introducing modifications to previous treatment methods. They also opened the way for new pharmacotherapeutics, offering alternatives to standard management.

Despite the limited availability of certain products in Poland, the paper presents all the recommended therapeutic options, focusing on the practical aspect of diagnostics and treatment. Based on the current state of knowledge, the most beneficial therapeutic option in moderate-to-severe GO is therapy with weekly pulses of glucocorticoids (GCs) (4.5 g methylprednisolone per 12-week cycle) combined with daily oral doses of mycophenolate. An equivalent option is the use of high-dose GCs (7.5 g of methylprednisolone in a 12-week treatment cycle, compared to the previously recommended 4.5 g). The second-line therapeutic options have also been updated. The treatment regimen for sight-threatening GO has not changed significantly.

Aetiology

Graves' orbitopathy (GO) is an autoimmune inflammatory disorder of the orbital connective, adipose and muscle tissues. It is a rare (0.54-0.9/100.000 males and 2.67-3.3/100.000 females), but dangerous extrathyroidal manifestation of Graves' disease. Apart from Graves'

disease (90% of all cases), orbitopathy may develop also in Hashimoto's disease (5%), as well as in patients without any clinical symptoms of thyroid disorders (5%). GO is caused by the effect of the immune complexes (mainly TRAb and IGF-1) on the orbital tissues. It leads to the infiltration of lymphocytes, plasma cells, macrophages and mast cells, followed by a release of cytokines and proinflammatory factors, resulting in cellular proliferation in the mentioned orbital tissues, and in damage to the visual system [1, 2].

Diagnosis

The basis of effective treatment of GO is an accurate diagnosis and referral to a reference centre. Specialist facilities may offer a broad range of therapeutic options, adapted to individual patients' needs and clinical status. The tasks of the physician, who sees the patient first, includes providing information about the risks associated with a non-treated disease (loss of vision), informing about the strict prohibition of smoking (including passive smoking!), and if thyroid dysfunction is observed, introducing pharmacological therapy (thyreostatic drugs). The risk factors for the disease, apart from the previously mentioned tobacco smoking, include previous radioiodine therapy, high antithyroid antibody titres (anti-TSH-R, i.e. TRAb) and hypercholesterolaemia [1, 3].

Classification

The classification is based on clinical activity (active/inactive) and severity of the course of the illness (mild, moderate-to-severe and sight-threatening).

- Activity is assessed using the CAS score (Table 1). The disease is considered active if the CAS ≥ 3.

Table 1. CAS score

Clinical characteristic	Score
Retrobulbar pain (at rest, spontaneous)	1
Pain with eye movement	1
Eyelid erythema	1
Conjunctival redness	1
Swollen eyelids	1
Swollen conjunctiva	1
Swollen caruncle	1

- Severity is assessed based on a clinical examination (Table 2).

Table 2. The severity of orbitopathy.

Orbitopathy	Symptoms
Mild	Typically ≥ 1 of the following symptoms occurs: — minor eyelid retraction (< 2 mm) — minor involvement of the orbital soft tissues — proptosis < 3 mm over the race- and sex-appropriate normal values — transient double vision or loss of vision — corneal lesions, subsiding after the use of hydrating agents
Moderate-to-severe	Typically ≥ 1 of the following occurs: — eyelid retraction ≥ 2 mm — moderate or advanced involvement of the orbital soft tissues — proptosis ≥ 3 mm over the race- and sex-appropriate normal values — transient or constant double vision
Sight-threatening	Optic nerve neuropathy and/or corneal damage

Treatment

General recommendations

The basic management, for every patient, is the elimination of the factors inducing and exacerbating the disease, as well as therapy regulating the concentrations of thyroid hormones. In most cases, the first-line pharmacotherapeutic is thiamazole (Metizol®/Thyrozol®) in a dose sufficient to maintain fT4 in the upper half of the reference range. Iatrogenic hypothyroidism must be avoided, as it is associated with an adverse prognosis.

Locally applied agents (artificial tears) are used as symptomatic treatment, recommended in most patients. Intraconjunctival GCs are not recommended. New guidelines also mention the use of swimming goggles during the night [4], as well as injection of botulinum toxin into the levator palpebrae superioris [5] in the case of severe conjunctival drying.

Mild GO

Apart from the previously mentioned general principles, in the mild phase, a six-month therapy is applied with 200 µg/day of selenium or 100 µg/day of selenomethionine on an empty stomach [6, 7].

If the quality of life deteriorates, low doses of immunosuppressants may be administered in active GO (Encorton 20-40 mg/day in two divided doses), or in the case of inactive GO (CAS < 3), surgical procedures for orbital decompression may be conducted.

Moderate-to-severe GO

Apart from the general principles, the new guidelines mention two potential lines of treatment [1]:

Table 3. First-line treatment of moderate-to-severe orbitopathy – therapeutic options.

OPTION 1		OPTION 2	
0.5 g of i.v. methylprednisolone once weekly, for 6 weeks + 0.72 g* of oral mycophenolate sodium per day		0.75 g of i.v. methylprednisolone once weekly, for 6 weeks	
Response or partial response	**No response**	**Response or partial response**	**No response**
0.25 g of i.v. methylprednisolone once weekly, for another 6 weeks + 0.72 g of oral mycophenolate sodium per day, for 18 weeks	Introducing second-line treatment	0.5g of i.v. methylprednisolone once weekly, for 6 weeks	Introducing second-line treatment
If a response is obtained, stop treatment and conduct outpatient monitoring		If a response is obtained, stop treatment and conduct outpatient monitoring	

*(0.72 g of oral mycophenolate sodium is equivalent to 1 g of mycophenolate mofetil)

- first-line treatment (active orbitopathy) – two equivalent therapeutic options are available (Table 3):

In the case of inactive orbitopathy, surgical treatment should be considered.

Option 1 is noteworthy, as it is a new addition to treatment standards. In a single-centre study (China) in 174 patients, the combined treatment with methylprednisolone and mycophenolate proved to be superior, providing 79% of remissions vs. 51% (for methylprednisolone alone) at 12 weeks of therapy, and 91% vs. 68% at week 24 of therapy [8].

Multicentre studies (Germany, France) confirmed a significant superiority of the combined treatment in terms of disease remission rates (71% vs. 53% at week 24 and 67% vs. 45.5 % at week 36 of follow-up) [9, 10].

Due to the significant benefits of the two-drug therapy, despite the fact that mycophenolate is not approved in Poland, for the treatment of Graves' orbitopathy, such treatment should be considered and offered to patients in reference centres. This approach is supported not only by the health benefits, but also by economic factors, including the relatively low cost of the therapy, reduction of the potential costs of second-line therapy, disease recurrences, or surgical treatment costs for the patient and the system.

The cost of the mycophenolate therapy for 01/05/2022 (taking into account 100% of the drug price, and considering the cheapest generic drug) is approximately 3.88 PLN/day for mycophenolate sodium (approx. 116 PLN/month), and approximately 3.22 PLN/day for mycophenolate mofetil (approx. 97 PLN/month).

- second-line treatment (active orbitopathy) – the guidelines recommend 6 equivalent therapeutic options, of which three are available in Poland, two are available in Poland in reference centres, but not approved for the treatment of GO, and one is not available in Poland.

Table 4. Second-line treatment of thyroid-associated orbitopathy – therapeutic options.

Available in Poland			Available in Poland for other indications		Available only in the USA
0.75g of i.v. methylprednisolone once weekly, for 6 weeks	Oral prednisone/prednisolone with oral cyclosporine (7.5 mg/kg/day) or oral azathioprine (1-3 mg/kg/day) [11]	Orbital radiotherapy with oral or intravenous glucocorticoids	rituximab	tocilizumab	teprotumumab

Teprotumumab, an antibody blocking IGF-1-R in orbital fibrocytes, is a new addition to the 2016 EUGOGO guidelines [3]. Studies demonstrated it has the strongest reducing effect on proptosis [1].

In inactive GO, surgical treatment is applied (orbital decompression, tarsorrhaphy). Pharmacotherapy of this form of GO is ineffective and not recommended.

Sight-threatening GO

As in the previous cases, the general guidelines apply, but urgent hospitalisation in a reference centre is required to implement the management presented in Table 5.

Table 5. Treatment of sight-threatening thyroid-associated orbitopathy.

<table>
<tr><td colspan="3">1. Single doses of i.v. methylprednisolone (0.5–1 g) daily, for three consecutive days (or on every second day).</td></tr>
<tr><td colspan="3">2. Daily monitoring of the patient's clinical status. After one week, evaluation of the indications for treatment continuation.</td></tr>
<tr><td colspan="2">3. A) Gradual improvement</td><td>3. B) Deterioration of the condition or lack of response</td></tr>
<tr><td colspan="2">4. Repeat the management in point 1
(0.5-1 g of methylprednisolone in a single dose, for three consecutive days, or on every second day).</td><td>Urgent orbital decompression surgery (qualification following imaging studies)</td></tr>
<tr><td>5a. Response:</td><td>5b. Partial response</td><td></td></tr>
<tr><td>0.5 g of i.v. methylprednisolone once a week (cumulative dose <8 g/cycle)</td><td>Urgent orbital decompression surgery (qualification following imaging studies)</td><td></td></tr>
</table>

Complications of systemic glucocorticoid therapy

The high doses of glucocorticoids required in the treatment of orbitopathy may lead to exacerbation or diagnosis of cardiometabolic diseases, of which the most often observed ones are arterial hypertension and diabetes mellitus [12]. These disorders are not indications for treatment discontinuation but require initiation or adjustment – in most cases temporary – of hypotensive therapy and insulin therapy. Intensive insulin therapy is the preferred option and since no insulin product or analogue has been demonstrated to be superior to others, the product and dose should be individually selected. In patients with type 2 diabetes mellitus treated with oral antidiabetic drugs, temporary intensive insulin therapy is also recommended [13].

Conclusion

The updated guidelines introduced changes in the treatment regimens, which may improve the management of orbitopathy, and reduce the need for second-line treatment. Despite the fact that some of the drugs are not available, or are not approved for the treatment of GO in Poland, an off-label therapy, especially with mycophenolate, should be offered to every patient. The safety and significant therapeutic superiority of this therapy, confirmed in multicentre studies, may improve the prognosis in many patients and reduce the need for surgical intervention or radiotherapy. It is beneficial not only for the patient but also for the entire healthcare system. Mild complications (hypertension, diabetes mellitus) are typically transient and require only standard hypotensive therapy and insulin therapy.

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REVIEW ARTICLE

MECHANISMS OF ACTION AND EXPECTED CLINICAL EFFECTS OF MODULATION OF THE MALT SYSTEM BY ORAL BACTERIAL LYOPHYLISATES

Mechanizmy działania i spodziewane efekty kliniczne modulacji układu malt przez doustne liofilizaty bakteryjne

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Abstract: The paper outlines mechanisms and describes expected clinical effects of MALT modulation by selected generally available oral immune vaccines that enhance anti-infective immunity. Non-specific vaccines (oral, intranasal and injectable ones) are used to prevent and treat recurrent infections of the respiratory tract, paranasal sinuses and middle ear, to reduce exacerbations of allergic respiratory tract inflammation, as well as in urogenital tract infections. Considering the current epidemiological situation, previous incidents of infectious disease epidemics, as well as diseases resulting from inadequate protection of the body against pathogens, the benefits of oral vaccine immunomodulatory properties should be taken under consideration. These products are safe, effective and reasonably-priced compared to traditional vaccines and are most commonly used in patients at risk of recurrent infections. They are most applicable in the group of patients exposed to recurrent infections. Patients suffering from chronic respiratory diseases (e.g. asthma, COPD) are a particular target group. Oral vaccines can influence various cells of the immune system by altering their activity and production of messenger proteins (cytokines, growth factors, chemokines, interferons). Observed clinical effects of oral vaccines most often include prevention or reduction of infection incidence, as well as shortening their duration and inflammation spread suppression, which leads to a reduction in the frequency and duration of antibiotic use. Taking oral immune preparations has also reduced the amount of medication being applied. Oral immune vaccines modulate MALT specifically and non-specifically, enhancing the mucosal and systemic immune system, resulting in improved clinical parameters.

Streszczenie: Celem pracy jest przedstawienie mechanizmów działania i opisanie spodziewanych efektów klinicznych modulacji układu MALT przez wybrane, ogólnodostępne doustne szczepionki immunologiczne podnoszące poziom odporności przeciwinfekcyjnej. Szczepionki nieswoiste (doustne, donosowe i iniekcyjne) stosuje się w profilaktyce i leczeniu nawracających zakażeń dróg oddechowych, zatok przynosowych, ucha środkowego, redukcji zaostrzeń alergicznego zapalenia dróg oddechowych a także w zakażeniach dróg moczowo-płciowych. Biorąc pod uwagę obecną sytuację epidemiologiczną, jak również wcześniejsze incydenty epidemii chorób zakaźnych, a także choroby wynikające z niedostatecznej ochrony organizmu przed patogenami, warto rozważyć korzyści, jakie niosą za sobą immunomodulujące właściwości szczepionek doustnych. Preparaty te są bezpieczne, skuteczne, korzystne cenowo względem tradycyjnych szczepionek. Największe zastosowanie mają w grupie pacjentów narażonych na nawracające infekcje. Doustne szczepionki mogą oddziaływać na różne komórki układu odpornościowego, zmieniając ich aktywność oraz produkcję białek porozumiewania komórkowego (cytokin, czynników wzrostu, chemokin, interferonów). Obserwowane efekty kliniczne stosowania doustnych szczepionek to najczęściej zapobieganie lub zmniejszanie częstości występowania infekcji, jak również skracanie czasu ich trwania oraz ograniczenie szczerzenia się stanu zapalnego, co w konsekwencji umożliwia zmniejszenie częstości i czasu stosowania antybiotyków. Przyjmowanie doustnych preparatów immunologicznych ograniczało też liczbę stosowanych leków. Oral immune vaccines modulate MALT specifically and non-specifically, enhancing mucosal and systemic immune system, resulting in improved clinical parameters.

Key words: immunomodulation, oral bacterial vaccines, MALT, increase of immunity.

Słowa kluczowe: immunomodulacja, doustne szczepionki bakteryjne, MALT, zwiększanie odporności.

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Introduction

Mucous membranes, covering a surface of up to 400 m² in an adult person, and the lymphoid follicles located in them [1], form the largest organ of the immune system, MALT (mucosa-associated lymphoid tissue) [2]. Mucous membranes are the main site of contact between the organism and the external environment, and the main entry route for infectious and potentially harmful factors. Therefore, apart from physicochemical protective barriers, the organism has developed a variety of innate and acquired mechanisms within MALT [3]. Their task is to defend the organism against external threats [4].

The lymphoid tissue of the mucosa, known as MALT, is located in the upper respiratory tract (NALT – nasal-associated lymphoid tissue), the lower respiratory tract (BALT – bronchus-associated lymphoid tissue), the gastrointestinal tract (GALT – gut-associated lymphoid tissue), the skin (SALT – skin-associated lymphoid tissue) or the genitourinary system. Although individual MALT structures are anatomically separated, they co-operate, forming the common mucosal immune system. The concept of the common mucosal immune system is based on the assumption that interaction between lymphocytes and an antigen in one part of the mucous membrane (due to the migration potential of these cells) may ensure immunity in the mucosa of other, distant systems or organs [4].

Immunomodulation with oral vaccinations appears thus to be a promising method for increasing immunity, as well as for therapy of acute or chronic infections. Contrary to traditional vaccinations, included in the vaccination programme, oral preparations induce a local immune response, in the gastrointestinal tract, against the antigens of the pathogens present in the vaccine, and thanks to the circulation of the immune cells, and their ability to populate other structures associated with MALT (salivary glands, mammary glands, respiratory mucosa and genitourinary mucosa), they also provide broad protection. Oral vaccinations supporting the immune system contain mainly bacterial antigens, to which specific immunity develops; however, by activating numerous defence mechanisms of MALT, they may also stimulate the non-specific defence mechanisms participating in the response to other pathogenic factors, which includes antiviral immunity. Building antiviral immunity following the administration of bacterial lysates is associated primarily with an increased expression of Toll-like receptors on lymphocytes. This property gains particular importance in disease prevention, especially now, when new types of viruses appear, demonstrating high virulence, and effective methods of their eradication have not been developed yet. A lack of effective treatment methods and the increasing infectivity of viruses result in a large number of infections with a severe and acute course, which may be associated with fatal outcomes.

1. Oral immune vaccinations – benefits

At present, due to many reasons, the development of oral vaccinations is preferred. They have numerous advantages over those administered by injection. Since the gastrointestinal mucosa covers the largest area of all the mucous membranes, administration of vaccines via this route is easy and ensures quick activation of the vaccine. The oral route is the most desirable and accepted by patients for the administration of medicinal products. Numerous analyses demonstrate that over 60% of commercially available low molecular-weight medicinal products are administered this way. However, and most importantly, the oral route enables the stimulation of both the humoral and cellular immune response, on a local and general systemic level, which leads to broader and more long-term protection [5].

2. Immune effect of oral vaccines

Oral vaccines, acting locally on the mucosa due to the use of proper adjuvants, induce a general systemic response – associated with IgG, a defence response – associated with sIgA, as well as a cytotoxic response – in the ADCC (antibody-dependent cell cytotoxicity) response, targeting pathogens. Thanks to the migration of the IgA-producing cells, local mucosal immunisation leads to the presence of antigen-specific IgA in distant areas of the mucosa. However, as soluble antigens may not be effectively caught during a transmucosal administration, and generally they induce immune tolerance, mucosal immunisation requires the use of adjuvants and/or efficient carriers as antigen delivery systems. Therefore, it has been postulated that the perfect mucosal vaccine should:

- contain antigens that are protected against enzymatic or chemical degradation,
- reduce their elimination or excessive dissolution in the organism,
- facilitating a preferential internalisation of antigens by antigen-presenting cells (APCs) and epithelial cells in order to adequately stimulate specific immunity (sIgA), as well as T-cytotoxic (LTc) and/or T-helper (LTh) lymphocytes. In this mechanism, the secretory IgA coat the bacteria, thus blocking colonisation of the mucosal epithelium by these pathogens, and demonstrate a strong anti-adhesive effect, which reduces the risk of bacterial penetration inside the organism. sIgA inactivate also bacterial and viral protein toxins and can activate cells capable of spontaneous or antibody-

mediated cytotoxicity (NK cells, LTc), which translates into anti-infective protection.

3. Immunology of the gastrointestinal tract following the administration of an oral vaccine

After the administration of an oral vaccine, its antigens reach the small intestine. There they are in contact with the mucous membrane and the associated structures, e.g. accumulation of lymphoid tissue in the form of dispersed or grouped lymphoid follicles, present in the gastrointestinal tract in Peyer's patches. The groupings of lymphoid tissue contain immune cells that can present antigens. They include dendritic cells, B lymphocytes (BL) and macrophages. The GALT system also contains specialised M cells, as well as T cells, NK cells, granulocytes, mast cells and others. After the antigen is presented to T lymphocytes (CD4) by the APCs (antigen-presenting cells), the lymphocytes differentiate into LTh2, demonstrating anti-inflammatory properties, or LTh1, with a pro-inflammatory effect. By producing certain cytokines, LTh2 stimulate BL to generate specific antibodies against the identified antigen, which initiates the humoral response. The stimulated B lymphocytes transform into plasma cells and produce specific antibodies. They can also migrate over long distances, via systemic circulation, to lymph nodes, where they reside, ready to react once more to the presence of a known antigen. Simultaneously, dendritic cells migrate to lymph nodes to activate the humoral and cellular response by interacting with T lymphocytes and B lymphocytes residing in germinal centres [5].

4. Mechanisms of action and expected clinical effects of using selected oral immune vaccines

The non-specific bacterial vaccines with immunomodulating effects available on the market vary in composition. They contain antigens of different pathogenic bacteria, typically responsible for respiratory and genitourinary disorders, as well as other infective diseases (typhoid fever, cholera). The composition of a vaccine is determined by its prophylactic goal and the manufacturer's choice. Similarly, the doses of antigens of individual bacterial strains may vary between preparations. The basic ingredients in these products are bacterial lysates and ribosomal fractions, as well as components of bacterial cell walls obtained from the species that most often cause respiratory infections, such as *Staphylococcus aureus*, *Streptococcus viridans*, *Streptococcus pneumoniae* (several serotypes), *Streptococcus pyogenes*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Moraxella catarrhalis* and *Haemophilus influenzae*. Previously described was the composition of the Broncho-Vaxom vaccine (OM Pharma SA, Portugal). 1 capsule of Broncho-Vaxom contains 7 mg or 3.5 mg (version for children) of the bacterial lysate, whereas 1 tablet of another vaccine – ISMIGEN (Lallemand Pharma Europe, Italy) – contains 7 mg of the bacterial lysate, containing 6 billion of the following bacteria: *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus viridans*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Haemophilus influenzae*, *Neisseria catarrhalis*, *Streptococcus pneumoniae* and 43 mg of glycine. UROVAXOM (OM Pharma SA, Portugal) contains a lyophilisate of 60 mg of *E.coli*.

However, regardless of the composition and dose of the antigen, these preparations stimulate the natural defence mechanisms of the organism, which improves immunity to respiratory or urinary infections. This effect is due to the activation of macrophages, T lymphocytes and B lymphocytes. Therefore, treatment outcomes depend on the composition and dosing of the preparation, but also on the individual reaction of the patient's immune system.

Presented above are the general mechanisms of action of bacterial immunity-stimulating preparations. Table 1 presents the composition of antigens in selected vaccines, their dosing, and some study results regarding the immunostimulation mechanisms of individual products.

5. Potential use of oral vaccines in the therapy of COVID-19

Using oral immunological preparations in the prevention and treatment of COVID-19 has a lot of potential. Clinical studies demonstrated that the OM-85 Broncho-Vaxom® bacterial lysate helps to reduce viral infections of the respiratory tract [57, 58]. Infection of the epithelial cells by SARS-CoV-2 depends on the interaction between its spike protein (S protein) and the proteins of the hosts' cellular membrane. One of the studies investigated the effect of OM-85 on the expression of S-protein binding proteins by human bronchial epithelial cells. Human bronchial epithelial cells were treated with OM-85 over 5 days. OM-85 significantly reduced the expression of the ACE2 protein ($p < 0.001$), a receptor for the virus' S-proteins. All effects of OM-85 were concentration- and time-dependent. The results suggest that OM-85 might reduce the binding of SARS-CoV-2 S-protein to epithelial cells by modification of the host cell membrane proteins and specific glycosaminoglycans. Therefore, OM-85 may be considered as a supportive therapy for COVID-19 [59]. The protective effect of oral bacterial vaccines against COVID-19 was also observed in clinical trials. Studies involving paediatric patients emphasised the safety and effectiveness of immunisation with bacterial lysates in the prevention of SARS-CoV-2 infection [60].

It is worth noting that viral mutations may reduce the effectiveness of the currently used vaccines against COVID-19 (i.e. Comirnaty, COVID-19 Vaccine Janssen, Moderna, Astra-Zeneca). Modulation of the leukocyte function due to the bacterial extract in the Broncho-Vaxom (BV) vaccine may provide beneficial results during a coronavirus infection, also due to the stimulation of the immune system.

Table 1. Characteristics, antigen composition, mechanisms of action described in the literature, and dosing of selected bacterial preparations of oral lyophilisates with immunomodulating effects.

Name of the preparation	Antigen composition	Characteristics	Mechanism of action	Dosing regimen
1	2	3	4	5
Broncho-Vaxom (BV)	• *Haemophilus influenzae* • *Streptococcus (Diplococcus) pneumoniae* • *Klebsiella pneumoniae ssp. pneumoniae and sp. ozaenae* • *Staphylococcus aureus* • *Streptococcus pyogenes and sanguinis (viridans)* • *Moraxella (Branhamella/Neisseria) catarrhalis*	BV used in adults and children for the treatment and prevention of recurring respiratory infections [6-11]. Significantly better effects were observed in the group using BV, compared to the control group, in terms of the duration of antibiotic therapy, infection, fever, cough and wheezing. Patients in the BV treatment group demonstrated a higher level of serum immunoglobulins (IgG, IgA or IgM) and T lymphocytes (CD3+, CD4+ or CD8+) compared to the control group [11].	Non-specific activation of mucous membranes and the general systemic immune response. Activation of the immunity mediated by the Toll-like receptor [9, 12, 13]. In allergic rhinitis, BV was associated with symptom reduction, decreased IL-4 and IL-13 concentrations, increased INF-γ concentrations, and reduced eosinophil count [14]. It demonstrated an anti-inflammatory effect, regulates the Th1/ Th2 response, increased IL-10 concentrations, and reduces IL-17 concentrations [15].	The recommended dosing regimen for 3 consecutive months: 1 capsule/sachet per day, on an empty stomach, for 10 consecutive days in a month.
Uro-Vaxom (UV)	• *Escherichia coli*	The UV bacterial extract contains the strains of bacteria frequently involved in the pathogenesis of urinary tract infections. It improves innate immunity by increasing the neutrophil and macrophage count and their phagocytotic potential, and by stimulating dendritic cells [16-20]. It reduces the frequency of urinary infection episodes [21, 22-30].	It increased the metabolic activity of lymphocytes in peripheral blood, reducing spontaneous apoptosis of polymorphonuclear neutrophils. The immunomodulating effect in the urinary tract stimulates the immune response and reduces excessive inflammation [32].	Dosing regimen in the prevention of lower urinary tract infections: • 6 mg once daily, • the drug is to be taken before a meal, • treatment duration: 90 days (3 months). Dosing regimen in the supportive treatment of acute infections: • 6 mg once daily, • the drug is to be taken before a meal, • the drug should be taken until the symptoms subside, for at least 10 days, • the drug may be used in combination with other antibacterial medications.
Luivac (LV)	• *Staphylococcus aureus* • *Streptococcus pneumoniae* • *Streptococcus pyogenes* • *Streptococcus mitis* • *Haemophilus influenzae* • *Moraxella catarrhalis* • *Klebsiella pneumoniae*	Activation of the mucosal immune system. Induces a specific and non-specific immune response. Reduced frequency and duration of respiratory tract infections [31].	Reduced GAS biofilm mass. The direct effect of LV on GAS may complement its immunostimulating function, as GAS biofilms may be associated with recurrent, antibiotic-resistant infections of the respiratory tract [33].	Dosing regimen for adults and children over 4 years of age: • the preparation should be taken for 28 consecutive days in two cycles separated by a 28-day interval, • the tablets are to be taken on an empty stomach, with a small amount of water, • administration of LV usually starts in an infection-free period, • in the case of acute infection, LV may be used

Name of the preparation	Antigen composition	Characteristics	Mechanism of action	Dosing regimen
1	2	3	4	5
				together with antibiotics, but it cannot replace an anti-inflammatory treatment.
Ribomunyl	• *Streptococcus pneumoniae* • *Streptococcus pyogenes* • *Haemophilus influenzae* • *Klebsiella pneumoniae*	Numerous double-blind, placebo-controlled trials with the use of Ribomunyl immunostimulatory in adults have been conducted. The frequency of infections, as well as the number and duration of antibiotic therapies, were significantly reduced in the case of recurring respiratory infections [34]. Prevention of infection recurrence in COPD. Reduced frequency of otitis media, sinusitis and nasopharyngitis [35, 36]. Reduced frequency of recurrent ear, nose and throat infections [37]. The *K. Pneumoniae* fraction of Ribomunyl has been recently described as a powerful TLR-2 stimulator with adjuvant properties in vaccines [38, 39]. Moreover, the immunostimulator has been demonstrated to increase the production of various cytokines, including TNF-α, monocyte chemotactic protein-1, IL-8 and IL-6, involved in the inflammatory reaction. It has also been shown that Ribomunyl induces INF-γ production by NK cells [40]. Similarly to other immunostimulators, it can induce the non-specific activation of T lymphocytes and B lymphocytes. In allergic disease, its regulating effect on the Th1/Th2 response was demonstrated, due to the stimulation of Th1 response. Reduction in IgE secretion was shown [41-43].	Stimulation of antibacterial defence, undertaken directly by innate immunity. Stimulation of specific immune response related to the activation of M cells and dendritic cells present in MALT [42, 44, 45]. Stimulation of the immunity associated with phagocytes[46], increased expression of adhesive molecules. Stimulation of the antiviral response through the stimulation of dendritic cell maturation for processing and presenting antigens to T lymphocytes [41, 476]. Stimulation of the production of IgA that inhibit bacterial adhesion to the epithelium [48, 49].	Dosing schedule: • 1 sachet once daily for 4 consecutive days of the week over 3 weeks, then in the first 4 days of each month, for 2-5 months. • Dissolve the content of the sachet in water.
Ismigen	• *Staphylococcus aureus* • *Streptococcus pyogenes* • *Streptococcus (viridans) oralis* • *Klebsiella pneumoniae* • *Klebsiella ozaenae* • *Haemophilus influenzae* • *Neisseria catarrhalis* • *Streptococcus*	Used in the prophylaxis of upper respiratory infections and severity of exacerbations in COPD [50, 51].	Activation and strengthening of IgM memory B lymphocytes and the lymphocytes expressing the IL2 receptor, involved in the humoral or cellular immunity [52].	Dosing schedule: • once daily, before a meal, for 10 consecutive days of the month, over three months, • the tablet should be placed under the tongue to dissolve.

Name of the preparation	Antigen composition	Characteristics	Mechanism of action	Dosing regimen
1	2	3	4	5
	pneumoniae			
Dukoral	• *Vibrio cholerae O1 Inaba*, classical biotype (heat inactivated) • *Vibrio cholerae O1 Inaba*, El Tor biotype (formalin inactivated) • *Vibrio cholerae O1 Ogawa*, classical biotype (heat inactivated) • *Vibrio cholerae O1 Ogawa*, classical biotype (formalin inactivated) • Recombinant cholera toxin B subunit.	Inactivated oral vaccine, containing killed whole *V. cholerae O1* of a few strains (*Inaba* and *Ogawa* serotypes, classical and El Tor biotypes) and the purified B-subunit of the cholera toxin (WC/rBS). It is intended to stimulate anti-toxin and antibacterial immunity against cholera. It induces the protective response of IgA anti-toxin and immunity to the bacteria [53].	The protection against diarrhoea caused by enterotoxigenic *Escherichia coli* strains (ETEC) after vaccination is mediated by a specific immunity to toxins, not by antibodies against the bacterial cells. The structural similarities between the cholera toxin and the heat-labile ETEC toxin explain the cross-protection against the latter, resulting from the immune response to the former. The vaccine provides effective protection against ETEC, regardless of the type of toxin produced [54, 55].	Dosing regimen for children aged 2-6 years old: • the primary vaccination comprises 3 doses, to be administered orally, at intervals of at least one week, within a maximum of 6 weeks, • the granulate should be mixed with half of the buffer solution, • the child should receive the first dose no later than 3 weeks prior to the planned journey, • the second dose should be administered at least a week after the first one, • the third dose should be administered at least a week after the second one, and not later than one week prior to the planned journey, • for continuous protection, a booster dose is recommended within 6 months, and if more than 6 months have elapsed since the last dose, the primary course should be repeated (3 doses). Dosing regimen for adults and children over 6 years of age: • the primary vaccination comprises 2 doses, to be administered at intervals of at least one week, within a maximum of 6 weeks, • for continuous protection, a booster dose is recommended within 2 years, and if more than 2 years have elapsed, the primary course should be repeated (2 doses).

Name of the preparation	Antigen composition	Characteristics	Mechanism of action	Dosing regimen
1	2	3	4	5
Vivotif	• Viable cells of *Salmonella enterica* serovar Typhi Ty21a	The attenuated *Salmonella typhi* Ty2la strain is the primary ingredient of the preparation – the only attenuated viable oral vaccine for typhoid fever [56]. It is indicated for adults and children over 5 years of age. Vaccination is especially recommended in well-developed countries for high-risk populations, in particular those who travel to destinations where the risk of infection with typhoid fever is high. The vaccine may also be administered in the prophylaxis of malaria.	Stimulation of local, cellular and general systemic immunity. It has been demonstrated that the vaccine induces a good local production of IgA to O antigen, and a good humoral and cellular immunogenicity against the O antigen. Stimulates the increase of serum antibody concentration. Stimulates a strong general systemic CD4+T lymphocyte response; booster doses induced a significant increase of IgG and IgA anti-LPS antibodies. Stimulates the increase of specific plasmablasts expressing receptors in the intestines (a437). Stimulates opsonofagocytosis against S typhi and, to a lesser degree, against S paratyphi A and B.	The recommended dosing regimen (a full vaccination cycle) comprises the ingestion of three capsules: • one capsule is taken every other day, following the schedule: the first capsule is to be taken on a selected day – this is day 1, the second capsule is to be taken on day 3, and the third one is to be taken on day 5, • the vaccination should be completed at least one week prior to travel to an endemic area, • after 3 years, a booster vaccination is recommended – it comprises the ingestion of three capsules, which should be taken as for the original vaccination schedule.

Bacterial vaccines not only protect against infections but also may prevent pulmonary complications of COVID-19. For instance, it has been observed that modulation affects the pathways of the genes responsible for secretion and synthesis of interferon during the treatment with Broncho-Vaxom, virus clearance increases, as well as pulmonary integrity, due to a higher macrophage count in the lungs, which leads to an increased coronavirus clearance and reduced apoptosis of the immune cells and respiratory cells [61].

6. New options for the use of oral bacterial immunological preparations in the treatment of selected diseases

Not all immunomodulation mechanisms of vaccines containing bacterial antigens are used. Moreover, many of their effects have not been fully understood. Therefore, further research is still required on these preparations and their effectiveness against different diseases, especially those in which infection mechanisms significantly affect disease onset, progression or exacerbation (e.g. COPD). Also, the question regarding the possibility and effectiveness of using immunomodulating preparations with other drugs in combination therapy remains open. Interestingly, one of the studies analysed for this paper explored the options of using immunotherapy in the treatment of cardiovascular diseases, which are among the most common causes of death. Based on the evidence, it has been suggested that the mechanism of action of bacterial vaccines in the treatment of atherosclerosis might rely primarily on their anti-inflammatory effect. Some studies demonstrate that therapies with oral bacterial vaccines regulates the Th1/Th2 immune response, improves the Th2 response, and increases the secretion of IL-10, demonstrating an anti-inflammatory effect [15]. The effectiveness of such management in the treatment of atherosclerosis was described in a study by Nilsson and Hansson, who pointed out the considerable potential of mucosal immunisation in the prevention of atherosclerosis [62]. Similarly, studies on animals demonstrated that the administration of Broncho-Vaxom increases HDL concentrations [63].

Other beneficial consequences of the immunomodulating effect of bacterial vaccines include their antioxidative properties. Following Broncho-Vaxom therapy, a significant increase in the activity of superoxide dismutase and catalase in the lungs was demonstrated, as well as a higher glutathione content in erythrocytes The antioxidative effect of the therapy with oral bacterial vaccines is still not fully utilised. They could be used in the treatment of conditions such as neurodegenerative diseases (e.g. Parkinson's disease, Alzheimer's disease), cardiovascular diseases, including atherosclerosis or arterial hypertension, and neoplastic diseases, or they may be considered as supportive therapy of certain causes of infertility [64].

There are numerous potential options for combining oral

immunological vaccines with various dietary supplements, e.g. the combination of oral bacterial vaccines with proven effects in allergy treatment [14, 15] and selenium, the oral supplementation of which, as demonstrated in studies, may modulate allergic reactions to whey protein [65]. Such a combination could strengthen the immunomodulating and synergistic effect of both products. Extending our knowledge about the immunological effects of bacterial lysates used in oral vaccines may enable finding new applications for them in the role of immunomodulators.

Conclusions

Oral vaccines affect various kinds of immune cells. They ensure the activation and proliferation of phagocytes, as well as stimulate their phagocytic function. In addition, these preparations increase the expression of adhesive molecules on certain phagocytes and reduce neutrophil apoptosis. Oral vaccines have a similar effect on lymphocytes, as they activate, stimulate proliferation, regulate their immune function, as well as restore and maintain the balance between Th1/Th2 and CD4/CD8 Moreover, oral vaccines induce activation and maturation of dendritic cells in peripheral blood and in the mucosal membrane. Oral immunological preparations also demonstrate effects on certain immune proteins, i.e. stimulate the production and optimise concentrations of IgG, IgA and IgM immunoglobulins already present in blood serum. Oral vaccines increase concentrations of C3 complement in the blood serum. Additionally, they stimulate the production of certain cytokines, including TNF-α (tumour necrosis factor α), monocyte chemotactic protein, and interleukins IL-8, IL-6, IL-12. Moreover, oral vaccines provide a strong stimulation of Toll-like receptors 2 (TLR2), which recognise the molecular patterns associated with pathogens. In conclusion, there is a large body of evidence to indicate that the oral route for the administration of immunomodulating substances ensures stimulation of the humoral and cellular immune response, not only at the site of contact with the mucosa, but also in distant areas, or in other systems in the organism, as well as stimulation of the general systemic immune response.

The clinical effects of using oral vaccines presented in the analysed literature are usually related to prevention, reduced frequency and the duration of infections, including recurring infections. In genitourinary infections, the administration of oral immunological preparations also limited the frequency of acute infections, as well as proved to be an effective preventive strategy in high-risk patient populations (e.g. pregnant women). Regarding the respiratory tract, oral immunological vaccines appeared to be effective in the treatment, prevention and reduction of the frequency of bacterial episodes and viral infections, reducing symptoms such as cough, fever, shivers or muscle pain. Oral immunological vaccines improved treatment effectiveness, reduced the risk of recurrences and severity of otitis media, sinusitis and nasopharyngitis, as well as general inflammation of the respiratory tract. The available literature data also indicates that oral vaccines may demonstrate a supportive role in the treatment of allergic diseases, such as allergic rhinitis. They may alleviate certain symptoms, such as itching, nasal discharge and sneezing. In addition, using oral preparations affects pharmacotherapy, i.e. reducing the duration of antibiotic therapy, the number of antibiotics used and the courses of antibiotic therapy, it may also eliminate the need for corticosteroids or enable a reduction in their dose in patients with COPD exacerbations, as well as increase the effectiveness of the drugs used in the standard therapy. According to the patients, taking oral immunological vaccines allowed them to reduce the number of days in ill health, days of hospitalisation and days of absence from school or work. The clinical effects are observed in adults, children and infants.

In summing up, modulation of the MALT immune response with the use of oral vaccines activates an immune response not only in the local but also distant parts of the mucosa, as well as a general systemic response. These vaccines provide specific immunity to the bacterial pathogens they contain, as well as a non-specific immunity, also against viruses, which develops due to the stimulation of other mechanisms in the MALT system. Many of the discussed studies demonstrated a broad spectrum of benefits of using oral preparations with bacterial lysates, with none or minor adverse effects. Therefore, identifying and understanding the mechanisms through which oral vaccines provide general systemic immunity is very important. Intensification of the research on a transmucosal vaccination route, including oral vaccines, may be of great consequence for the future management of frequent and common infections.

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REVIEW ARTICLE

THEORETICAL PRINCIPLES OF COLOR DOPPLER IMAGING IN OPHTHALMIC ULTRASOUND (PART I)

Zasady użycia kolorowego dopplera w badaniach okulistycznych (cz. I) – podstawy teoretyczne

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Abstract: Doppler examination in the assessment of retrobulbar arteries is a valuable supplementary tool in the imaging diagnostics of orbital and eyeball diseases. The article describes the history of the use of ultrasound in medicine, its use in ophthalmic diseases, the development of Doppler diagnostics and the theoretical basis of the hemodynamic measurements, including the detailed characteristics of the Doppler examination in the assessment of the ophthalmic artery, the middle retinal artery and short posterior ciliary arteries. Ultrasound images of the eyeball, together with the assessment of blood flow in the retrobulbar arteries, have proven to be reliable and repeatable, provided that the basic recommendations described in the article are followed. The methodology of measurements and the proposed norms of hemodynamic readings are helpful in the practical application of this modality in ophthalmic diagnostics.

Streszczenie: Badanie Doppler w ocenie naczyń tętniczych pozagałkowych jest cennym uzupełnieniem diagnostyki obrazowej chorób oczodołu i gałki ocznej. W artykule opisano rys historyczny zastosowania ultrasonografii w medycynie, zastosowanie w chorobach okulistycznych, rozwój diagnostyki dopplerowskiej i podstawy teoretyczne uzyskiwanych pomiarów hemodynamicznych z uwzględnieniem szczegółowej charakterystyki badania dopplerowskiego w ocenie tętnicy ocznej, tętnicy środkowej siatkówki i tętnic rzęskowych tylnych krótkich. Obrazy ultrasonograficzne gałki ocznej, wzbogacone o ocenę przepływów w naczyniach tętniczych pozagałkowych, cechują się potwierdzoną wiarygodnością i powtarzalnością pod warunkiem stosowania się do podstawowych zaleceń, które opisano w artykule. Metodyka pomiarów I zaproponowane normy odczytów wartości hemodynamicznych są pomocne w praktycznym zastosowaniu tej modalności w diagnostyce okulistycznej.

Key words: Colour Doppler, ophthalmology, retrobulbar vessels.

Słowa kluczowe: kolorowy Doppler, okulistyka, naczynia rejonu pozagałkowego.

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Introduction

Ultrasound is one of the most popular and recognised diagnostic methods. Its benefits include a non-invasive character, availability, low cost, as well as reliability and repeatability of results. Technological advances, such as elastography, 3D and 4D imaging or the use of high frequencies, guarantee continuous development of this discipline, creating opportunities for improvements in diagnostic skills.

History of ultrasound diagnostics

The discovery of piezoelectricity by the French scientists and brothers, Pierre and Jacques Curie, in 1880 may be considered the beginning of the development of ultrasonography [1]. The effect was based on the deformation of barium crystals under the influence of an electric field and vice versa. Therefore, the crystals can both generate and receive a sound wave, which provided the basis for the construction of ultrasound transducers. An effect consisting in the change in frequency of a wave in relation to a moving source and receiver was discovered in 1842 by the Austrian physicist and astronomer, Christian Andreas Doppler, and was named after him, the “Doppler effect” or “Doppler shift” [2]. It is worth emphasising that this applies to all types of waves, electromagnetic and acoustic, and which can be used in many devices measuring speed or distance, such as radars, sonars or laser meters.

The first B-mode (brightness-mode) scanner was created in 1951 by John Wild and John Reid [3]. In the 1950s, ultrasound was also used for the first time in ophthalmology for the measurement of the distance between the consecutive eyeball layers, which gave rise to the development of A-mode (amplitude mode) presentation [4]. The first Doppler studies were performed in the 1960s. Initially, they were used for the diagnostics of blood flow in large vessels, in particular in cardiology, vascular surgery and obstetrics [5, 6, 7]. Further progress in engineering enabled the illustration of blood flow in smaller vessels, including orbital vessels [8, 9, 10]. At present, colour Doppler imaging (CDI) provides a qualitative and quantitative assessment of blood flow, including in small retrobulbar vessels, such as the central retinal vein or artery, or short posterior ciliary arteries.

Indications for Doppler studies in ocular diagnostics

The CDI test is a valuable complementation of any B-mode study. It is performed in the case of injuries (suspected retinal detachment, choroidal detachment, intraocular haematomas), diagnostics of intrabulbar and extrabulbar tumours, changes in the lacrimal gland and eyelid tissues, and, primarily, in the diagnostics of hemodynamic disorders associated with the optic nerve pathologies, systemic diseases, diabetes, and other civilisation diseases, such as glaucoma or hypertensive angiopathy. Table 1 presents the most common indications for a Doppler test of the eye.

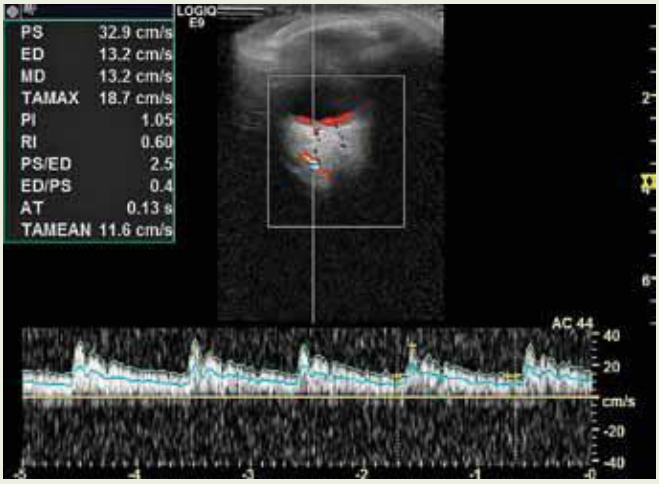
Table 1. Main indications for a Doppler test in ocular diagnostics.

Vascular pathologies	• Embolism of the central retinal artery • Thrombosis of the central retinal vein • Acute and chronic insufficiency of the carotid artery (stenoses) • Arteriovenous fistulas (cavernous fistula) • Diabetes mellitus, arterial hypertension • Ischaemia of the optic nerve (glaucoma) • Systemic diseases (RA, other connective tissue diseases)
Tumours	• Melanoma, other tumours and metastases to the eye • Lacrimal gland pathologies (lymphomas) • Orbital focal lesions • Tear duct pathologies
Orbital inflammatory disorders	• Wegener's granulomatosis • Grave's disease
Injuries	• Orbital bone fracture • Intramural haematomas of the eye • Injuries to the optic nerve • Detachment of the eye wall membranes
CNS diseases	• Cerebral strokes • Increased intracranial pressure (tumours, injuries, intracranial haematomas) • Assessment of the efficiency of the circle of Willis before and after endovascular procedures

Blood flow parameters measured with the Doppler method

Maintaining the correct operating methodology provides the correct presentation of the blood flow spectrum in the vessel, reflecting the movement of blood cells in its lumen. An ultrasound device provides a lot of information about blood flow hemodynamics, see Figure 1.

Figure 1. Blood flow spectrum in the ophthalmic artery.



Presentation of the hemodynamic parameters:
PS – peak systolic velocity
ED – end diastolic velocity
MD – mean diastolic velocity
TAMAX – time-averaged maximum velocity
PI – pulsatility index
RI – resistive index
AT – acceleration time
TAMEAN – time-averaged mean velocity
The angle of insonation used (AC): 44 degrees.

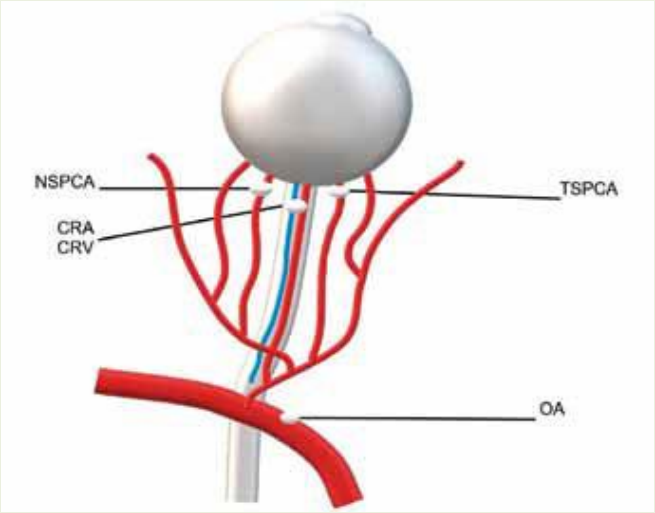
In ocular diagnostics, the following parameters are used for the assessment of arteries: peak systolic velocity (PS), end-diastolic velocity (ED), mean diastolic velocity (MD), time-averaged maximum velocity (TAMAX), Puercelot's resistive index (RI) and Gosling's pulsatility index (PI). The last two parameters are derived from the velocity parameters according to the formulas:

RI = (PS-ED) / PS

PI = (PS-ED) / TAMAX

The test is most frequently used to assess blood flow in the ophthalmic artery (OA), central retinal artery (CRA), short posterior ciliary arteries (SPCA) on the nasal and temporal side of the optic nerve, and in the central retinal vein (CRV). Figure 2 presents the measurement sites for these vessels.

Figure 2. Diagram presenting the measurement sites for the retrobulbar vessels using colour Doppler ultrasound.



OA – ophthalmic artery
CRA – central retinal artery
CRV – central retinal vein
nSPCA – nasal short posterior ciliary artery
tSPCA – temporal short posterior ciliary artery

In pathological tumour vascularisation, the aim of the test is to find the leading vessels and to assess the blood flow spectrum of the tumour vessels.

Doppler effect and its use in ultrasonography

Colour Doppler imaging (CDI) combines B-mode ultrasonography with imaging based on the Doppler shift (ΔF), determined by the formula:

$$(\Delta F) = Fe - Fo = 2 \times Fo \times V/C \times \cos\alpha$$

where: Fe – frequency of the wave emitted by a transducer, Fo – frequency of the reflected wave, V – blood flow velocity, C – velocity of wave propagation in tissues (approx. 1540 m/s), and α – the angle of insonation. The angle of insonation is the angle between the studied tissue and the ultrasound beam emitted by the transducer, and a correct position of the transducer affects the reliability of test results. In practice, the value should not be more than 60° [11].

Test technique

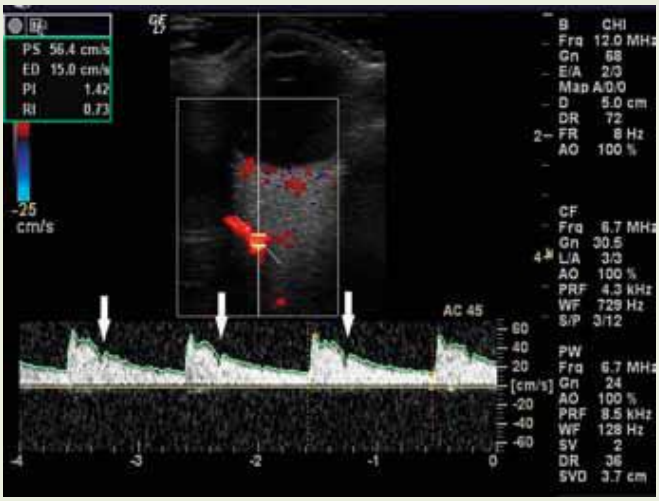
In ophthalmological tests, linear transducers working at frequencies of 6-18 Mhz are used, which offers a compromise between the resolution and the depth of beam penetration.

It is worth remembering that the pressure of the transducer head on the eyeball increases the intraocular pressure, and falsifies the results (the blood flow appears to be reduced). Therefore, it is recommended to fill the orbit with a larger amount of ultrasound gel, to act as a "spacer", to prevent eye compression. Understanding the anatomy of the retrobulbar space is necessary to obtain reliable and repeatable CDI measurements [9].

Ophthalmic artery (OA)

The ophthalmic artery is a branch of the internal carotid artery, and it comes off at the cavernous sinus. Although it is the largest of the vessels examined in the orbit, it is not visible in B-mode. Colour-coding of the blood cell flow in the Doppler test allows the sonographer to identify the OA. It is typically found at approximately 10-15 mm behind the eyeball, where it crosses over the optic nerve, and moves from the lateral to the medial part of the orbit. The flow spectrum in OA shows intermediate resistance, with a typical dicrotic notch on the descending arm, due to the closing of the aortic valve in the heart [12]. Figure 3 presents a normal spectrum.

Figure 3. A normal spectrum of blood flow in the ophthalmic artery.

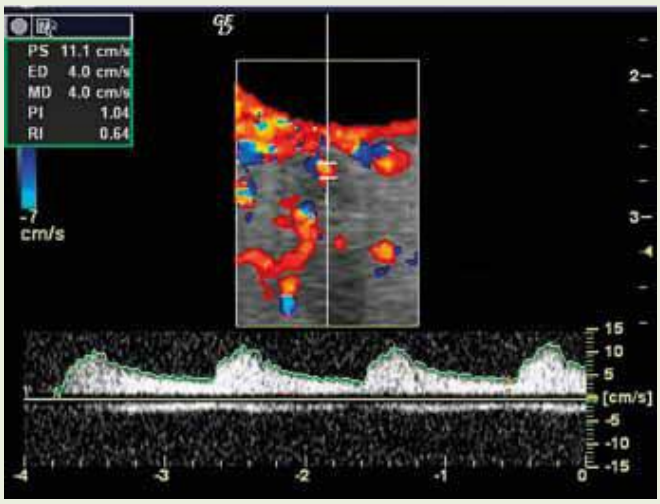


The dicrotic notch on the descending arm of the spectrum is marked with an arrow. The angle of insonation (aC) determined by the investigator, relative to the direction of the vessel, is 45°.

Central retinal artery and vein

The central retinal artery (CRA) is approximately 0.2 mm in diameter, and it is the only branch of the ophthalmic artery with a fixed position. Its terminal section, together with the vein of the same name (CRV), traverses within the optic nerve sheath. A coloured signal map assigns the colour red to the blood flow in the CRA towards the head of the transducer. The colour blue codes the flow in the opposite direction, in this case in the CRV. The sampling gate should be set at > 2 mm behind the optic disc. Measurements at the cribriform plate should be avoided, as at this site the CRA lumen narrows physiologically, which results in a significant (40-70%) overestimation of the velocity parameters [13, 14]. A proper selection of the measurement site, adequate velocity range on the measurement scale, and the right angle of insonation (in the range 0-20°) determines the reliable assessment of the hemodynamic parameters in the CRA and CRV. Over the baseline, the arterial spectrum shows a characteristic, low-resistance profile, and a clearly marked peak velocity. Below the baseline, simultaneously, a phase spectrum from the central retinal vein can frequently be observed. Figure 4 presents a normal blood flow spectrum in both vessels.

Figure 4. Results of a Doppler test of the central retinal artery and vein.

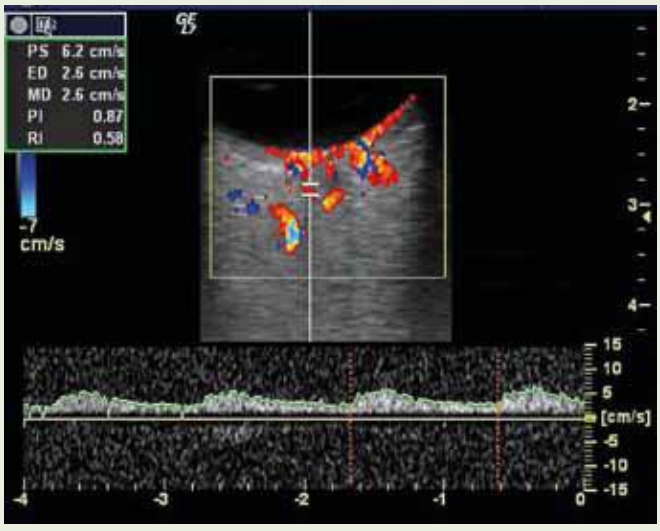


The CRA spectrum is outlined in green. The CRV spectrum is below the baseline. No correction of the angle of insonation.

Short posterior ciliary arteries

The short posterior ciliary arteries are small branches of the ophthalmic artery. The perineural branches, in the form of a few vessels on the nasal and temporal side of the optic nerve, are the only vessels responsible for blood supply to the frontal section of the optic nerve. The peripheral branches, in the vicinity of long ciliary arteries, are responsible for blood supply to the choroid. The ultrasound test should be used to locate any branches located close to the echo of the optic nerve. The gate of a colour Doppler includes the optic disc area. A blood flow signal (red) is visible in the vicinity of the optic nerve band, see Figure 5.

Figure 5. Example of a measurement of a short posterior ciliary artery located on the nasal side of the optic nerve disc.



Doppler standards of blood flow in the retrobulbar arteries

It should be noted that blood flow in the retrobulbar arteries is determined by a number of overlapping factors. Numerous metaanalyses demonstrate that it is rather difficult to establish a precise norm for the general population, although the results of the analyses of control groups from various studies do not differ significantly [15].

It appears that the choice of age groups considerably determines the obtained results of the Doppler tests, as confirmed by studies from the late 1990s [16]. Many authors, including Galassi and Meyer, reported that in elderly patients the hemodynamic changes were present, resulting in impaired eye perfusion in the form of reduced maximum and end-systolic velocity in the OA, reduced end-systolic velocity and elevated resistive index in the CRA and SPCA [17, 18]. The changes in the blood flow parameters in the arteries supplying the optic nerve disc area may also be associated with age-dependent reduction of the cardiac output, volume of the blood flow, as well as an increase in peripheral resistance [16]. Table 2 presents the hemodynamic normal ranges proposed by the author for individual retrobulbar vessels [19].

Table 2. Normal ranges from the blood flow in retrobulbar vessels examined in a colour Doppler test [19].

VESSEL	DOPPLER TEST PARAMETERS		
	PS (cm/s)	ED (cm/s)	RI
OA	39.7 ± 7.3	10.9 ± 3.2	0.72 ± 0.05
CRA	11.5 ± 2.0	4.0 ± 1.0	0.66 ± 0.06
nSPCA	12.1 ± 3.3	5.4 ± 2.5	0.60 ± 0.06
tSPCA	12.3 ± 4.2	4.9 ± 2.0	0.60 ± 0.06
CRV	5.9 ± 1.2	4.1 ± 0.9	29.9 ± 5.4

Conclusions

Colour Doppler ultrasound is a valuable addition to a standard ultrasound test, as it provides a quantitative and qualitative, non-invasive assessment of blood flow in intrabulbar and retrobulbar focal lesions, as well as in the orbital veins and arteries. Its advantages include availability, low costs of the procedure, no need for patient preparation, repeatability and reliability of the results, and safety, provided a proper test method is applied. This article presents a historical outline, the most important indications for a colour Doppler test in ophthalmology, special conditions for vascular examination, and the applicable normal ranges for the test results.

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LABORATORY DIAGNOSTICS OF KIDNEY FUNCTION AND ITS ROLE IN THE MONITORING OF PATIENTS TAKING NEW ORAL ANTICOAGULANTS OR CONTRAST AGENTS

Diagnostyka laboratoryjna funkcji nerek i jej rola w monitorowaniu pacjentów przyjmujących nowe doustne antykoagulanty lub środki kontrastowe

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Abstract: The evaluation of kidney function is one of the key laboratory elements in determining the general condition of a patient, regardless of the disease diagnosis. Serum creatinine concentration usually poses a preliminary assessment of kidney condition. Estimated glomerular filtration rate (eGFR) – calculated from creatinine concentration – is important when determining doses of contrast agents used in medical imaging. Tests that most adequately assess glomerular filtration are known as clearances.
One must also be aware that none of the tests proposed so far is 100% reliable. This study reviews the available literature in terms of kidney function assessment methods and their clinical utility. In particular, emphasis is placed on their usefulness in imaging diagnostics and for patients taking anticoagulants.

Streszczenie: Ocena funkcji nerek jest jednym z kluczowych laboratoryjnych elementów określających stan ogólny pacjenta, bez względu na rozpoznanie chorobowe. Stężenie kreatyniny w surowicy jest zazwyczaj wstępnym badaniem oceniającym stan tego narządu. W oparciu o jego wynik wylicza się szacunkową filtrację kłębuszkową *(estimated glomelural filtration rate*, eGFR), będącą podstawą m.in. do ustalenia dawki środków kontrastowych wykorzystywanych w badaniach obrazowych. Badaniami, które w bardziej adekwatny sposób oceniają przesączanie kłębuszkowe, są tzw. klirensy. Należy jednak mieć świadomość, że żadne z dotychczas oferowanych badań nie jest pozbawione wad. Niniejsza praca stanowi przegląd dostępnej literatury na temat metod oceny funkcji nerek i ich użyteczności klinicznej ze szczególnym uwzględnieniem przydatności w diagnostyce obrazowej oraz u pacjentów przyjmujących leki przeciwkrzepliwe.

Key words: chronic kidney disease, creatinine, creatinine clearance.

Słowa kluczowe: przewlekła choroba nerek, kreatynina, klirens kreatyniny.

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Evaluation of the renal filtration function is one of the necessary elements of the tests used for patients, regardless of their age, sex or diagnosis. The basic parameter used for an initial estimation of the efficiency of this organ is serum creatinine concentration.

Creatinine is the end product of the metabolism of creatine, whose synthesis substrates are amino acids, arginine, glycine, and S-adenosylmethionine. Creatine is phosphorylated to phosphocreatine – a source of energy in cells. Both compounds are spontaneously and irreversibly transformed to creatinine, and its blood concentration depends on age, sex, race and diet. Elevated concentrations of this compound in the organism may cause chronic kidney disease (CKD), a serious medical and social problem [1]. Moreover, according to the current recommendations, *Kidney Disease: Improving Global Outcomes* (KDIGO) from 2012, a sudden increase in blood serum creatinine by 0.3 mg/dl or more in 48 h, or reduction of diuresis < 0.5 ml/kg/h for 6 hours, is diagnosed as acute kidney injury (AKI), which is an immediately life-threatening condition [2].

It should be noted that despite the fact that the

determination of blood serum creatinine concentration is commonly ordered for both prophylactic and diagnostic purposes, this parameter is not sufficiently sensitive or specific enough to confirm CKD or AKI. However, it forms a valuable supplement to medical history, physical examination and imaging diagnostics.

Patient preparation for the test

Creatinine concentration can be determined in the blood serum, plasma or urine, in a suitable dilution. The blood should be collected on an empty stomach, between 07:00 and 10:00, after at least 8 hours of night rest, with limited smoking and physical exercise the day before the test. Using an ammonium heparin tube is not recommended if the plasma creatinine concentration is to be determined based on the measurement of ammonium levels. Other anticoagulants have not been shown to change the results of plasma creatinine assays [3]. Creatinine excretion is assessed based on daily urinary collection (DUC). Incorrect collection of DUC is the main cause of unreliable test results. Every laboratory performing this type of test should have properly formulated instructions for patients (Fig. 1). It is of the utmost importance that the person preparing for urine collection does not change their dietary habits, and uses dedicated containers for DUC. The physician ordering the test should explain to the patient during the visit the importance of following the laboratory instructions.

Figure 1. Instructions for daily urinary collection.

Methods of evaluating the renal glomerular filtration

The available methods include:

- clearance tests,
  - renal tests,
  - blood plasma tests,
- mathematical indexes, calculated based on the concentration of a given marker in blood serum.

Clearance tests

Clearance of a given substance, i.e. the volume of blood plasma from which all substance is removed in a unit of time, is a measurement of glomerular filtration rate (GFR). At present, this parameter is considered the best tool to assess renal function insufficiency and to determine the CKD stage [4]. Based on the type of substance removed from the organism, we distinguish exogenous and endogenous substance clearance.

Inulin, an exogenous substance administered in a continuous intravenous infusion, is a gold standard for GFR assessment, but, due to its limited availability and invasive procedure, it is rarely used in clinical practice. Other markers include radioactive compounds, such as 51Cr-EDTA and 125I-iothalamate, as well as non-radioactive ones, e.g. iohexol and iothalamate. Using radioactive compounds in a routine hospital practice is slightly easier, but disposal of this type of waste may be problematic [5].

Clearance tests of endogenous substances are easier to perform, as intravenous infusions are not required. In Poland, the most often determined endogenous substance is creatinine, primarily due to the simplicity of the analysis as well as the low cost of the test. However, the reliability of results depends largely on the pre-analytic phase, including patient preparation for the test. It should be emphasised that GFR and creatinine clearance are not the same, as 5% of creatinine undergoes tubular secretion [6]. Table 1 presents the markers used in clearance tests.

Table 1. Markers used in clearance tests.

Clearance	Renal	Plasma
Test material	Serum/plasma, urine	plasma
Exogenous substances	Gold standard: inulin in continuous infusion	• silver standard: inulin in bolus • radioactive compounds
Endogenous substances	Bronze standard: creatinine in DUC	• creatinine for eGFR calculation • cystatin C

Mathematical formulas to estimate the glomerular filtration rate

Due to numerous technical problems associated with the proper performance of the clearance tests, as well as to ensure patient comfort, the concept of "estimated glomerular filtration rate" (eGFR) was introduced in the late 1990s, and it has been commonly used in clinical and outpatient practice.

Formulas to assess blood serum creatinine concentration

In 1976, Cockcroft and Gault proposed the first formula to calculate eGFR on the basis of creatinine concentration in the blood serum depending on the age, sex, race and body weight of the patient. It is worth noting that when the formula was developed, serum creatinine concentration

Table 2. The most commonly used formulas to estimate glomerular filtration rate [13].

Name of the formula	Equation [ml/min/1.73 m^2]
MDRD (Modification of Diet Renal Disease) – full	eGFR = A x B x 170 2 $Alb^{+0.318}$ x $P_{creat}^{-0.999}$ x $age^{-0.176}$ x $BUN^{-0.170}$ P_{creat} – serum creatinine concentration [mg/dL]; BUN – blood urea nitrogen concentration [mg/dL]; Alb – serum albumin concentration [g/dL]; A=1 for males; 0.762 for females; B=1.18 for Black races; B=1 for other races
Simplified MDRD	eGFR = A x B x 175 x $P_{creat}^{-1.154}$ x $age^{-0.203}$ P_{creat} – serum or plasma creatinine concentration [mg/dL]; A = 1 for males; 0.742 for females; B=1.21 for Black races; B=1 for other races
Schwartz (2009) – for children with mild to severe CKD (eGFR between 15 and 75 ml/min/1.73 m^2)	$eGFR = \frac{k \times A}{P_{kreat}}$ A – body height [cm]; k – a coefficient based on the child's age and birth weight; P_{creat} – serum creatinine concentration [mg/dL];

was determined using the Jaffé method, which is associated with a considerable systematic error, and prone to interferences (i.e. from glucose, ketones, ascorbic acid and proteins). The factors limiting the use of this formula include age (the formula does not work in young children), obesity, water balance disorders, and a high-protein diet (athletes).

In 1999, KDGIO proposed the MDRD (*Modification of Diet in Renal Disease*) equation, which ignores the patient's body weight. To calculate eGFR based on this formula, creatinine concentration in blood serum should be determined using the enzymatic method, which is less prone to interference. Of clinical significance are the values below 60 ml/min/1.73 m^2, presented as exact numbers, whereas any result above this limit is described as > 60 ml/ min/1.73 m^2 [7].

In 2009, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) organisation proposed a formula using the same variables. It was based on a larger study group, comprising patients with more diverse health statuses. Standardisation of the determination of creatinine concentrations in the blood serum was performed with the use of a reference method, namely Isotope Dilution Mass Spectrometry (IDMS). The metaanalyses comparing the Cockcroft-Gault (CG) formula, MDRD and CKD-EPI demonstrated that MDRD has a higher diagnostic sensitivity, defined as the rate of positive results in all patients, than CKD-EPI [8]. Therefore, positive and false-positive results will dominate, which reduces the risk of overlooking patients with the disease. On the other hand, CKD-EPI demonstrates the highest analytic accuracy, i.e. the correspondence between the obtained result and the actual value [9].

Assessment of renal function in children, whose glomerular filtration changes with age, is not an easy task. From the few mathematical formulas, the Schwartz equation was developed in the 1980s and is still commonly used in clinical practice, as it takes into account the creatinine concentration in blood serum and the patient's height. Initially, creatinine concentration assessed using the Jaffé method was used for this formula. In 2002, the equation was corrected, and it now uses the creatinine concentration determined by the enzymatic method (Tab. 2) [10].

Michels et al. compared the formulas for estimated glomerular filtration rate, namely MDRD, CKD-EPI and CG with the reference GFR method based on an exogenous substance, i.e. 125I-iothalamate. MDRD presented the highest accuracy (Tab. 3) [11].

Formulas including the cystatin C concentration in blood serum

In recent years, the interest in the determination of cystatin

Table 3. Comparison of the formulas to estimate glomerular filtration rate with a higher standard of assessment of renal function using a clearance test based with a clearance of 125I-iothalamate [13].

Formula	Overall mean bias [%]	Overall precision [%]	Overall mean bias [%]	Absolute precision [%]	Accuracy within 30%* [%]
Cockcroft-Gault	9.9	19.2	15.3	15.2	74.2
MDRD	0.8**	24.7	14.6	19.9	81.2
CKD-EPI	4.5	16.7	12.3**	12.1	84.5***

** Percentage of patients with an estimated kidney function within 30% limits of the measured GFR*
*** p ≤ 0.01 vs. other formulas*
**** p < 0.01 vs. Cockcroft-Gault, P=0.14 vs. MDRD*

C (CysC), a cysteine protease inhibitor, as a marker for GFR estimation has been growing. 99% of cystatin C is resorbed in renal tubules, and its concentration in the blood serum does not depend on sex, height, body weight, muscle mass, diet or ethnicity. Therefore, eGFR CysC is used as a test confirming reduced glomerular filtration, previously detected by an eGFR assessment achieved by determining the blood serum creatinine. Based on the determination of the CysC concentration in the serum with immunochemical methods, i.e. particle-enhanced nephelometric immunoassay (PENIA) or particle-enhanced turbidimetric immunoassay (PETIA), new equations for the calculation of eGFR have been developed, e.g. Hoek's, Larson's and Grubb's formulas. These equations are continuously modified. Many researchers prefer to use these formulas to determine GFR in children and elderly patients [12].

Quality control of the results of determining the creatinine concentration in blood serum

Following the Resolution of the Polish Minister of Health of 23 March 2006, every medical diagnostic laboratory must conduct continuous in-house control of the laboratory tests performed. In the case of serum creatinine assays, all methods should be metrologically consistent with the definitive IDMS method. The acceptable imprecision of the method is < 8%, and the acceptable systematic error (compared to IDMS) is < 5% [13]. Moreover, medical laboratories are obliged to participate in the programme of external laboratory quality control organised by the Centre for Quality Assessment in Laboratory Diagnostics. The results of the tests performed in a given facility are compared with those from other laboratories, according to the test method, the reagents used, and the laboratory apparatus. Based on the results of this assessment, a centre receives a certificate of participation, but only if the results of the selected parameters are satisfactory [14].

Monitoring the creatinine concentrations in the blood serum of patients using new oral anticoagulants

Thromboembolic disorders affect most of society, and are more frequently observed in elderly patients, who also suffer from chronic kidney disease [15]. New oral anticoagulation medicines include direct thrombin inhibitors, such as dabigatran, and direct inhibitors of activated factor X, e.g. rivaroxaban and apixaban, which are not vitamin K antagonists, such as acenocoumarol and warfarin [16]. NOAC (non-vitamin K antagonist Oral Anticoagulants), contrary to vitamin K antagonists, do not require drug dose monitoring according to prothrombin time (PT), expressed as INR (International Normalised Ratio). However, it is worth mentioning that the above preparations, through their effect on the blood coagulation system, change the results of basic coagulation tests (Tab. 4). In selecting the optimal therapy for a patient, one should consider the elimination routes of both new generation drugs [17].

Table 4. Effect of anticoagulants in the results of basic coagulation tests.

Test	Dabigatran	Rivaroxaban
PT (prothrombin time)	↑	↑↑↑
APTT (activated partial thromboplastin time)	↑↑	↑↑
TT (thrombin time)	↑↑↑	No changes

About 85% of dabigatran is eliminated through the kidneys, thus special care is advised when using the medicine in patients with a creatinine clearance below 30 ml/min [18], whereas 35% of rivaroxaban is eliminated through kidneys, so it should be used with caution in patients with a creatinine clearance of 15-29 ml/min. The drug is not recommended in patients with a creatinine clearance below 15 ml/min. Caution should also be exercised in patients with a moderate renal function disorder (creatinine clearance 30-49 ml/min), and/or those who use

Table 5. Treatment decisions made about dabigatran in patients with atrial fibrillation, based on the renal function from the MDRD method [20].

Dabigatran therapy based on MDRD	Measured values by CG and MDRD methods	Patients < 80 years of age		Patients ≥ 80 years of age	
		N	%	N	%
Contraindication incorrectly identified by MDRD	CG ≤ 30 and MDRD < 30	41	1.5	13	0.9
Dose reduction incorrectly identified by MDRD in a given clinical situation	CG ≥ 50 and MDRD 30 -< 50	149	5.5	-	-
Correctly treated		2351	86.9	1190	84.1
Overdose – no dose reduction based on MDRD	CG 30 -< 50 and MDRD≥50	144	5.3	-	-
Overdose – contraindication missed by MDRD	CG < 30 and MDRD ≥ 30	21	0.8	211	14.9
All patients		2706.		1404	

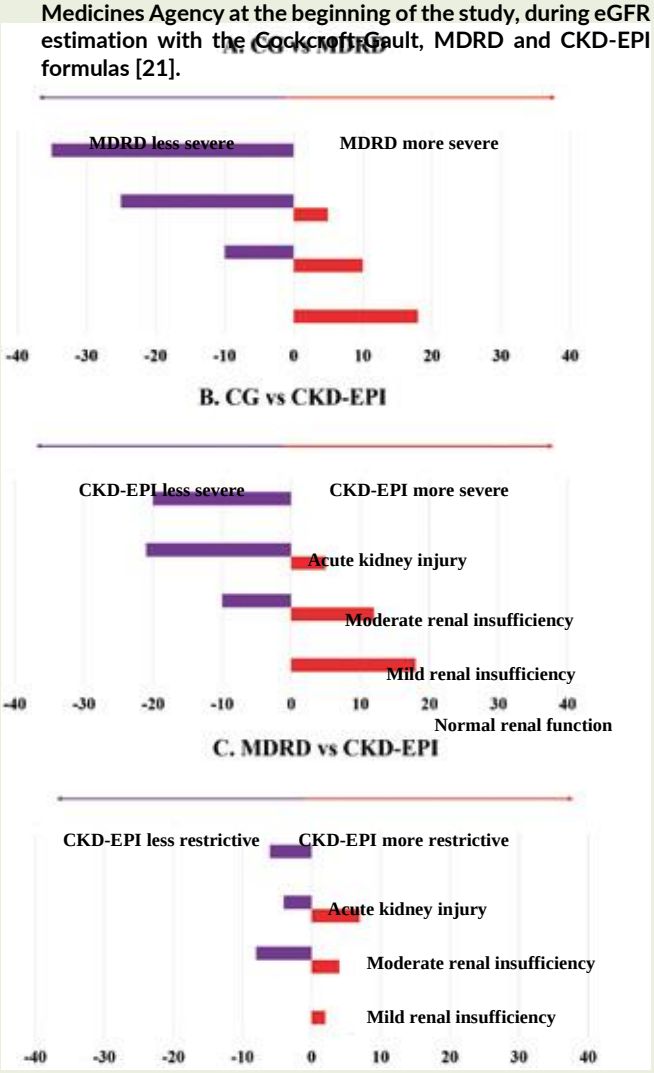
medications that increase the rivaroxaban concentration in the plasma [16, 17]. According to the New York National Kidney Foundation, for the assessment of renal filtration capacity based on estimations according to creatinine concentration in the blood serum, the CKD-EPI formula should be used. It has been demonstrated that the results obtained with this formula reflect well all stages of CKD [19]. However, when choosing a proper oral anticoagulation therapy, the Cockcroft-Gault formula is recommended, as it was used in the clinical trials for these drugs. Recently, the effectiveness of the dose adjustment of new oral anticoagulants depending on the formula (MDRD, CKD-EPI, CG) used for the assessment of the renal filtration function was compared. MacCallum et al. demonstrated that qualification based on the MDRD formula, instead of the CG formula, in patients with atrial fibrillation using NOAC, in the case of patients over 80 years old in nearly 15% of cases resulted in an incorrect qualification for dabigatran therapy, and in the case of patients < 80 years old, in 5% of cases it led to an incorrect dosing recommendation (Tab. 5) [20].

Many studies also analysed the incidence of CKD in patients using NOAC due to cardiac indications. It has been demonstrated that disorders in renal glomerular filtration increase during an anticoagulatory treatment, which necessitates monitoring of the renal filtration function during a therapy involving NOAC [21]. The compliance between the MDRD and CG formulas in the assessment of the renal filtration function was up to 80%, but as the glomerular filtration deteriorated, the correspondence decreased significantly, similarly to the correspondence between the CKD-EPI and CG equations. However, high compliance between the MDRD and CKD-EPI formulas has been shown (Fig. 2) [22].

Manzano-Fernandez et al. demonstrated that in cardiac patients, elderly individuals or patients with reduced creatinine clearance, the discrepancy between the results of MDRD and CKD-EPI compared to CG was up to 30%, which was reflected in inadequate dosing of dabigatran (Fig. 3) [23].

Freyburger et al. demonstrated that both dabigatran and rivaroxaban prolong the activated partial thromboplastin time (APTT) and prothrombin time (PT). Rivaroxaban increases APTT and PT 1.5-fold, on average, while d

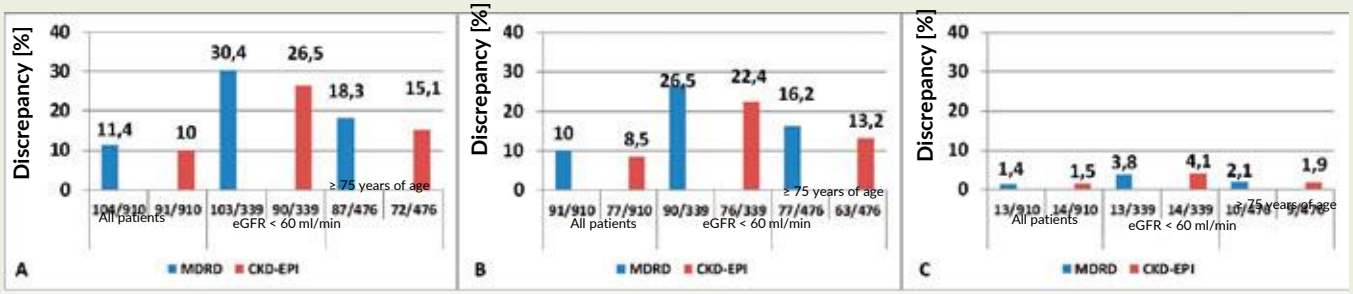
Figure 2. Percentage of patients with atrial fibrillation re-classified to various stages according to the European Medicines Agency at the beginning of the study, during eGFR estimation with the Cockcroft-Gault, MDRD and CKD-EPI formulas [21].



formula. A – dabigatran, B – rivaroxaban, C – apixaban [22].

abigatran increases APTT by a factor of 2 and PT by a factor of 1.2. The results of coagulation tests were characterised by high intersubject variability, which make establishing proper reference ranges for patients with impaired glomerular filtration using NOAC impossible[24]. It has been demonstrated that impaired renal glomerular filtration increases the time of drug elimination from 12 to even 34 hours [25]. In patients over 75 years who used the drug

Figure 3. Discrepancies in dosing recommendations for new oral anticoagulants based on the MDRD and CKD-EPI formulas, compared to the dosing based on the Cockcroft-Gault formula. A – dabigatran, B – rivaroxaban, C – apixaban [22].



regularly at doses of 150 mg/day the risk of massive haemorrhage was 5% higher per year. In patients with eGFR of 30-50 ml/min who used dabigatran, the blood concentrations of the drug were two or even three times higher than in patients with a normal renal filtration function, and the risk of a massive haemorrhage was 5.3% higher. Table 6 presents the proposed dosing of the drug, according to the estimated creatinine clearance. Table 7 presents a proposed perioperative management system

for patients using dabigatran, based on the renal filtration function and severity of the planned procedure [25].

Table 6. Proposed dabigatran dosing based on the patient's creatinine clearance [24]

Creatinine clearance	Dose
< 30 ml/min	150 mg twice daily, orally
15-30 ml/min	75 mg twice daily, orally
< 15 ml/min or patients on hemodialysis	Not recommended

Hassan et al. demonstrated that using NOAC in patients undergoing open-heart surgery, especially if their renal filtration function was impaired, significantly prolongs their stay in intensive medical care units. The researchers suggest discontinuation of NOAC 10 days prior to the planned surgery [26].

If acute kidney injury develops, the anticoagulation treatment with NOAC medications should absolutely be discontinued. Patients with kidney diseases receiving NOAC therapy should be under the constant care of a physician. The European Cardiac Society has published guidelines that recommend in this group of patients the control of creatinine concentration in the blood serum and determination of eGFR should occur at least once every 12 months. If the eGFR values are < 60 ml/min, experts suggest that the frequency of creatinine clearance controls in a year is determined by dividing the last eGFR value by 10. When additional risk factors are present, such as advanced age and numerous comorbidities, an increased frequency of assessment of this parameter should be considered, especially if the patient uses dabigatran [27].

Assessment of the renal glomerular filtration before the administration of contrast media

Following the European Society of Urogenital Radiology (ESUR) guidelines, prior to the administration of gadolinium- or iodine-based contrast media to patients ≥ 18 years of age, the renal filtration function should be assessed on the basis of blood serum creatinine concentration, and estimation of the glomerular filtration rate using the CKD-EPI formula. This formula has different coefficients, depending on the race, sex and blood serum creatinine concentration. In women the limit value is 62 µmol/L (0.70 mg/ dL) and in men it is 80 µmol/L (0.90 mg/dL). In children, the revised Schwartz formula should be used, and if possible, the creatinine concentration in blood serum should be determined using the enzymatic method [13, 28]. The formulas are presented in detail in Table 8. Typically, a patient arriving for a magnetic resonance or computed tomography study is informed in advance that on the day of the test they should present a current result of serum creatinine concentration.

Conclusions

An optimal marker for the assessment of renal filtration function has been sought for decades. Although endogenous creatinine is not a perfect marker, due to the low cost of obtaining a result of the test, and its widespread use, this parameter is considered in most clinical decisions. GFR assessment based on creatinine clearance in daily urine collection is the closest to the values obtained by the reference method, but only if the urine collection was conducted properly. To avoid a preanalytical error, the renal glomerular filtration rate is usually calculated using mathematical equations.

In patients undergoing diagnostics for CKD and receiving

Table 7. Proposed perioperative management regimen in patients using dabigatran, based on the renal function and severity of the planned procedure [24].

Creatinine clearance	Dabigatran's half-life [hours]	Procedures with a low risk of haemorrhage	Procedures with a high risk of haemorrhage
≥ 50 ml/min	15 (12-34)	Last dose of the drug 24 h before the procedure	Last dose of the drug 48-72 h before the procedure
30-49 ml/min	18 (13-23)	Last dose of the drug 48-72 h before the procedure	Last dose of the drug 96 h before the procedure
< 30 ml/min	27 (22-35)	Last dose of the drug 96 h before the procedure	Last dose of the drug 96 h before the procedure

Table 8. The CKD-EPI formula to calculate eGFR recommended for use in patients before the administration of gadolinium- and iodine-based contrast media [27].

Sex	Serum creatinine concentration (sCr) [µmol/L]	eGFR [ml/min/1.73 m^2]	Comments
Women	≤ 62	$144 \times (sCr/62)^{-0.329} \times 0.993^{age}$	• age in years • in African-origin patients the equation value should be multiplied by 1.159 • creatinine conversion rate: 1 mg/dL = 88.4 µmol/L
	> 62	$144 \times (sCr/62)^{-1.209} \times 0.993^{age}$	
Men	≤ 80	$141 \times (sCr/80)^{-0.411} \times 0.993^{age}$	
	> 80	$141 \times (sCr/80)^{-1.209} \times 0.993^{age}$	

imaging tests with the use of contrast media, the assessment of the renal filtration function should be based on the eGFR calculation using the CKD-EPI formula. Oral anticoagulants, such as dabigatran and rivaroxaban, as well as contrast media, are largely excreted by the kidneys. Therefore, patients, especially those with cardiac diseases and preparing for surgical procedures, should be assessed in terms of renal function. However, it is important to remember that in the clinical studies on anticoagulation drugs, only the Cockcroft-Gault formula was used to assess renal filtration sufficiency.

Oral anticoagulants from the NOAC group are increasingly often prescribed and gaining popularity, i.e. because dose adjustment, based on regular assessments of INR values, is not required. However, due to the fact that these drugs are eliminated through the renal route, periodic assessment of renal sufficiency should become a standard in the diagnostic and therapeutic process in this group of patients.

Co-operation between the clinician, laboratory diagnostician and the personnel performing tests is of key importance for accurate diagnosis and proper therapy of patients who require assessment of the renal filtration function.

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ACTIVITY OF SPA RESORTS IN BUSKO-ZDRÓJ AND SOLEC-ZDRÓJ IN 1939-1945

Działalność uzdrowisk w Busku-Zdroju oraz w Solcu-Zdroju w latach 1939-1945

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Abstract: The activity of the spa resorts in Busko-Zdrój and Solec-Zdrój during the German occupation is poorly described in Polish historiography. Only enigmatic mentions may be found in publications about their activities. The main reason for this could be attributed to the poor state of the sources – especially concerning Solec-Zdrój. The goal of the article is to characterize the activity of the spa resorts in Busko-Zdrój and Solec-Zdrój between 1939 and 1945, and the description of the scale of the destruction they suffered as a result of the actions of the German occupier. Both spa resorts, Busko-Zdrój and Solec-Zdrój, suffered significant losses during the German occupation. Spa facilities changed their purpose, being mainly a place of convalescence for the Germans. It should be noted that access by the Polish population to them was almost completely limited. Some of the spa facilities were destroyed and their equipment was plundered. As a result of the German occupation, the accommodation base in Busko-Zdrój and Solec-Zdrój was also devastated. In Busko-Zdrój the number of rooms for patients decreased by 350. While in Busko-Zdrój, patients were admitted as early as 1945, Solec-Zdrój was opened as a year-round health resort in 1961.

Streszczenie: Funkcjonowanie uzdrowisk w Busku-Zdroju oraz w Solcu-Zdroju w czasie okupacji niemieckiej jest tematyką pomijaną do tej pory w historiografii polskiej. Na temat ich działalności można znaleźć jedynie enigmatyczne wzmianki. Głównej przyczyny tego stanu rzeczy można upatrywać w ubogim stanie źródeł – mowa tutaj zwłaszcza o materiałach dotyczących Solca-Zdroju. Przedmiotem niniejszego artykułu jest m.in. omówienie działalności uzdrowisk w latach 1939-1945 a także skali zniszczeń, jakie poniosły w wyniku działań okupanta niemieckiego.

Uzdrowiska w Busku-Zdroju oraz w Solcu-Zdroju poniosły duże straty w czasie okupacji niemieckiej. Zakłady lecznictwa uzdrowiskowego zmieniły swoje przeznaczenie, i stały się przede wszystkim miejscami rekonwalescencji dla Niemców. Warto zauważyć, że ludności polskiej niemal całkowicie ograniczono do nich dostęp. Część zakładów zdrojowych uległa zniszczeniu, a ich wyposażenie zrabowano. W wyniku okupacji niemieckiej zdewastowano także bazę noclegową w Busku-Zdroju I Solcu-Zdroju. Tylko w Busku-Zdroju liczba pokoi dla kuracjuszy zmniejszyła się o 350. Podczas gdy w Busku-Zdroju kuracjuszy przyjmowano już w 1945 roku, Solec-Zdrój został otwarty jako całoroczne uzdrowisko w 1961 roku.

Key words: spa resorts, spa equipment, German occupation, German repressions.

Słowa kluczowe: uzdrowiska, wyposażenie uzdrowisk, okupacja niemiecka, represje niemieckie.

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Introduction

The spa resorts of Busko-Zdrój and Solec-Zdrój are famous for their grounds, as they are rich in sulphur water springs and peat. In the inter-war period, a popular saying went: "If Busk doesn't help you, only holy ground can" [1]. Prof. Józef Dietl, on the other hand, characterised the Solec springs in 1858 as follows: "the Solec spring is one of the strongest and most effective of its kind in the whole of Europe" [2].

In the inter-war period, the spa resorts in Busko-Zdrój and Solec-Zdrój saw up to 10,000 visitors per year. The main conditions treated there included rheumatism, arthritis, tuberculosis, neuritis and neuralgia, but also skin diseases and allergies [3].

As a result of the German occupier's actions, the Busko-Zdrój and Solec-Zdrój facilities were both devastated. While the former managed to reopen on 15 May 1945, the latter did not return to full operation until 1961.

The activity of the spa resorts in Busko-Zdrój and Solec-Zdrój during the German occupation is poorly described in Polish historiography. Only enigmatic mentions can be found in publications about their activities. The main reason for this can be attributed to the poor state of the sources –

especially concerning Solec-Zdrój. The goal of the article is to characterise the activity of the spa resorts in Busko-Zdrój and Solec-Zdrój between 1939 and 1945, and the description of the scale of the destruction they suffered as a result of actions by the German occupier.

Activity of spa resorts in Busko-Zdrój and Solec-Zdrój in the period 1939-1945

The first bombs fell on the spa district of Busko-Zdrój on 1 September 1939, including in the vicinity of the Górka Children's Sanatorium, but with no damage to its grounds. One of the explosives destroyed the sanatorium owned by the Social Insurance Institution [4]. According to the memoirs of Dr Szymon Starkiewicz, long-time director of the Górka Sanatorium: "[...] When we arrived there, we saw a huge hole in front of the building, full of glass from broken windows, and our kitchen manager on the threshold with a smashed head. We were shocked because an hour before we had discussed the possibility of moving there some of the children from the Górka, where we thought it was not quite so safe" [5]. There were injuries as well as deaths caused by the raid. On 4 September 1939, the district authorities and some of their subordinate officials left Busko-Zdrój [6]. The spa management and staff also left the town, leaving 12 elderly and seriously ill patients to fend for themselves [7].

In the first days of September 1939, the overwhelming majority of those in treatment also left the Solec-Zdrój resort. Bogumił Hetnarski reported: "People recounted the tragic story of a couple fleeing on a motorbike. The woman allegedly carried a baby in her backpack. On top of that, she was burdened with some more luggage. When they stopped, they found to their dismay that they had lost their child. It was, indeed, the end of the world!" [8].

In September 1939, the Germans used the Busko-Zdrój sanatoriums as hospitals for German soldiers [9]. It is noteworthy that soldiers of the Polish Army wounded in the battle of Bronina were also brought to the Górka Children's Sanatorium. Eleven death certificates for Polish Army soldiers who died at the Górka due to wounds received in the battle of Bronina were registered in the books of the Blessed Virgin Mary parish in Busko-Zdrój [10]. These soldiers were Ludwik Bryłka, Stanisław Boczar, Władysław Debich, Franciszek Hrycko, Tymota Iwaneczko, Józef Leski, Czesław Mizgajski, Emil Muthwil, Stefan Sehman, Antoni Winnicki and Antoni Zawała.

Kreishauptmann Dr Wilhelm Schafer, who arrived in Busko-Zdrój in September 1939, described the spa resort as follows: "Busko was a town with around 6,000 inhabitants. A superb sulphur bath was found there, with an excellent therapeutic effect on rheumatism" [11]. In 1940, medical treatment in the General Government, including spas, was subordinated to the German administration. The Health Resort in Busko-Zdrój was headed by Otto Geigenmüller, who was also a fiscal inspector [12]. Some of the pre-war staff were dismissed by him, the Górka director, Dr Szymon Starkiewicz, was among them. He was replaced by Geigenmüller's wife. Starkiewicz described her in the following way: "Overbearing, ruthless, erratic, she began to interfere in various medical matters that she did not understand at all. At first I tried to explain things to her, to no avail, then I kept quiet" [13].

After the administrative changes in 1941, the Germans tightened their policy towards spa resorts. The children who remained at the Górka Sanatorium were taken by the Germans to different orphanages. The Military Therapeutic and Rehabilitation Hospital was reserved for Wehrmacht soldiers [14]. They also changed the purpose of the Górka Sanatorium, transforming it into a rheumatology clinic for adults (German: *Rheumaheilstaedte)* [15]. One consequence of the German policy towards spas was the almost total lack of access to spa treatment for the Polish population, which lasted until 1945. The patients in Busko-Zdrój were mainly Germans and Poles from the General Government, employed in the arms industry. One of the many enthusiasts of Busko's sulphur baths was Max Peter, an officer of the Security Police (German: *Sicherheitspolizei*). On 12 July 1944, soldiers who belonged to the Busko District of the Home Army's Union for Armed Struggle carried out a successful assassination attempt on Peter's return from the spa. Marian Wojnakowski, *nom de guerre* "Wodnik", was tipped off by his mother, who worked at the sulphur bath service, that Peter had finished his treatment. The execution could by no means be carried out in the vicinity of the spa, as a large number of Germans were stationed there. The successful, armed operation took place at the market square in Busko-Zdrój [16].

Table. Number of patients and sulphur baths provided in Busko-Zdrój from 1937 to 1945.

Year	Number of patients	Number of baths provided
1937	6,800	No data
1938	7,411	145,182
1939	5,267	98,369
1940	1,945	18,108
1941	2,235	26,893
1942	4,687	67,947
1943	3,230	42,123
1944	No data	No data
1945	371	No data

The German policy towards the spa in Busko led to a significant decline in the number of patients. The summer season turnout amounted to 1,945 people in 1940, 2,235 in 1941, 4,687 in 1942 and 3,3230 in 1943 [17]. In the whole of 1945, 371 people visited Busko-Zdrój. Comparing the number of visitors to the pre-war period, there were only half as many: in 1937 Busko-Zdrój received 6,800 visitors and in 1938 7,411. With the significant decrease in visitors, the number of sulphur baths also decreased. As many as 145,182 baths were provided in 1938, while in 1940 the number had dropped more than eightfold to 18,108, and in 1941 more than fivefold to 26,893 [18]. By 1946, it had risen again to over 82,000 [19].

In the pre-war period, the two spas in the Stopnica District, i.e. Busko-Zdrój and Solec-Zdrój, saw an annual number of up to 10,000 visitors, which contributed significantly to the prominent economic role of the area. On average, a patient staying in the spas during the inter-war period spent around PLN 300 a month, which added up to a substantial sum of around PLN 3,000,000 a year in the total income of the Stopnica District [20]. For reference, according to the list of prices applicable at the Busko spa resort in 1941, the fee for a four-week stay from 1 July to 31 August was PLN 24. The price for a two-week stay was PLN 17. A four-week visit to the spa between 1 September and 15 October was priced at PLN 17, while a two-week treatment during the same months was PLN 10 [21]. According to a price list of therapies from 1941, the spa in Busko offered sulphur, peat, mud and iodine-bromine baths. A drinkable treatment consisting of sulphur mineral water was also available. Prices for treatments varied from season to season, and ranged from PLN 2 to PLN 10. The rates were certainly greatly reduced for German soldiers.

Accommodation

In the pre-war period, there were 22 villas in Busko-Zdrój with a total of 545 rooms. These included guesthouses, such as: Angielska, Bristol, Sanato, Wiktoria, Zacisze and Zamek Dersława, as well as villas/manor houses: Bagatela, Brzozówka, Chopin, Krakowska, Oblęgorek, Ormuzd, Słowacki, Trzy Róże, Warszawska, Wersal, Winogór and Wiślica. And while the pre-war Busko-Zdrój provided 545 rooms, this number fell to 195 in the post-war period. In 1945, only Sanato, Słowacki, Wiślica, Oblęgorek and Chopin were available for patients in Busko-Zdrój. The pressing shortage of rooms meant that each of the rooms in the operating villas housed several patients.

During the German occupation, the villas located in the vicinity of the spa park were used for a variety of purposes. Unoccupied guesthouses in Busko-Zdrój were used by the Germans to accommodate displaced inhabitants of Wielkopolskie [22]. The Wersal villa, located on Mickiewicza Avenue, housed the headquarters of the German gendarmerie. Its cellars served as a detention facility, through which hundreds of *Kreishauptmannschaft* Busko residents passed [23]. After the war, the building housed the district headquarters of the Citizens' Militia. In 1949, the villa was converted into flats for Citizens' Militia officers. As many as 60 rooms for potential patients were lost as a result of the above actions [24].

The Trzy Róże villa, located near the Wersal, was used during the German occupation as the Central Egg Storage for the District Agricultural and Trading Cooperative. A detachment of gendarmes consisting of Poles mainly from the eastern part of Poland was quartered there in June 1944 [25]. In the 1950s, the building was handed over to a high school as a girls' dormitory. Not far from the Trzy Róże was the Warszawska villa, which belonged to Mojżesz Cukierman before the war. It was converted into social flats in the 1945-1960 period.

In the Urocza villa, owned by Josek Topioł before the war, the Germans organised a Fruit and Vegetable Warehouse. The upper floors, on the other hand, contained flats for Germans and people displaced from Wielkopolskie [26]. After the end of the war, the Urocza villa was used for social housing.

Zamek Dersław, located down on Mickiewicza Avenue, was renamed *Willa Zumriter*. Between 1940 and 1944, a German symphony orchestra was accommodated there, and it also served as a hotel for female artists who came to Busko-Zdrój for their performances. After the war, Zamek Dersław became the office of the State Machinery Centre.

In the 20 years between the wars, the Bristol villa, which belonged to Erzil Cukierman, served as a Therapeutic Military Hospital. During the German occupation, the Germans turned it into social housing for German gendarmes. It was also used for social housing after the end of hostilities. The Sanato guesthouse at 1 Maja Street was partly converted by the Germans into patient rooms. Part of it also contained social housing for German people [27].

Villas in Solec-Zdrój were no less ruined. This was particularly true for Pod Brzozami and Mickiewiczówka, while the Organistówka was partly damaged in January 1945. The period of World War II was an era of progressive devastation of the Świt sanatorium as well. From the autumn of 1940 to the spring of 1941, the German army and later the *Baudienst* were quartered there. The building became a fertiliser warehouse after the war [28]. Another partly destroyed villa was the Prus. In August 1944, the building served as the headquarters for a section of the German front. However, later that month, a bomb hit the central part of the building during an operational meeting. After the end of the war, the undamaged wing of the villa was used by the former owners until the Spa Establishment was nationalised.

Property losses of the Busko-Zdrój and Solec-Zdrój spa resorts

The spa facilities and equipment in Busko-Zdrój were ruined during the German occupation. The damage to the spa resort was also compounded by the incursion of the Soviet Army in January 1945. Light therapy and electrotherapy machines, medical office equipment, and X-ray and analytical equipment were all taken away. As a result of the devastation described above, the mud bath department, the light therapy and electrotherapy department, and the therapeutic physical exercise department were out of use in 1945 [29]. The spa archive was destroyed as well. The Górka Children's Sanatorium sustained enormous losses. Approximately 200 special beds intended for children were altered to accommodate German soldiers. Clothes, children's underwear and bedding were looted. The X-ray machine, diathermy apparatus, lamps and everything were taken away [30]. The spa facilities were vandalised not only by the activities of the German occupiers. The Busko-Zdrój health resort was reclaimed by the Polish authorities on 24 January 1945. As reported by the director of the facility: "[in the spa resort] there is probably not one square metre of the establishment's greenery that has not been disturbed, not five metres of fence that have not been strained, not a building that has not suffered, not a department that has not been marked by casual or intentional destruction" [31].

The Solec-Zdrój health resort suffered even greater harm. The town and spa resort were demolished in the war activities of 1944. The modern spa facilities built in 1923 were 80% destroyed during the German occupation of Solec-Zdrój, and the forest belonging to the spa and many trees from the spa park were also cut down. The spa equipment was almost completely looted. The resort was also stripped of such basic equipment as tables, stools, and beds [32]. The report of 12 September 1945 stated: "There used to be 65 bathtubs – now there are 25, there are only five stools, there used to be 72 couches – there are now nine, there are no beds, there are no tables. 90% of everything has been either destroyed or looted" [33]. In 1951, the Solec-Zdrój health resort was nationalised and incorporated into the Board of the State Spa Resort in Busko-Zdrój. Around 500 patients were treated there each year until 1958. In July 1961, Solec-Zdrój was opened as a year-round health resort [34].

Conclusion

The spa resort departments in Busko-Zdrój and Solec-Zdrój changed their purpose during the German occupation, serving mainly as convalescence sites for the Germans. It is worth noting that the Polish population was almost completely restricted from accessing them, which dramatically reduced the number of patients. As a result of the actions of the German occupiers, some of the spa buildings were destroyed and their equipment looted. The accommodation facilities in Busko-Zdrój and Solec-Zdrój were also vandalised, and were allocated almost exclusively for German use. The process intensified further after the end of hostilities. Amid the above events, the number of rooms for patients in Busko-Zdrój alone decreased by 350. After the war, the spas had to be rebuilt and while in Busko-Zdrój patients were admitted as early as 1945, Solec-Zdrój was opened as a year-round health resort in 1961.

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CAN AGNOR COUNTS AND CONFIGURATION PREDICT COMPLETE REMISSION IN ADULT ACUTE MYELOGENOUS LEUKEMIA PATIENTS?

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Abstract: The analysis of the AgNORs was performed in patients with acute myeloid leukemia (AML) to verify the role of AgNOR parameters in predicting complete remission (CR). Bone marrow aspirates from 24 patients with AML were stained with silver nitrate and underwent morphological, immuophenotypic, and genetic assessment. The mean AgNORs number, mean AgNORs area, and the mean AgNOR area-to-nucleus-area ratio were calculated for each case. After induction therapy, patients who achieved complete remission (CR) received intensive consolidation treatment. Fifteen patients underwent allogenic bone marrow transplantation. A higher mean AgNOR area-to-nucleus-area ratio was found in group with the CR status.

Key words: acute myeloid leukemia; argyrophilic nucleolar organizer regions; complete remission.

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Introduction

Proliferation and accumulation in the bone marrow of neoplastic blast cells leads to the development of acute myeloid leukemia [1]. The assessment of genetic alterations of a leukaemia clone using classical cytogenetics and molecular methods is a basic element of the diagnosis of acute leukemias. It is also the basis for their classification and provides information on the prognosis and possible therapeutic goals [1,2,3]. The prognostic factors in acute myeloid leukemias can be divided into those that are patient-dependent (which determine treatment tolerance and treatment-related early mortality) and factors that depend on the characteristics of the leukemic clone (which determine chemotherapy resistance). The prognostic factors dependent on the leukemic clone are cytogenetic and molecular abnormalities. The classification developed by the European LeukemiaNet (ELN) distinguished three prognostic groups. In clinical practice, the ELN is used to assess the risk [4]. In case of failure of cytogenetic analysis (lack of appropriate material for analysis or its insufficient amount, non-sterile material collection), prognostic assessment is impossible. The nucleolus organizing region (NOR) is the segment of the chromosome in which genes for the major ribosomal RNAs are found. A specific group of acidic, highly silver-absorbing, non-histone protein complexes located in the same places as the NOR allows for the precise and quick visualization of the nucleolus organizing regions by staining with silver nitrate [5,6,7]. Silver-stained NOR is referred to as AgNOR, and silver-staining NOR proteins as AgNOR proteins. Nikicz and Norback were the first to use the silver staining method to visualize NOR in bone marrow cells in healthy people. This study determined the applicability of AgNOR staining in the differential analysis of bone marrow hematopoietic cells [8]. Pich A. et all showed that AML patients who achieved the complete remission after induction course showed a greater amount of AgNOR in the blastic cells. The amount of AgNOR was correlated with the duration of remission: the higher amount of AgNOR – the longer duration of remission [9]. The above mentioned analysis of AgNOR in blasts cells is one of the last publications. In this study, we analyzed parameters of AgNOR in blast cells of 24 AML patients. The work was aimed to verify its role in predicting complete remission (CR).

Materials and Method

Group Characteristics

The study group consisted of 24 patients diagnosed, hospitalized and treated in the Department of Internal Medicine and Haematology between 2017 – 2021. Characteristics of the study group are presented in Table1 and Table 2.

Table 1. Characteristics of the study group.

	no (range)
Whole series	24
Age (range)	46,0 (20 – 64)
Sex (m/f) No [%]	10/14 (41/59)
WBC G/l (range)	49 (1,1 – 352)
Hgb g [%] (range)	9,4 (7,8 – 12,5)
PLT G/l (range)	68 (12 – 213)
Blasts in pb [%] (range)	36,8 (1 – 92)
Blasts in bm [%] (range)	56,7 (20 – 93)
FAB classification M0 M2 M4 M5	 2 13 7 2
Cytogenetic risk ELN2 ELN3	 16 8

Abbreviation: m – male, f – female, WBC – white blood cell count, hgb – hemoglobin, PLT – platelets, Bm – bone marrow, FAB – French-American-British, pb – peripheral blood, ELN – European LeukemiaNet.

All patients were treated according to the protocols of the Polish Adult Leukemia Group (PALG). The individual chemotherapy courses used in treatment are presented in Table2.

Table 2. Characteristics of the study group.

	Cr(-)	Cr(+)
ELN2	6	8
ELN3	5	2
Inductjon therapy (all patients)	daunorubicin 60mg/m2 i.v 1-3 days cytarabine 200mg/m2 i.v 1-7 days cladribine 5mg/m2 i.v 1-5 days (DAC)	
Re-induction therapy	cladribine 5mg/ m2 i.v 1-5 days, cytarabine 2000mg/ m2 i.v 1-5 days, mitoxantron 10mg/ m2 i.v 1-3 days	
Consolidation therapy (all patients)	cytarabine 2-3g/m2 i.v. on 1,3,5 day (HD ARaC) cytarabine 1.5g/m2 i.v. 1-3 days and mitoxantone 10mg/m2 on 3 and 4 day (HAM)	

Abbreviation: ELN – European LeukemiaNet, CR – complete remission.

AgNOR analysis

1. Preparation of bone marrow aspirate for analysis
   a) smearing marrow aspirate on a glass slide
   b) drying at room temperature
   c) immersion in ethyl alcohol for 10 minutes
   d) rising in distilled water
2. AgNOR staining
   a) preparing solution A 2% solution of gelatin dissolved in distilled water, to which formic acid was added until 1% concentration of final solution was obtained
   b) preparing solution B
   50% solution of silver nitrate in distilled water

The preparation was then stained for 20 minutes in a solution obtained by immediate, fast mixing of one volume of solution A with two volumes of solution B. The preparations were placed for 10 minutes in a 5% sodium thio-sulfate solution, and rinsed in distilled water.

3. Analysis of AgNOR parameters
   a) Slides were evaluated under an optical microscope (Olympus BX51 microscope, MDOB3 model, Tokyo, Japan). The total magnification was x1000.
   b) 200 blast cells were analyzed using a computerized image analysis system called cell* Soft Imaging System (Germany) and by the Microsoft Excel program.
   c) The nucleus and each selected AgNOR structure were outlined for each selected blast cell.
   d) The AgNORs parameters were measured: the mean number of AgNORs in the nucleus, the mean surface of AgNORs, and the ratio of AgNOR surface to cell nucleus surface.
   e) The data were calculated using the author's program and Excel.
   f) The structure and patterns of AgNOR in bone marrow blastic cells were classified according to the system developed by Nikicz, with author's modification. The modification consisted in differentiation AgNOR depending on surface size.

Statistical Analysis

The Python 3.8 and Statistica 13.3 software (Statsoft, TIBCO Software Inc., Dell Inc.,Plo Alto, CA, USA) were conducted. The $p < 0.05$ was set at statistical significance level.

Results

AgNOR parameters were calculated in leukemic cells in all patients with AML.

Figure 1. AgnOr staining in bone marrow smears of a patient with acute myeloid leukemia M2 (ELN2) with complete remission of CR (+).

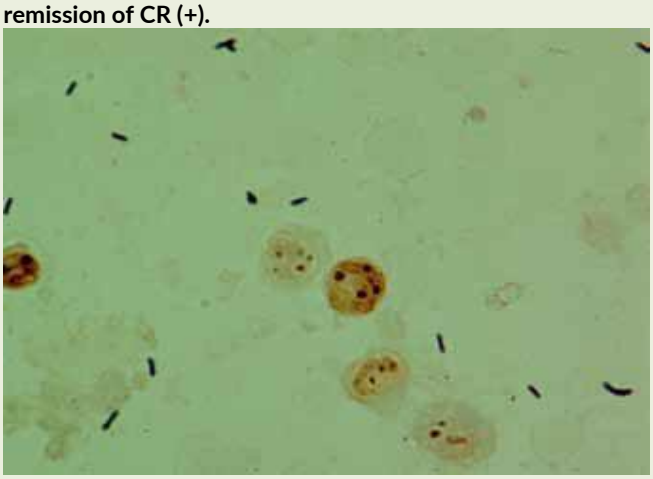
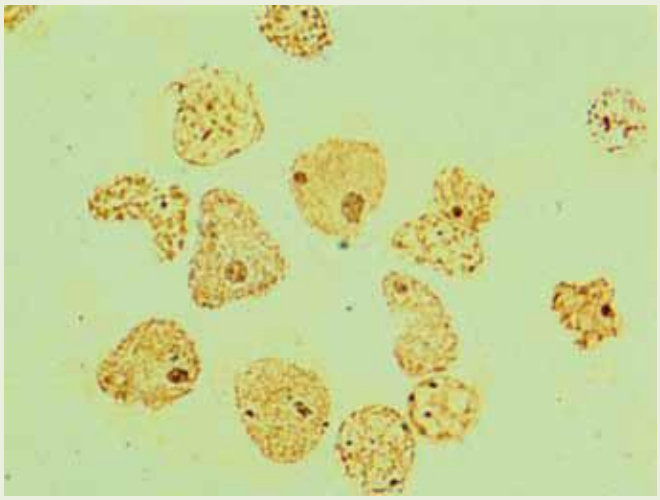


Figure 2. AgnOr staining in bone marrow smears of a patient with acute myeloid leukemia M4 (ELN3) without CR (-).



Significantly higher values of mean ratio of the AgNOR surface area to the nucleus surface area were found in patients who achieved CR compared to the group without this status (p= 0.02) (Table 3, Figure 3).

Table 3. AgNOR indexes in AML depending on remission status: the mean number, mean surface area, and mean ratio of AgNOR surface area to nucleus surface area, expressed as percentages.

AgNOR Cell Indexes	CR(+)	CR(-)	p
Mean number of AgNORs	(n=10)	(n=11)	
Mean surface of AgNORs [um2]	2.79+/-0.61	2.22+/-0.34	0.28
AgNOR surface/ nucleus surface[%]	14.44+/-3.31	13.77+/-3.74	0.06

Abbreviation: AgNOR – argyrophilic nucleolar organizer regions, CR – complete remission.

Figure 3. AgnOr indexes differences between patients who achieved CR and patients without CR: the mean number, mean surface area, and mean ratio of AgNOR surface area to the nucleus surface area.

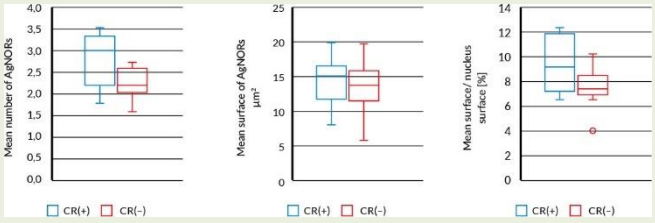
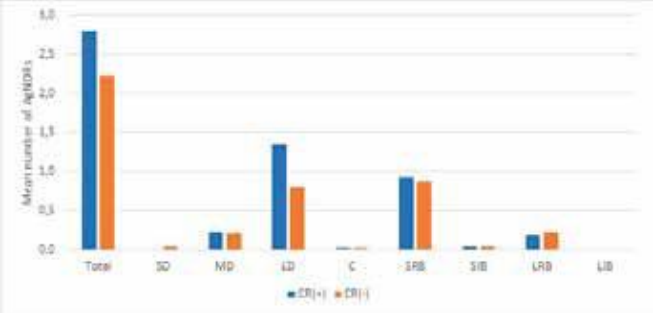
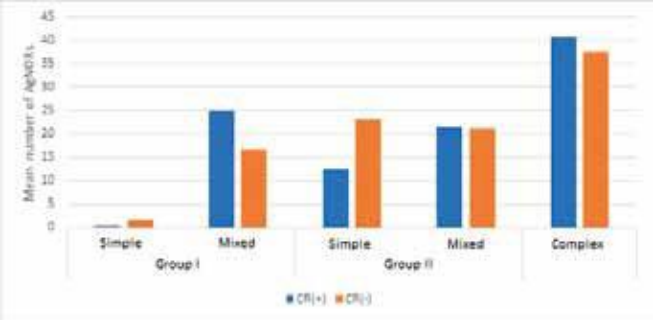


Figure 4. Presentation of particular structures dependent on remission status.



No statistically significant differences were found in the mean number of AgNOR in particular structures in AML depending on the remission status (Figure 4).

Figure 5. Presentation of the configuration of particular structures depending on remission status.



There were no statistically significant differences in group I among simple (p = 0.77) and mixed (p = 0.49) structures in the group of patients without remission in AML compared to patients who did not achieve this remission. Also in group II, no statistically significant differences were found among the simple (p = 0.54) and mixed (p = 0.33) structures in both groups (Figure 5).

Discussion

In our research the mean number of AgNORs, the mean surface area of AgNORs, and the ratio of AgNOR surface area to nucleus surface area were measured. Only in the case of the last parameter, our research showed a statistically significant difference between both groups. We observed a higher value of the mean number of AgNOR in the group of patients who achieved the CR status, but the difference was not statistically significant. Pich et all showed that in adult patients with acute myeloid leukemia who achieved disease remission, a higher content of AgNOR in the cell was obtained compared to patients without remission. The amount of AgNOR was correlated with the duration of remission: greater amount of AgNOR – longer duration of remission. These results suggested that patients with more AgNOR leukemia clones responded more easily to treatment. In contrast, in patients with low levels of AgNOR resistance to chemotherapy has been observed [9].

In the above-mentioned publication, an analysis was carried out in 40 patients with de novo AML. Cytogenetic analysis was done in 26 patients (chromosomal abnormalities were found in less than half of them). According to the literature available at that time, cytogenetic alterations were categorised in three prognostic groups: low (two patients), intermediate (17 patients), and high-risk group (seven patients) [10,11]. There was no relationship between AgNOR and cytogenetics. Patients in our study were classified according to ELN. Cytogenetic and molecular evaluation before the start of the treatment in patients with AML before starting treatment allows to plan it (including planning allo-hematopoietic steam cell transplant [allo-HSCT]). When comparing the two groups in terms of CR status depending on cytogenetic and molecular risk, it is difficult to make an ambiguous conclusion as to the chance of achieving remission depending on cytogenetic and molecular risk.

In our study the AgNOR classification proposed by Nikicicz and Norback for the analysis of normal bone marrow was used in our study [8]. Our analysis in relations to leukemic cells did not show any differences in all AgNOR structures and configuration. This may be due to the relatively small number of patients in groups compared in this study. We have no possibility of comparing our data with other studies.

The assessment of genetic disorders in the leukemic clone is an important element in the diagnosis of acute leukemias and is important in the assessment of patient's prognosis. The analysis of various AgNOR structures in acute leukemias can easily identify risk groups without the need for genetic tests.

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RIGHT SIDE SUDDEN DEAFNESS WITH PERIPHERAL VERTIGO AS A RESULT OF NEUROVASCULAR CONFLICT

Nagła głuchota prawostronna z zawrotami głowy typu obwodowego na tle konfliktu nerwowo-naczyniowego

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Abstract: Hearing loss, whether sudden or gradually progressive, is a significant health and socioeconomic problem. Sudden, idiopathic, sensorineural hearing loss is a great concern for both doctors and patients. Case report: a 27 year old patient was admitted to the Department of Otolaryngology, Laryngological Oncology, Audiology and Phoniatrics of the Military Medical Academy Memorial Teaching Hospital of the Medical University of Lodz due to the feeling of obstruction in the right ear accompanied by tinnitus and severe dizziness of a variable nature. The audiological and otoneurological diagnostics showed a sudden deafness of the right ear and MRI of the cerebellopontine angles showed a neurovascular conflict on both sides. Pharmacological therapy was introduced; however during hospitalization, it did not bring the expected results, therefore hyperbaric oxygen treatment was ordered. Sudden sensorineural deafness in about 90% cases is an idiopathic disease, the cause of which remains unknown. In other cases, it is in all likelihood possible to indicate the original cause. One of them may be neurovascular conflict.

Streszczenie: Utrata słuchu – zarówno występująca nagle, jak i postępująca przewlekle – stanowi istotny problem zdrowotny oraz społeczno-ekonomiczny. Największe obawy lekarzy i pacjentów wzbudza nagłe, idiopatyczne, odbiorcze uszkodzenie słuchu. Opis przypadku: Pacjent 27 lat, przyjęty do Kliniki Otolaryngologii Onkologii Laryngologicznej, Audiologii i Foniatrii Uniwersyteckiego Szpitala Klinicznego im. WAM w Łodzi w trybie pilnym z powodu uczucia zatkania ucha prawego z tożstronnym szumem usznym oraz silnych zawrotów głowy o zmiennym charakterze. Przeprowadzona diagnostyka audiologiczna i otoneurologiczna wykazała nagłą głuchotę ucha prawego, a MR kątów mostowo-móżdżkowych konflikt naczyniowo-nerwowy obustronnie. Włączono leczenie farmakologiczne, które nie przyniosło spodziewanych efektów w trakcie hospitalizacji, w związku z czym chorego skierowano na leczenie hiperbarią tlenową. Nagła głuchota czuciowo-nerwowa w ok. 90% przypadków jest chorobą idiopatyczną, której przyczyna pozostaje nieznana w świetle przeprowadzonej diagnostyki. W pozostałych przypadkach można z dużym prawdopodobieństwem wskazać przyczynę wyjściową jej wystąpienia. Jedną z nich może być konflikt naczyniowo-nerwowy.

Key words: sudden deafness, vertigo, neurovascular conflict.

Słowa kluczowe: nagła głuchota, zawroty głowy, konflikt nerwowo-naczyniowy

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Introduction

Loss of hearing, both sudden and gradually progressing, represents a significant health and socio-economic problem. Although it is the most common disorder of the sensory organs, the exact number of people affected by it is unknown [1].

It is estimated that over 4.5 million individuals from different age groups in Poland may suffer from hearing loss [2]. As the type of hearing impairment the patient is suffering from has important clinical implications, locating the source of the primary damage is required – the outer, middle, or inner ear, or in the central sections of the auditory tract.

From the patient's point of view, sudden hearing loss is the most unsettling, regardless of its underlying cause. From the physician's perspective, the greatest concern is raised by a sudden, idiopathic, receptive hearing impairment (sudden sensorineural hearing loss, SSNHL), which requires immediate diagnostics and therapy.

Following the most widely recognised guidelines in scientific publications, sudden idiopathic deafness can be diagnosed based on receptive hearing loss of an unknown aetiology, greater than 30 dB in at least three consecutive audiometric frequencies which occur within 3 days. In the international literature, we find modifications of this definition, regarding all the mentioned parameters, however we consider the definition originally mentioned to be valid, as it is consistent with the position of the Polish Society of Audiology and Phoniatrics [3, 4].

The incidence of SSNHL is estimated at 5-20 cases per 100,000 citizens per year, most often in people between the fifth and sixth decade of life, regardless of sex. A vast majority of cases are unilateral. Bilateral manifestation is found in less than 10% of patients with sudden idiopathic deafness. This number may be underestimated as, due to a spontaneous recovery observed in 32-65% of affected patients, they do not seek medical care [5-6].

Case study

A 27-year-old patient was urgently admitted to the Department of Otolaryngology, Laryngological Oncology, Audiology and Phoniatrics of the Military Medical Academy Memorial Teaching Hospital of the Medical University of Lodz due to a sudden hearing impairment in the right ear and vertigo. The patient reported that on the day of admission, approximately 7-8 hours earlier, during a strength workout, while performing a "deadlift", associated with significant tension of the abdominal press and increased pressure in the upper body, he experience a feeling of right ear blockage with ipsilateral tinnitus. Next, strong vertigo occurred, presenting as a spinning movement of the environment to the left, and persisting for no more than 20 minutes. The sensation was associated with nausea and vomiting. The symptoms resolved spontaneously, except for the loss of hearing in the right ear.

No other abnormalities were found in the medical history. The patient did not report any similar episodes in the past, he denied chronic diseases, taking medications, using supplements or hormones used in bodybuilding, while the training sessions at the gym were to help him reduce body weight.

The physical examination revealed slight obesity (BMI 31) and no other significant abnormalities. The laryngological examination did not reveal any signs of upper respiratory infection, and the otoscopic findings in both ears were normal. No nystagmus was observed. Tuning fork tests: Weber – left-sided lateralisation, Rinne – RE (+), LE (+). The Romberg's sign: (-). No abnormalities in the facial nerve function were found.

The basic and biochemical blood tests did not reveal any abnormalities, the coagulation system was normal, and the inflammatory markers were not elevated.

Following the basic audiological diagnostics: a tonal audiometry test (Fig. 1) and an impedance audiometry test, pharmacological treatment was initiated: prednisone 60 mg/day p.o., piracetam 16 g/day i.v., vinpocetine 20 mg/day i.v.

On day 2 of hospitalisation, the patient again reported vertigo. However, the symptom did not resemble the experience from the previous day – it was non-systemic, and persisted for a few hours. A videonystagmography revealed second-degree spontaneous nystagmus to the left, with an amplitude of 2.1 to 2.30/s. It was not visible in direct observation without the elimination of gaze fixation. The hearing status did not change.

On day 3 of the treatment, the diagnostics were extended to include a full VNG test, with the following findings: spontaneous nystagmus – absent, positional nystagmus: seated position – absent, supine position – absent, head

Fig. 1. Results of the threshold tonal audiometric test before the treatment.

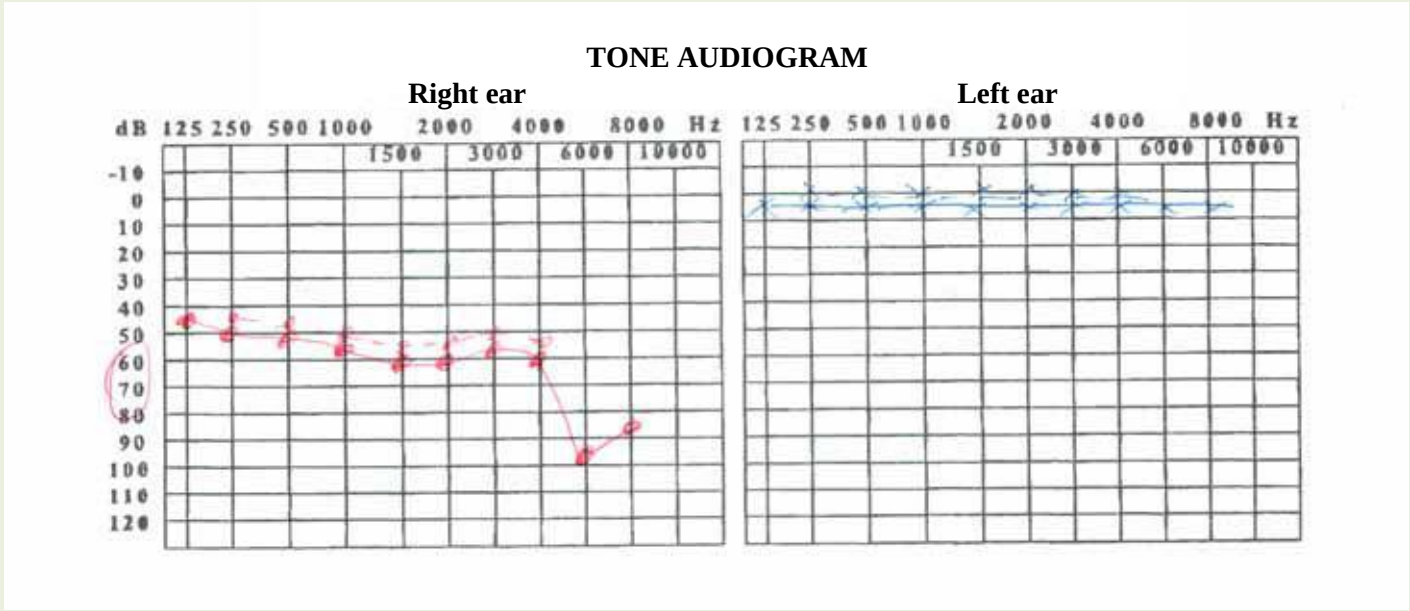
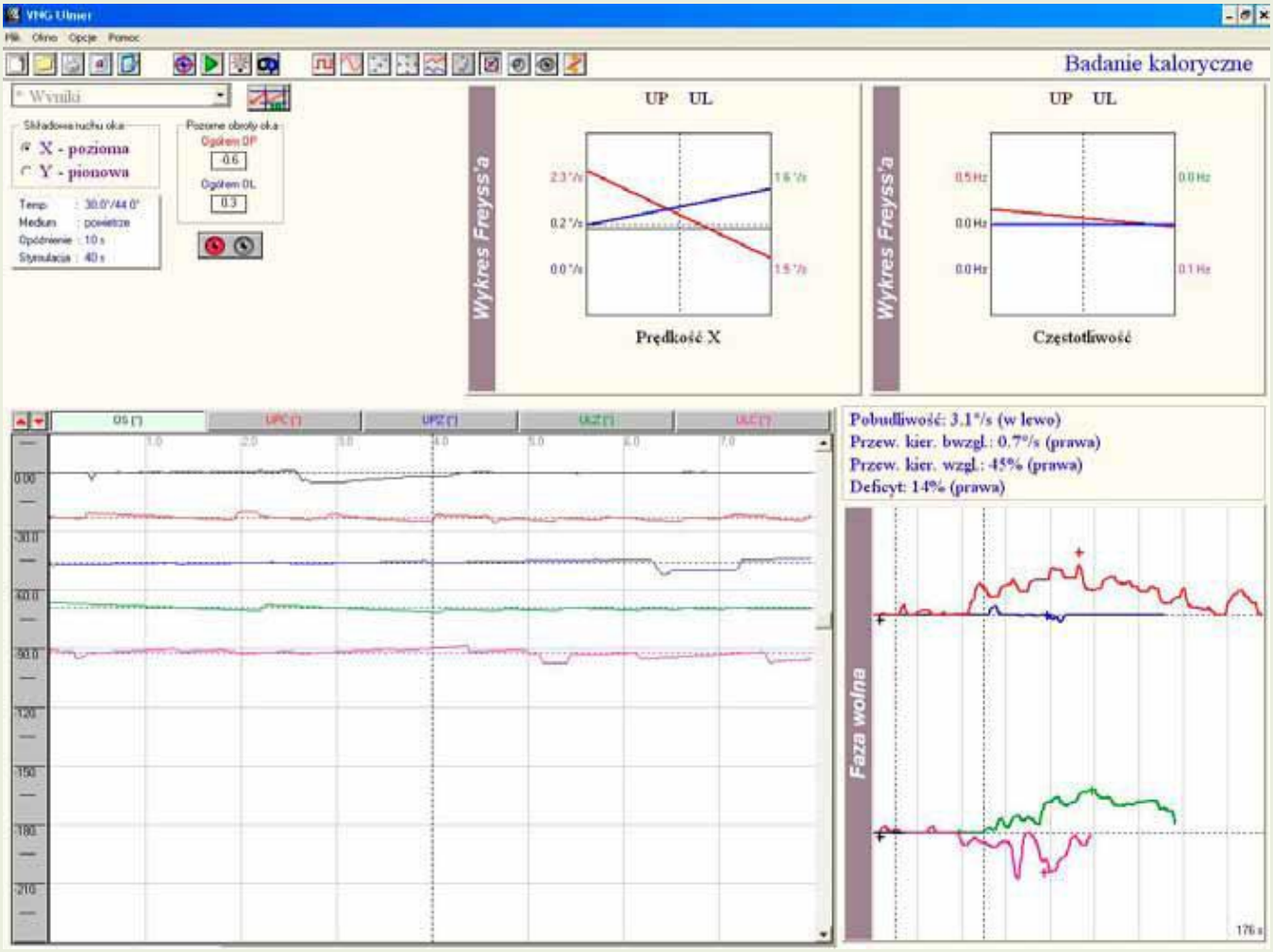


Fig. 2. Fitzgerald-Hallpike caloric test result.



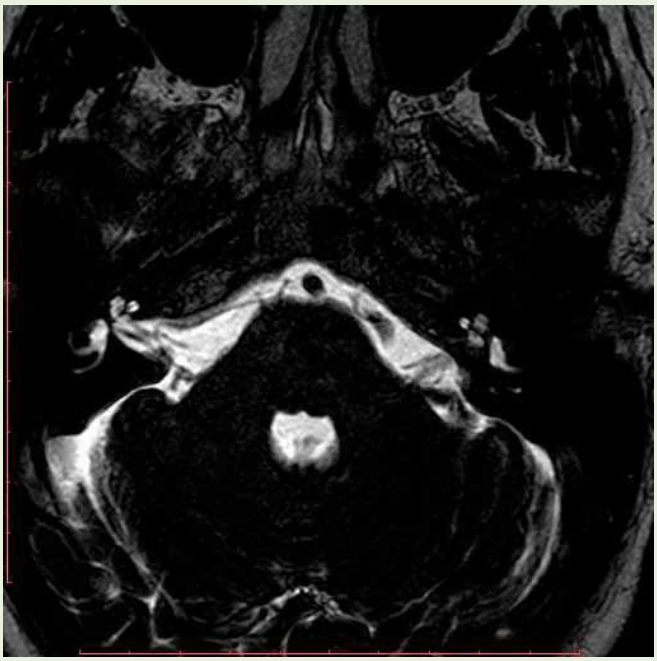
turned right – individual square waves, head turned left – individual square waves, on the right side – absent, on the left side – absent, Rose's position – individual square waves; caloric test – excitability: 3.10/s (left ear), absolute directional advantage – 0.70/s (right ear), relative directional advantage – 45% (right side), unilateral deficit – 14% left ear (Fig. 2).

An X-ray of the cervical spine with a functional test did not reveal any changes in the bone structures or limited mobility.

On day 4 of the treatment, a follow-up threshold tonal audiometry revealed worsening of the hearing loss compared to the baseline test, as well as a complete loss of speech comprehension in the affected ear.

It should be noted that in the patient's subjective assessment the hearing status did not change relative to the day of admission to the hospital. Therefore, a neurological consultation was arranged, and an MR test of the cerebellopontine angles was ordered. The findings of the neurological examination, apart from the right-sided hearing loss, were normal. The contrast-enhanced MR study revealed bilateral vascular loops in the vicinity of the facial nerve and the vestibulocochlear nerve, branching off

Fig. 3. Head MR test with a visible neurovascular conflict on the right.



from the anterior inferior cerebellar artery, possibly meeting the neurovascular conflict criteria (Fig. 3).

After 8 days of pharmacological treatment, hearing improvement was not achieved, and the patient was referred for hyperbaric oxygen therapy. The further course of the disease is unknown, as the patient did not come for the follow-up examinations after the hyperbaric oxygen therapy.

Conclusions

Sudden sensorineural deafness in about 90% of cases is an idiopathic disease, the cause of which remains unknown based on the diagnostics conducted. In other cases, it is in all likelihood possible to indicate the original cause. One of them may be neurovascular conflict. The term was first used in a publication by Jannetta et al. in 1984 [7]. The pathophysiology of symptoms due to a neurovascular conflict assumes a direct compression of a nerve axon by a vessel, which damages the nerve's myelin sheath, and, as a consequence, the nerve itself, resulting in a pathological, ectopic excitation and clinical symptoms [8].

The clinical manifestation comprises a set of various symptoms, including vertigo, balance disorders, hearing loss or tinnitus. As the symptoms are not permanent, their intensity varies, and they fluctuate, then they may be suggestive of other diseases, complicating an accurate diagnosis [9]. Differential diagnostics should consider tumours of a cerebellopontine angle, multiple sclerosis, Ménière's disease or perilymphatic fistula.

The treatment of a patient with neurovascular conflict may include pharmacological therapy with betahistine preparations, medicines improving blood circulation, nootropics, steroids, vitamins B, oxygen therapy and anti-nausea medications, as well as carbamazepine, but the effectiveness of such treatment cannot be guaranteed.

The only causal treatment of a neurovascular conflict involving the vestibulocochlear nerve is microsurgical nerve decompression, and if the observed symptoms resolve after the surgery, their vascular origin is confirmed [10].

In conclusion, neurovascular conflict is not the most frequent cause of hearing loss, vertigo or tinnitus, and it may occur in healthy individuals without any pathological symptoms [11]. Nevertheless, it should be considered during the diagnostics of a patient whose symptoms are not specific, and the audiological and otoneurological examinations do not provide a clear explanation for the origin of the symptoms.

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SELECTIVE EMBOLIZATION OF THYROID ARTERIES AS AN ALTERNATIVE TREATMENT TO AMIODARONE – INDUCED HYPERTHYROIDISM

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Abstract: Background: A selective embolization of thyroid arteries (SETA) is a rarely performed procedure. Although 35 years have passed since the first description of the SETA application, only about 150-200 procedures have been published so far.
Case presentation: We present the case of a patient successfully treated for amiodarone-induced hyperthyroidism using the SETA method. The patient had a history of paroxysmal atrial fibrillation (PAF), diagnosed three years earlier, treated with an anticoagulant – rivaroxaban. During a 35 month period, amiodarone was used as a method for treating the PAF. During the treatment, the patient developed hyperthyroidism. The patient was treated with thiamazole, propranolol and sodium perchlorate. After obtaining euthyreosis, SETA was performed. The patient underwent selective embolization of the left superior and right inferior thyroid arteries with a sclerosing agent, polyvinyl alcohol, with a good clinical effect. The thyrosthetics agents were discontinued.
Conclusions: This case demonstrates difficulties in the differential diagnosis of this type of amiodarone-induced hyperthyroidism. A normal ultrasound image of the thyroid gland and absence of antithyroid antibodies suggests type II amiodarone-induced hyperthyroidism. With a good, fast response to thyrostatics – type I, it would seem that the diagnosis of the mixed type of amiodarone-induced hyperthyroidism was justified. Further research is also required to assess the safety and efficacy of SETA in amiodarone-induced hyperthyroidism in larger groups of patients.

Key words: embolization, hyperthyroidism, amiodaron, thyroid arteries, sodium perchlorate.osis.

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Introduction

Selective embolization of thyroid arteries (SETA) is a rarely performed procedure. Although 35 years have passed since the first description of the SETA application, only about 150-200 procedures have been published so far [1, 2]. This is most likely due to the availability of traditional forms of thyroid disease treatment options: pharmacotherapy, radioactive iodine treatment (RIT) and surgery. Each of the above methods has its limitations and is not always acceptable by both the patient and the physician. It seems that treatment of amiodarone-induced hyperthyroidism may be a special indication for the use of SETA. Pharmacological treatment with thyrostatics is associated with the possibility of allergic reactions, liver and bone marrow injury and secondary agranulocytosis and thrombocytopenia. Administration of RIT is not useful due to the blocking of iodine uptake by long-term use of amiodarone. Surgical treatment may be particularly dangerous due to frequent comorbid cardiac arrhythmias, exacerbation of heart failure, and the possibility of bleeding complications [3, 4]. We present the case of a patient successfully treated for amiodarone-induced hyperthyroidism with the use of the SETA method.

Case report

A fifty-nine year old patient had been under the care of the Department of Endocrinology and Isotope Therapy of the Military Medical Institute for 3 months. The patient was referred due to hyperthyroidism non-reactive to a thyrostatic treatment with thiamazole. The patient had a history of paroxysmal atrial fibrillation (PAF), diagnosed three years earlier, treated with an anticoagulant – rivaroxaban. In addition, the patient had also a history of benign prostatic hypertrophy and degenerative spine disease. Amiodarone had been used for 36 months as a method for treating the PAF. Subsequently, the drug was discontinued due to poor tolerance to physical effort, increased palpitations, hand tremors and symptoms of NYHA class II heart failure. In the ECHO exam, moderate enlargement of the left atrial area (LAA) – 26 cm^2,

borderline size of the right atrium and right ventricle was found. In addition, borderline thickness of left ventricular muscle was described, without segmental contractility disturbances, with a left ventricular ejection fraction (LVEF) of 63%. The heart valves were without abnormalities. The chest X-ray was normal. The ultrasound examination revealed a non-enlarged, normal, echogenically homogeneous thyroid, with right lobe dimensions: 18x25x48 mm, left lobe 20x21x51 mm, with normal vascular flow in the entire gland. A single, isoechogenic, solid-cystic focal lesion of 7x7 mm, with a peripheral type of vascularization, was visualized in the superior pole of the right lobe. No abnormalities were found in the regional cervical lymph nodes. In the additional tests, thyrotropin (thyroid stimulating hormone – TSH) concentration was <0.005 uIU/ml (0.27-4.2 uIU/ml), free triiodothyronine (FT3) – 8.14 pmol/l (3.2-6.9 pmol/l), free thyroxine (FT4) 54.83 pmol/l (12-22 pmol/l). Neither the TSH receptor antibodies TRAb, thyroglobulin, nor thyreoperoxidase antibodies were found. Due to the confirmed thyrotoxicosis, thiamazole was increased to 60 mg/day, beta-blocker – propranolol to 240 mg/day and sodium perchlorate to a dose of 4x10 drops, as an equivalent of 800-1000 mg sodium perchlorate per day. Additional tests were performed after 7 days. No abnormalities were found in the peripheral blood morphology. There was an improvement in free hormone concentrations: FT4 decreased to 37.08 pmol/l and FT3 to 5.51 pmol/l. After 14 days of treatment, a significant further reduction in FT4 to 32.12 pmol/l, and FT3 to 4.28 pmol/l was achieved with the accompanying improvement in well-being, resolution of palpitations and improvement of physical performance. After 3 weeks of treatment, further improvement, in FT4 concentrations to 26.07 pmol/l, was observed. The patient was qualified for selective embolization of the thyroid arteries due to the possibility of only short-term use of sodium perchlorate, up to a maximum of 4 weeks. Initial selective arteriography of the superior and inferior thyroid arteries was performed from the incision of the right femoral artery, using the Seldinger method, under local anaesthesia (1% procaine). The examination revealed narrow arteries: inferior left and superior right thyroid arteries. The decision about the extent of the embolization procedure was made based on the angiographic and clinical data. The patient underwent selective embolization of the left superior and right inferior thyroid arteries with a sclerosing agent – polyvinyl alcohol (PVA) (Figure 1A, 1B and 2A, 2B). The procedure was carried out without complications.

During the follow up over the next few days, the patient did not report any symptoms. There was no pain in the neck area. Laboratory tests showed a temporary reduction in total calcium concentration to a minimum value of 8.3 mg/dl (8.6-10.2 mg/dl), with no typical symptoms of tetany. In laboratory tests a further reduction of FT3 to 2.8 pmol/l and FT4 to 22.76 pmol/l was found 3 days after SETA. The patient was discharged from the Endocrinology and Isotope Therapy Department on the fourth day after the procedure, in good clinical condition, with the recommended use of thiamazole at a dose of 20 mg/day and propranolol 4x120 mg. Four weeks after SETA, clinical euthyreosis was found with a TSH concentration of 1.56 uIU/ml, FT3 – 2.36 pmol/l, FT4 – 16.25 pmol/l. The thiamazole dose was gradually reduced, and after 4 weeks the medication was discontinued. After achieving euthyreosis, an electrical cardioversion was performed, which proved to be ineffective. After 3 weeks of electrical cardioversion, atrial fibrillation recurred.

Discussion

The presented clinical case requires a detailed discussion. Diagnosis of the disease and the determination of the cause of hyperthyroidism raise doubts. A long-term history of amiodarone treatment makes it easier to diagnose amiodarone-induced hyperthyroidism. However, it is difficult to differentiate between type I and II of the disease, which have completely different pathogenesis and treatment options [5].

The normal ultrasound picture of the thyroid gland – no nodular goiter with non-increased vascular flow, and the absence of antithyroid antibodies suggest the diagnosis of type II amiodarone-induced hyperthyroidism. This is mostly a self-limiting disease, responding to glucocorticosteroid treatment. It is believed that it is possible to distinguish the type of amiodarone-induced hyperthyroidism on the basis of color flow Doppler sonography (CFDS) for up to 80% of cases [6]. The CFDS method is effective, especially if the tests are performed sequentially, but it is not useful in cases of earlier application of thyrostatic drugs, which happened in this case. Here the normal CFDS has made differential diagnosis difficult. Discontinuation of amiodarone did not inhibit thyrotoxicosis but, on the contrary, exacerbated the course of the disease. The patient was admitted with symptoms of heart failure, with atrial fibrillation, fast ventricular rate of 160/min, and a lack of clinical response to thyrostatic and beta-blocker therapy in full doses. Prednisone was not started due to concerns about the possible side effects of glucocorticosteroids (GSK), especially the increase in the volume of body fluids and its implications. In addition, according to the available literature, the efficacy of oral glucocorticosteroids at FT4 concentrations exceeding 50 pmol/l is limited [7, 8]. Sodium perchlorate (Irenat®) treatment, at a dose of 1000 mg/day, was included for the rapid control of hyperthyroidism symptoms. Sodium perchlorate competitively inhibits the sodium-iodide symporter, thereby blocking the iodine uptake system by the thyroid follicular cells. In addition, it inhibits thyroid peroxidase, thereby reducing the incorporation of iodine into organic compounds. An additional effect of sodium perchlorate is the elimination of a follicular iodine pool not bound to thyroglobulin from the cell, and blockage of reutilization of the iodine released from thyroid hormones; as a result, renal iodine excretion increases [9]. The drug after oral administration binds to albumin, it is not metabolized, and is excreted in an unchanged form by the kidneys. Sodium perchlorate is active very quickly and over a short time period. The effect of sodium-iodide symporter inhibition lasts up to several hours and even shorter in the case of concurrent hyperthyroidism. The administration of sodium perchlorate with thiamazole enhances the clinical effects, which was used in this case. The application of sodium perchlorate

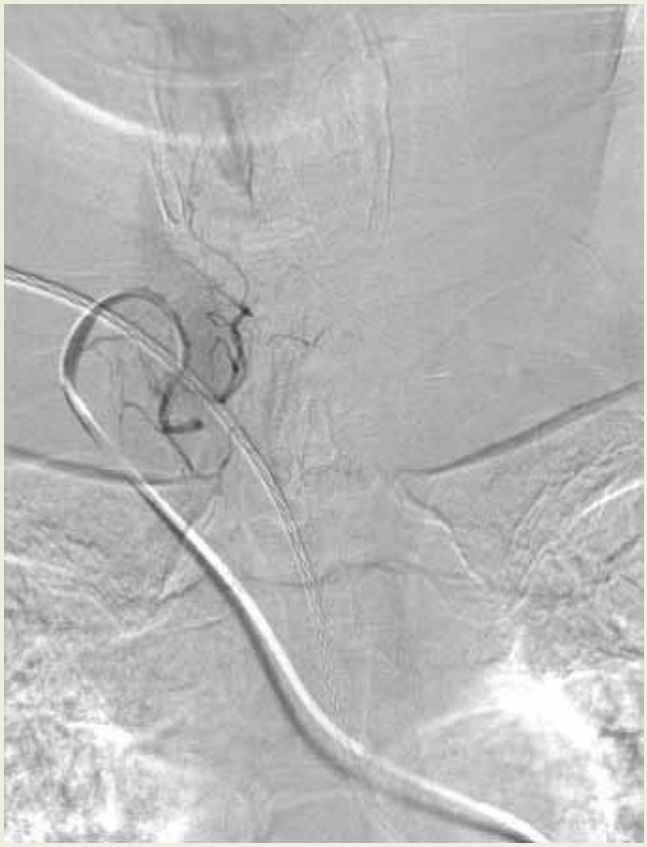

Figure 1A. Selective arteriography for the superior right thyroid artery before effective embolization with PVA.

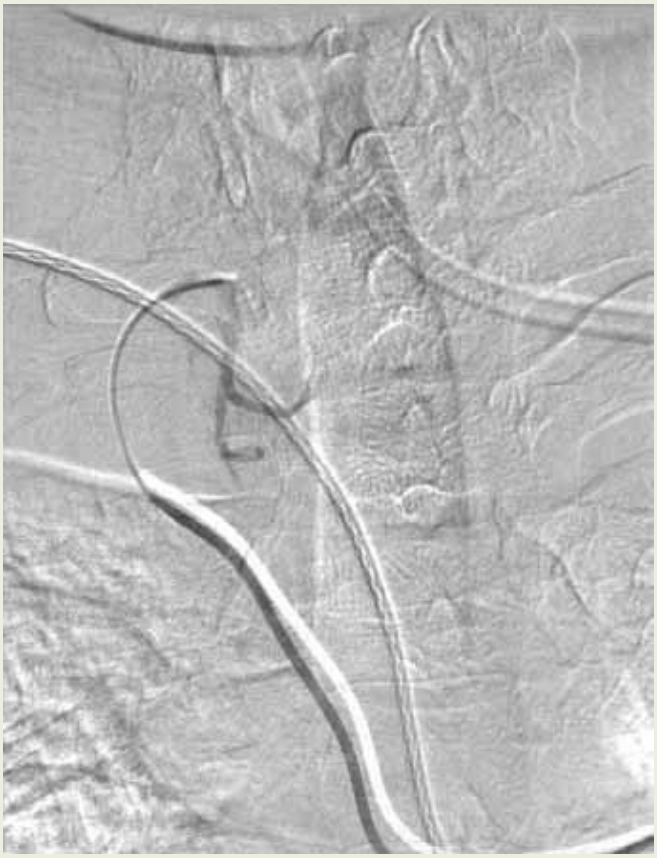

Figure 1B. Selective arteriography for the superior right thyroid artery after effective embolization with PVA.

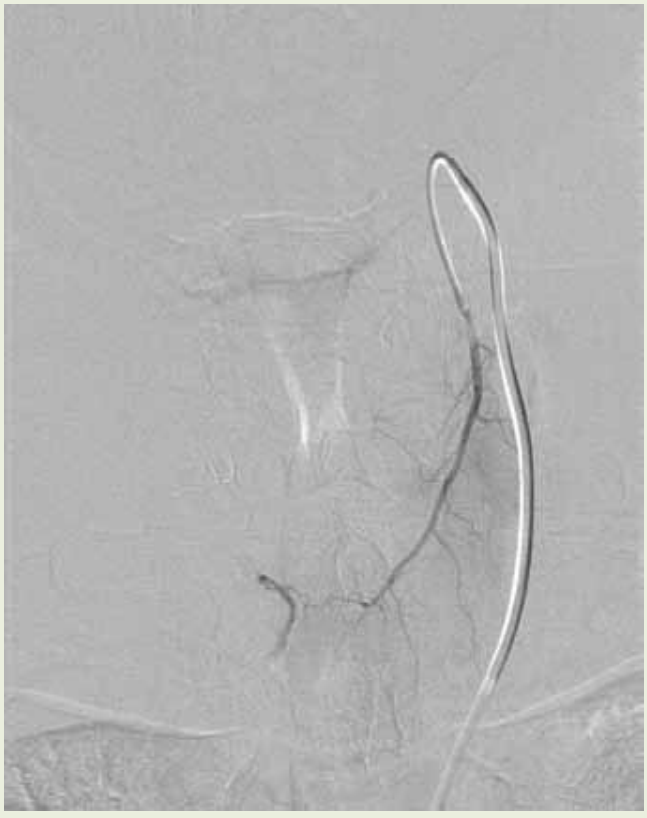

Figure 2A: Selective arteriography for the inferior left thyroid artery before effective embolization with PVA.

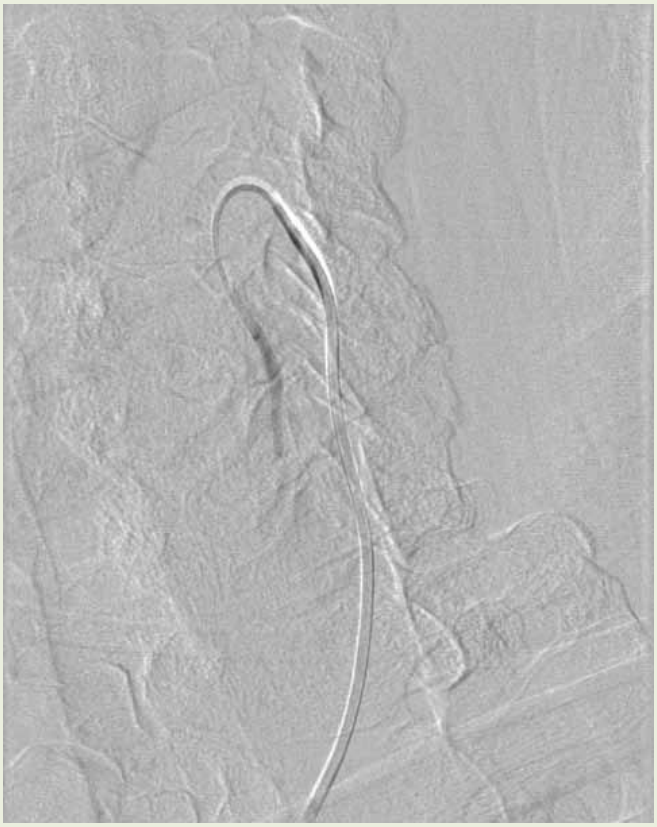

Figure 2B: Selective arteriography for the interior left thyroid artery after effective embolization with PVA.

resulted in a relatively rapid achievement of euthyreosis. This drug, however, should not be used for more than 4 weeks. Its toxicity increases, especially to the bone marrow (significant risk of agranulocytosis) and to the kidneys [9, 10].

That good response to the treatment with thyrostatic medications on the contrary suggests the diagnosis of type I amiodarone-induced hyperthyroidism. Non-standard plasmapheresis may be considered in the absence of response to thyrostatic drugs in order to achieve rapid euthyreosis [13]. After achieving euthyreosis, a method has been sought that would stabilize the clinical effect. Surgical treatment was postponed due to the prophylactic treatment with a new oral anticoagulant (NOAC) – ri-varoxaban, high risk of hemorrhagic complications, and the lack of patient's consent for the proposed thyroidectomy [11, 12].

Thus it was decided to perform SETA. Procedures for embolization of the thyroid arteries had already been described in 1984. The first treatments concerned patients with parathyroid glands, who were disqualified from surgery due to difficulties in surgical access [13]. Procedures involving embolization of the thyroid arteries can be effectively performed as a rescue treatment after iatrogenic damage to the thyroid vessels. The successful experience of the Endorinology and Isotope Therapy Department, as well as the available results of clinical trials, prompted the qualification of the patient for embolization of the thyroid arteries. Since 2004, about 30 SETA procedures have been performed at the Department of Endocrinology and Isotope Therapy, Military Institute of Medicine. In the years 2004-2005, we conducted the clinical trial that assessed SETA effectiveness. Fifteen patients were included in the study, where one patient suffered from amidarone-induced hyperthyroidism. In 67% of the cases, two of the four thyroid vessels were embolized, most often the inferior right and left thyroid artery. After 12 weeks, euthyreosis was obtained in 75% of the patients. Only 3 patients required substitution treatment with L-thyroxine [14]. Adverse events were rare. Most often it was a slight pain in the neck area and a temporary decrease in the total calcium blood concentration without clinical symptoms [15]. Similar results were obtained by other groups [16]. The patient discussed was qualified for SETA on the basis of the promising examination results. The procedure proved to be effective, safe and minimally invasive.

To summarize, the presented case demonstrates difficulties in the differential diagnosis of the type of amiodarone-induced hyperthyroidism. A normal ultrasound image of the thyroid gland and absence of antithyroid antibodies suggests type II amiodarone-induced hyperthyroidism. A good, fast response to thyrostatics suggests type I. It seems therefore that the diagnosis of the mixed type of amiodarone-induced hyperthyroidism is justified. Further research is also required to assess the safety and efficacy of SETA in larger groups of patients with amiodarone-induced hyperthyroidism in larger groups.

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CASE REPORT

BRAIN ABSCESS CAUSED BY *NOCARDIA ABSCESSUS*

Ropień mózgu wywołany przez *Nocardia abscessus*

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Abstract: Nocardia bacteria are aerobic actinomycetes causing severe infections in humans and animals. There are more than 30 species pathogenic to humans. The most frequently isolated strains include: *N. nova complex*, *N. abscessus*, *N. transvalensis complex*, *N. farcinica*, *N. asteroidestyp VI (N. cyriacigeorgica), and N. brasiliensis*, which are responsible for a wide variety of diseases ranging from cutaneous to pulmonary and multi-organ forms. Occasionally, they can cause also brain abscess, especially in immunosuppressed individuals. Immunocompromised patients are the most susceptible group. Proper identification of Nocardia bacteria is difficult. It is necessary to use molecular biology methods because new species sometimes do not show any phenotypic differences among themselves. Correct identification is necessary for the implementation of an appropriate antibiotic therapy.

Streszczenie: Bakterie z rodzaju Nocardia zaliczane są do tlenowych promieniowców wywołujących poważne infekcje ludzi oraz zwierząt. Występuje ponad 30 gatunków chorobotwórczych dla człowieka. Najczęściej izolowane szczepy, m.in.: *N. nova complex*, *N. abscessus*, *N. transvalensis complex*, *N. farcinica*, *N. asteroidestyp VI (N. cyriacigeorgica) i N. brasiliensis*, są odpowiedzialne za wiele różnych chorób począwszy od postaci skórnej, poprzez płucną oraz wielonarządową. Sporadycznie mogą powodować także ropień mózgu, zwłaszcza u osób w immunosupresji. Grupą najbardziej podatną na zachorowania są pacjenci z obniżoną odpornością. Właściwa identyfikacja bakterii z rodzaju Nocardia jest trudna. Niezbędne jest wykorzystanie metod biologii molekularnej, gdyż nowe gatunki niekiedy nie wykazują żadnych różnic fenotypowych między sobą. Prawidłowa identyfikacja jest konieczna do wdrożenia właściwej antybiotykoterapii.

Key words: actinomycetes, brain abscess, nocardiosis, Nocardia.

Słowa kluczowe: promieniowce, ropień mózgu, Nocardia, nokardioza.

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Introduction

Nocardia bacteria can cause a disease called nocardiosis. It most often spreads among cattle, dogs and fish. In humans, most infections are reported in individuals with various immunity disorders, and the manifestations of the disease may be cutaneous, pulmonary or diffused, and affect multiple organs [1, 2]. The pulmonary form of the disease is usually a consequence of inhalation of air contaminated with pathogens, which then colonise the respiratory tract. Primary cutaneous nocardiosis may be a result of an infection due to an injury of the skin and subcutaneous tissues [3, 4, 5].

In 1888, Edmond Nocard, a veterinarian, isolated a Gram-positive organism with a filamentous structure. The material was collected from the diseased lymph nodes of animals with glanders. The cultured microorganism was called *Streptothrix farcinica*. In 1889, the same microorganism was described by Trevisan, and it was named *Nocardia farcincia*. The microorganisms grown by Eppinger a year later was named *Cladotrix asteroides*. The study material was obtained from glass factory workers suffering from lung disease, additionally complicated by a brain abscess. After six years, the name was changed to *Nocardia asteroides*. The first case of nocardiosis,

successfully treated, was described in 1940. The therapy was based on antibacterial sulfonamides [3, 4, 6, 7].

Nocardia are aerobic, catalase-positive, mesophilic microorganisms forming branching structures, both in growing cultures and in host cells. They stain Gram-positive, demonstrating a delicate, filamentous structure in a microscopic preparation [1, 2]. They resemble the hyphae of the mould fungi or bacteria of the *Actinomyces spp.* [12, 13, 14]. Some forms cannot be coloured by Gram staining [8, 9, 10]. Most *Nocardia* isolates demonstrate weak staining and sometimes resemble Gram-negative structures. They may have characteristic Gram-positive "granulations" inside the cells. This is due to the resemblance in the structure of the cellular wall to that of bacilli [8], which contains 10-methyl stearic acid (tuberculostearic acid), mycolic acids, meso-diaminopimelic acid, galactose and arabinose. Therefore, *Nocardia* demonstrates weak acid-fast staining [2, 11, 12]. They may form airborne structures, or grow on a bacteriological medium. They undergo spontaneous or mechanical fragmentation. The optimal growth temperature for them is 30-37°C. *Nocardia* bacteria grow on most bacteriological media in the presence of 5-10% carbon dioxide [12, 15]. If infection with this microorganism is suspected, diagnostics with the use of selective media are recommended [16]. Too early discontinuation of the culture growth may prevent the detection of the *Nocardia* genus. Typical *Nocardia species* colonies are chalky-white to yellow, pink or orange. They produce a specific, musty smell [15].

The *Nocardia* species have been demonstrated to be facultative organisms, acting inside macrophages, where their cord factor helps to inhibit the endosome-lysosome fusion. They neutralise the acidic pH of the lysosome and avoid the bactericidal effect of phosphatase, as they decompose the enzyme and use it as a source of carbon. The main virulence factor of *Nocardia* species is avoiding lysis via phagocytosis. Upon contact of phagocytic cells (macrophages, neutrophils and monocytes) with a pathogen, an oxidative burst occurs, releasing reactive oxygen forms. However, *Nocardia* bacteria protect themselves against free radicals by secreting catalase and superoxide dysmutase. Therefore, for the optimal therapeutic effect, antibiotics that can penetrate inside cells should be selected [11].

The taxonomic classification of *Nocardia species* has not been well-organised and remains controversial. In the past, the bacteria of this genus were grouped based on their ability to degrade carbohydrates, or their susceptibility to antibiotics [3, 11]. It was only due to gene sequencing methods and DNA-DNA hybridisation that proper taxonomic relationships were demonstrated [4, 11, 25]. At present, *Nocardia spp.* comprises 87 described species, over half of which are of clinical importance for humans [3, 23]. All *Nocardia* species are classified as follows: class: *Actinobacteria*, subclass: *Actinobacteriadae*, order: *Actinomycetales*, suborder: *Corynebacteriales*, family: *Nocardiceae*, genus: *Nocardia* [3, 6, 24].

The most common species are *Nocardia asteroides complex*, including *Nocardia asteroides*, *Nocardia nova* and *Nocardia farcinica*, followed by *Nocardia cyriacigeorgica*, *Nocardia brasiliensi*, *Nocardia transvalensis*, *Nocardia africana*, *Nocardia kruczakiae*, *Nocardia veterana* and *Nocardia otidiscaviarum* [3, 4, 23, 25].

Epidemiology

Nocardia species are omnipresent environmental saprophytes living in soil, organic matter and water. They are widespread and cause chronic infections [2, 5, 8, 12, 14]. They are not components of human microflora. Infection is usually caused by aspiration of the pathogens to the respiratory system [15]. The microorganism can also invade the organism through the mouth or gastrointestinal tract, following the ingestion of contaminated food, or through wound contamination [15]. Transmission of the disease from animals to humans (zoonosis) has not been observed. However, there is a potential risk of human-to-human transmission. Infections are observed primarily in the high-risk groups, in patients who are weakened, have HIV infection, or suffer from cellular immunity disorders [2, 14, 15, 17]. The last group includes patients awaiting bone marrow transplantation, and organ transplantation, as well as immunocompetent patients suffering from chronic diseases, e.g. bronchiectasis, emphysema, bronchitis and asthma [10, 19]. Cases of nocardiosis have also been reported in patients with a normal immune function [2, 15, 18, 20]. Factors such as alcoholism, chronic lung disease (especially pulmonary alveolar proteinosis), solid organ transplants, using corticosteroids, connective tissue diseases, renal insufficiency, inflammatory bowel diseases and Whipple's disease also increase the risk of nocardiosis [2].

Its course may be acute, subacute or chronic [9, 15, 18]. In the acute form, necrotic foci typically occur, and an inflammatory reaction develops. In chronic disease, abscesses surrounded by inflammatory granulation tissue occur, forming granulomas [18]. Nocardiosis is typically manifested by respiratory symptoms, although it may spread to other organs, not only from the lungs but also from the cutaneous lesions [15]. Unfortunately, due to non-specific symptoms, such as fatigue, fever, shivers, cough, dyspnoea, chest pain, and loss of body weight, the disease is often not diagnosed or misdiagnosed as pneumonia, lung tuberculosis, neoplasm or lung abscess [15]. Cutaneous nocardiosis leads to cellulitis, pyoderma, inflammation of the cutaneous lymphatic vessels, paronychia and abscesses [15, 18]. Brain abscess caused by *Nocardia spp.* is a very rare disease of the central nervous system, developing gradually, and typically presenting with fever and headache [19]. However, in most cases, nervous system infections are caused by *N. asteroides* (approximately 90%). Other species rarely cause diseases in humans.

Very often nocardiosis remains undiagnosed, either due to delays in conducting the necessary diagnostics in severely ill patients or due to a partial or complete response to infection treatment with empirical broad-spectrum antibiotic therapy. I*n vitro* and *in vivo* studies, clinical observations and taxonomic development indicate that antibacterial therapy should be adjusted to the grown *Nocardia* species, its drug susceptibility profile, and the site

and type of infection. *Nocardia spp*. Infections must also be considered in differential diagnosis with other diseases of the central nervous system, caused by fungi or Mycobacterium tuberculosis [2, 9].

Case study

A 58-year-old patient with arterial hypertension was urgently admitted to the Department of Neurology of the Mazowiecki Specialist Hospital in Radom due to muscular weakening, increasing for approximately 2 weeks, and pain in the cervical spine, persisting for a few months. The clinical examination after admission revealed moderate left-sided hemiparesis. A head CT scan revealed finger-like oedema in the upper part of the right parietal lobe – a proliferative lesion was suspected. During the hospitalisation, the neuroimaging diagnostics were extended to magnetic resonance imaging, which demonstrated a tumour with a polycyclic outline, of approximately 2.1 x 1.3 cm, located in the upper part of the right parietal lobe, surrounded by extensive oedema. Following the intravenous administration of the paramagnetic contrast medium, signs of peripheral contrast enhancement were found.

Table 1. Basic laboratory tests of the 58-year-old patient admitted to the Department of Neurology, Mazowiecki Specialist Hospital in Radom.

Parameter	Value	Reference normal range
Alanine aminotransferase	20 U/L	0-41
Aspartate aminotransferase	27 U/L	0-34
C-reactive protein	2 mg/L	< 5
Serum potassium	4.3-4.5 mmol/L	3.5-5.1
Serum sodium	140-141 mmol/L	136-145
Serum chlorides	105 mmol/L	98-107
Serum glucose	101-106 mg/dL	74-106
Serum creatinine (Jaffe)	1.08-0.81 mg/dL	0.70-1.20
Urea	21-33 mg/dL	18-55
White blood cells (leukocytes)	9.60x10^3/ µL	3.9-10.2 [10^9/L]
Red blood cells (erythrocytes)	5.51x10^6/ µL	4.30-5.75 [10^{12}g/L]
Haemoglobin	16.9 g/dL	13.5-17.2
Platelets	339x10^3/ µL	150-370 [10^9/L]

Additionally, small, bilateral, subcortical focal lesions of vascular origin were found. The remaining brain structures were unremarkable. The cerebral ventricular system was dilated, with signs of cortical atrophy. The results of the basic laboratory tests were normal (Tab. 1). The analyses were performed at the Department of Laboratory Diagnostics of the Mazowiecki Specialist Hospital in Radom.

Diagnosis: brain tumour of the right parietal lobe with extensive oedema.

Based on the test results, a decision was taken to remove the tumour surgically. A right parietal parasagittal craniotomy of 5 cm x 5 cm was performed. At a depth of approximately 1 cm, a cystic tumour filled with white-yellow fluid was found. The cystic part was emptied, revealing shiny, whitish tumour walls, and the tumour was removed using tumour tweezers. Due to the suspicion of a proliferative lesion of the CNS, the collected material was sent for histopathological assessment. Because of the cerebral oedema, the dura matter was sutured appropriately to the clinical situation, duraplasty was performed, and the bone flap was not put back in place. The procedure was without complications. After the craniotomy, the left-sided hemiparesis persisted and even worsened.

Small tissue specimens of a total volume of 15 ml were sent for histopathological examination and fully used for the tests. The microscopic examination of the brain samples revealed the presence of a pseudocystic space surrounded by a wall demonstrating necrotic changes, an intensive, acute inflammatory infiltration, signs of the proliferation of thin-walled vessels surrounded by oedema. Moreover, amorphous necrotic masses were also found (Fig. 1). No neoplastic structures were observed. No fungi were found. The microscopic presentation might be consistent with an early abscess.

Figure 1. Brain abscess wall. HE stain, magnification 100x (own material).

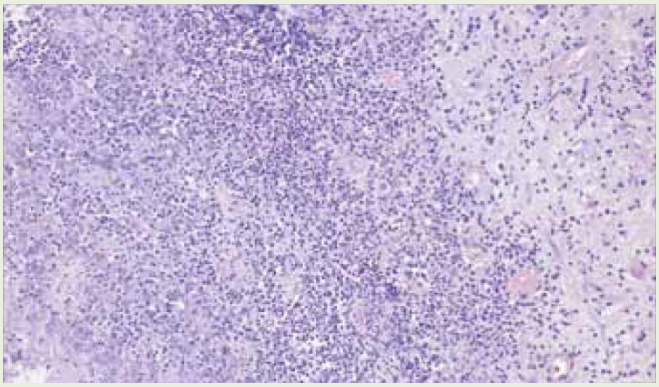
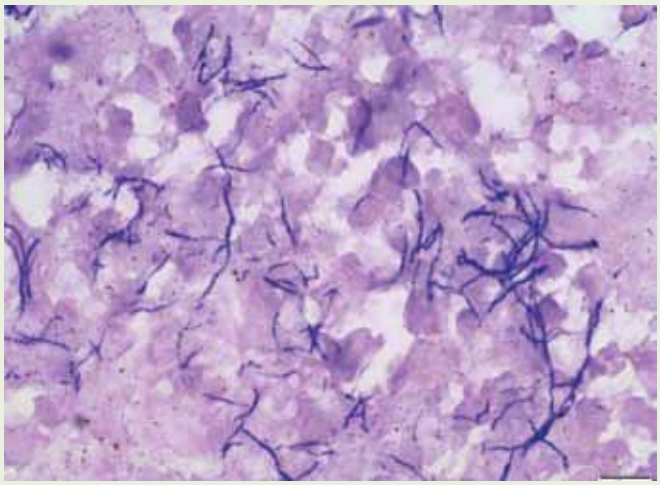


Figure 2. Filamentous, Gram-positive bacterial structures. Gram stain, magnification 1000x (own material).



On day 5 after the surgery, the patient developed a fever of 38.3°C-39.4°C. In the following two days, the body temperature was reduced to 36.4°C. The patient remained in the hospital. After approximately a month following the surgery, a follow-up head CT revealed contrast enhancement in the area of the bed of the removed lesion. The image was suggestive of an abscess. During the re-operation, another oval, encapsulated brain abscess mass was found. The abscess was separated from the glial tissue, and removed in full, together with the capsule. Next, the material was sent for microbiological diagnostics.

Nocardia abscessus was cultured, and the strain had been the aetiological factor behind the disease. Based on the microbiological tests, targeted therapy was introduced. The patient received a 6-week treatment with Biodacyna (amikacin), Biotrakson (ceftriaxone), Linezolid , Biseptol (trimethoprim/sulfamethoxazole), Mannitol and Dexaven (dexamethasone phosphate). Ten days after the re-operation and removal of the abscess in the right brain hemisphere, a follow-up CT revealed a larger focal fluid collection in the frontal-parietal area of the right hemisphere, containing a small amount of gas. The contrast enhancement on the periphery of the lesion was considerably weaker, as well as the oedema in the post-surgical area was less pronounced. After the results of the microbiological tests were obtained, the preparations were reanalysed, and new ones were prepared. In the deeper layers of the necrotic masses, a single grouping of filamentous Gram-positive structures was found (Fig. 2).

After the removal of the abscess and the introduction of the treatment, a small improvement in the mobility of the left lower limb was achieved. The patient was discharged in good general condition. He was transferred to the Department of Neurological Rehabilitation of the hospital in Radom with palsy of the left upper limb and a deep paresis of the lower limb.

Discussion

Brain abscesses caused by *Nocardia spp*. are extremely rare, account for 1-2% of all brain abscesses, and are characterised by a higher incidence and fatality than those caused by other bacteria strains [1, 9, 19]. According to the data presented by Pereira and Cortés [34], the reported fatality rates are 55%, and even up to 90% in the case of late diagnosis. Brain abscesses may cause acute, subacute or chronic infection, and they are typically found in immunocompromised patients. Other authors, Trujillo et al. [26], report that *Nocardia spp*. infection is possible in a previously healthy and immunocompetent patient, without a history of risk factors. They present a case of a patient which pulmonary parenchymal and cutaneous involvement, which resulted in the development of a brain abscess. Richards et al. described another clinical case involving diffused bilateral subretinal abscesses caused by *N. beijingensis* in Australia [27]. According to Eschle-Meniconi et al., in the years 1967-2007, 38 reported cases of endogenous ocular *Nocardia* (EON) infections were published. One of them was observed in a man with Hodgkin's disease, treated with chemotherapy. The patient received a vitreoretinal surgery for the diagnosis and therapy of a subretinal abscess [28].

Nocardioses are frequently opportunistic infections in immunosuppressed patients [2, 19]. In the majority of cases, they are caused by *N. asteroides complex* and *N. brasiliensis* [9, 15]. There is a clinical case presented in the literature of a patient with compromised immunity, treated for systemic lupus erythematosus, and diagnosed with pneumonia. The microorganism then spread from the lungs to the eye and brain, causing a subretinal abscess. The infection was caused by *N. farcinica*, a strain resistant to trimethoprim/sulfamethoxazole [29]. According to Pereira and Cortés [34], a patient with a primary brain abscess due to *N. farcinica* was successfully treated with intrathecal amikacin administration through a ventricular drain, in addition to surgical evacuation and intravenous antibiotic therapy. In this case, a radiological and clinical improvement was observed after the initiation of intrathecal therapy.

The most common antibacterial drug used in the treatment of *Nocardia spp*. is Biseptol [1, 14, 15]. However, there are species commonly resistant to this antibiotic, such as *N. otitidiscaviarum* [1], and occasionally resistant, such as *N. nova* and *N. farcinica* [14]. Alternative therapies include amikacin, imipenem, meropenem, ceftriaxone, cefotaxime, minocycline, tigecycline, moxifloxacin, levofloxacin, linezolid, and amoxicillin-clavulanic acid [2, 9, 11, 14]. Lekosha et al. reported a unilateral choroidal abscess caused by *N. farcinica* in a 41-year-old immunocompromised man with chronic myeloid leukemia. The bacteria were isolated from a subcutaneous abscess, and sulfonamide therapy was introduced. However, three weeks after the discontinuation of the treatment the disease recurred with the involvement of the vitreous body. The infection was controlled with the same drug [30].

The primary treatment of nocardiosis should take at least 6 months, and when the symptoms resolve it should be extended by another month. In immunosuppressed patients, the recommended therapy should always be continued until symptom resolution. In cutaneous nocardiosis, one antibiotic can be used. In pulmonary or diffused infections, the empirical therapy should be a combined therapy comprising 2-3 antibiotics [2].

Sulfonamides, especially those with good brain penetration, are the first-line drugs in the treatment of CNS abscesses [3]. Abscesses caused by *Nocardia spp*. often require incision and drainage. Surgical intervention is required if the abscess is large, or no improvement has been observed after 2 weeks of treatment [2]. Therapeutic prognosis in nocardiosis depends on the severity and duration of infection, the immune status of the patient, or the involved organ. In the case of cutaneous or soft tissue involvement, the prognosis is much better than in pulmonary infections or diffused forms of the disease. Most patients with cutaneous nocardiosis quickly recover, whereas in the case of brain abscesses the recovery rate is less than 60% [23]. The clinical case described by George et al. presents an immunocompromised patient diagnosed with cellulitis of the right arm. In addition, diffused subcutaneous nodules, resembling erythema nodosum, were found in the lower limbs. The material was collected through a biopsy of the subcutaneous nodule on the leg, and the second sample was collected during a surgical debridement of an arm wound. *N. asteroides*. was cultured from these samples. The infection was successfully treated with trimethoprim/sulfamethoxazole [31]. Another clinical case of purulent skin disease on a ring finger, reported in a publication by Bogaard et al. [32], presented a 46-year-old man, treated for 8 years with azathioprine and budesonide due to Crohn's disease. Surgical drainage was performed, and amoxicillin and flucloxacillin were introduced, but the disease spread to the hand and forearm. *N. asteroides*. was cultured from the wound. Complete recovery was achieved with cotrimoxazole, but only after 8 months of the treatment. Cotrimoxazole is the therapy of choice, and it is almost always effective in cutaneous nocardiosis [32]. In a 25-year-old female patient with post-traumatic nocardiosis of the lower limbs, *N. brasiliensis* was identified as the aetiological factor. In the first phase of treatment, an intravenous infusion of flomoxef sodium was applied, followed by oral minocycline hydrochloride, and the disease process subsided after 9 weeks. The case of the Japanese patient described by Fukuda et al. was considered to be a rare example of lymphocutaneous nocardiosis [33].

Most bacterial species may be identified using biochemical profiling confirmed with 16S rRNA and 18S rRNA gene sequencing. Currently, however, diagnostic laboratories increasingly often use mass spectrometry to identify *Nocardia* bacteria [4, 8]. MALDI-TOF has become a reliable method for a fast and perfect identification and classification of microorganisms, based on their protein profile. The obtained spectrum provides a specific "fingerprint", which is characteristic of a given microorganism and remains unchanged in further analyses of other clinical cases involving this type of infection [20, 21, 22].

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COL. DR MARX (MARKS) MIECZYSŁAW (1879-1953) – DOCTOR, FIREFIGHTER AND SOCIAL WORKER

Płk dr Marx (Marks) Mieczysław (1879-1953) – lekarz, strażak, społecznik

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Abstract: The subject of the publication is the figure of an outstanding, forgotten doctor – Mieczyslaw Marx (Marks). During the research, the author tried to recreate the biography as accurately as possible by conducting an in-depth search in the Central Military Archives of the Military Historical Office and the State Archives in Lodz. The colonel's family also provided a lot of valuable information and photographic documentation. The article presents the fate of Colonel Mieczyslaw Marx (Marks) from his birth in Brzesc nad Bugiem (29 November 1989), through the period of education and studies, successively during World War I, to the interwar period and after 1945. The figure of Col. Mieczyslaw Marx (Marks) is important to the city of Lodz – it was with this city that he was associated for most of his life. He held important military positions in Corps District No. IV in Lodz – while from 18 June 1930 he was the Sanitary Chief at Corps District No. IV in Lodz. In addition to performing medical and military functions, he was also affiliated with the fire department. From January 1936, he was the commander of the Volunteer Fire Department in Łódź. Less is known about his fate during the Second World War, but it is known that he stayed in Warsaw and during the Warsaw Uprising he looked after the wounded and sick in a hospital in Milanowek. In October 1944 he moved to Radom. After the war, he returned to Lodz.

Streszczenie: Przedmiotem publikacji jest postać wybitnego, zapomnianego lekarza płk. dr. Mieczysława Marxa (Marksa). W trakcie badań autorka starała się, jak najdokładniej odtworzyć jego życiorys, dokonując wnikliwej kwerendy w Centralnym Archiwum Wojskowym Wojskowego Biura Historycznego oraz w Państwowym Archiwum w Łodzi. Dużo cennych informacji oraz dokumentacji fotograficznej dostarczyła także sama rodzina pułkownika. W artykule zostały przedstawione losy płk. dr. Mieczysława Marxa (Marksa) od momentu jego narodzin w Brześciu nad Bugiem (29 listopada 1989 r.), poprzez okres nauki i studiów, kolejno w trakcie trwania I wojny światowej, aż po okres międzywojnia i po roku 1945 Postać płk. dr. Mieczysława Marxa (Marksa) jest ważna dla miasta Łodzi – to właśnie z nią związany był przez większość swojego życia. Pełnił ważne stanowiska wojskowe w Okręgu Korpusu nr IV w Łodzi, m.in. od 18 czerwca 1930 r. był Szefem Sanitarnym przy Okręgu Korpusu nr IV w Łodzi. Oprócz sprawowania stanowisk medycznych i wojskowych związany był także ze strażą pożarną. Od stycznia 1936 r. był komendantem Ochotniczej Straży Pożarnej w Łodzi. Jego losy w okresie II wojny światowej są słabiej znane, jednak wiadomo, że przebywał w Warszawie I w czasie Powstania Warszawskiego opiekował się rannymi i chorymi w szpitalu w Milanówku. W październiku 1944 r. przeniósł się do Radomia. Po wojnie powrócił do Łodzi.

Key words: Lodz, biography, military doctor, IV Military District, Mieczyslaw Marx.

Słowa kluczowe: Łódź, biografie, lekarz wojskowy, IV Okręg Korpusu, Mieczysław Marx.

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After Poland regained its freedom, matters relating to protecting the health of the population of the independent state, alongside the need to regulate other important social issues, such as the organisation of the municipal police, were among the major areas of concern addressed by the government of Jędrzej Moraczewski. Sanitary structures initially began to form within the agencies of the Polish Army as early as the autumn of 1918. On 30 October 1918, three territorial inspectorates were established, along with a number of smaller subordinate military districts. However, the structures created were quickly reorganised. By the Order of the Ministry of Military Affairs of 17 November 1918, the territory of independent Poland was divided for the first time into General Districts (Polish: *Okręg Generalny*, OGen.) [1]. The following General Districts were established: 1st General District in Warsaw, 2nd General District in Lublin, 3rd General District in Kielce, 4th General District in Łódź and 5th General District in Kraków.

Figure 1. Antonina Goławska and Gustaw Jan Kazimierz Marx – Mieczysław Marx's parents [10].

The foundation of the military health service at Łódź General District (OGŁ) was the chief physician of the district and the doctors from the individual military districts of Łódź, Kalisz, Łowicz and Włocławek, who reported to him. In January 1919, a Sanitary Department headed by Col. Jakób Arct MD was established at the Łódź General District Command (DOGŁ) [2]. By the Order of 18 August 1919, the health service was merged into the 9th Sanitary Division, headed by a chief sanitary officer [2].

The year 1921 brought significant changes to the Polish Army, as the demobilisation of the military and the arduous process of reorganising it under the 'peacekeeping system' began. General District Commands were abolished and replaced by Corps District Commands (Polish: *Dowództwo Okręgu Korpusów*, DOK). OGŁ was disbanded on 15 November 1921, and Łódź Corps District No IV was created in its place [2]. Arms and service authorities, including a health authority, were then established in line with the new organisational structure of the district command. The organisation of peacetime health services was announced on 20 August 1921. The Łódź sanitary authority was headed by a chief sanitary officer, who managed the entire health service within his subordinate territory [2].

Although there were many military physicians serving in Łódź Corps District No IV, they are now forgotten. The main purpose of this paper is, therefore, to celebrate their lives and achievements. Military physicians were part of the health corps of the Polish Army alongside dentists, pharmacists and sanitation officers. However, the doctors from Łódź Corps District No IV played the most important role. They made up the largest group and held the highest positions [3, 4].

As for regional historiography, a research gap remains due to the lack of studies devoted to the lives of many prominent doctors of Łódź Corps District No IV between 1921 and 1939. Using the method of archival source criticism, focusing mainly on the Central Military Archives at the Military Historical Office and the State Archives in Łódź, the author attempts to offer some insight on Col. Mieczysław Marx MD [5]. Much valuable information and photographic documentation was also provided by the doctor's family, for which I would like to express my sincere gratitude.

Figure 2. The Marx siblings. Upper row, left to right: Julia Marx (1888-1962), Stefan Marx (1895-1945). Middle row, left to right: Mieczysław Marx (1879-1953) and Kazimiera Marx (1881-1942). Władysław Marx is lying down (1883-1965) [10].

Mieczysław Konstanty Alfons Marx was born on 29 November 1879 in Brest-on-the-Bug [6-8]. He was the son of Gustav and Antonina (née Goławska) (Fig. 1). Gustaw Jan Kazimierz Marx worked as a physician. The family probably moved from Brest-on-the-Bug to Kowel and then to Radom. There, from 1888 to 1898, Mieczysław attended secondary school [9] (Fig. 2).

In 1898, he began his studies at the University of Warsaw and graduated as a Doctor of Medicine in 1904 [7]. Marx practised medicine in Lviv and Austria between 1905 and 1907 [9]. He then moved to Zgierz, where he began his work as a city doctor. From March 1910 to 1 August 1914, Marx lived in Łódź and was the Head of the Department of Surgery and Gynaecology at the Scheibler Hospital in Łódź [9, 11].

He was married twice, first to Janina, née Kocowska, and then to Helena, née Herc [8, 12]. He did not have children.

As a reserve officer, in November 1904 Mieczysław Marx was appointed junior doctor at the General Staff of the Ataman of the Don Cossack Host, and then on 1 August 1914 he was called up to the Russian army [13]. He was referred to the Osowiec Fortress Hospital, where he served as Senior Head of the Surgery Department and was wounded during an attack by German troops in September 1914. Marx was stationed at Evacuation Hospital No 178 from 15 November 1915 as Chief Medical Officer, and from 1 June 1916 served as Chief Medical Officer to the 36th Infantry Division. In March 1918, he was taken prisoner by the Germans with the remaining members of his division and stayed in captivity until 1 May 1918.

From June 1918 to August 1919, Marx was Head of the Surgery Department at the City Hospital in Łódź. As President of the Sokół Association in Łódź, in November 1918 he led the disarmament of the Germans [14].

When he joined the Polish Army on 14 August 1919, he already held the rank of captain [9, 12].

During the Polish-Soviet War, he was assigned from 7 August 1919 to the Sanitary Department of the Ministry of Military Affairs, and from 14 August 1919 worked a surgeon at the Main Quartermaster Office of the Volhynian Front High Command in Lutsk. From 20 September 1919 to 18 January 1920, Marx was transferred to the reserve staff of the Ujazdowski Hospital in Warsaw. In January 1920, he was appointed Commanding Officer of the military hospital in Vawkavysk [15]. On 1 April 1920, Mieczysław Marx was promoted to the rank of major. From 23 October 1920 to 14 August 1921, he was Commanding Officer of the Military Hospital in Łódź [9]. Then he went on to become a physician to the 28th Regiment of Kaniów Riflemen in Łódź. From 5 October to 17 November 1921, Marx attended a training course for professional military physicians at the Application School of the Sanitary Officers Corps in Warsaw, which he completed with a positive result [9]. He was then assigned to the Mobilisation and Organisation Department in the Sanitary Headquarters of Łódź Corps District Command No IV. He became a lieutenant colonel in 1922, and colonel on 1 January 1928. From 18 June 1930, as Chief Sanitary Officer, he headed

Figure 3. Mieczysław Marx, c. 1938 [20].

the Polish Army District Corps No IV in Łódź [16], and held this position until leaving the service on 30 June 1934 [17]. He ran a private practice in Łódź at 40 Zagajnikowa Street [18].

He often engaged in debate on the pages of "Przegląd Kawaleryjski", a Polish military journal [19]. Marx was also involved in the Polish Red Cross – he was a member of the Łódź District Board as Head of Sanitation from 1930 to 1938 [20]. For his social activities, he was awarded the 3rd degree Badge of Honour of the Polish Red Cross (Fig. 3).

As a promoter of culture, Mieczysław Marx was an honorary member of the Lutnia Singing Society in Zgierz [21]. In addition, he was involved in the Volunteer Fire Department in Łódź. Having joined on 4 August 1906, he was first listed as a member of the Board in 1921 and is mentioned, in the available documents, as a Łódź VFD Board member until 1937 [22, 23]. He served as Commander of the Volunteer Fire Department in Łódź [24] from January 1936 to 15 October 1938, at which point, due to ill health, he was granted medical leave until 1 December 1938, extended subsequently from 15 January 1939 to 15 July 1939. [25]. Listed in the 1927 report as a member of the 'disability examination committee' and the Small Staff Council, he was also part of the 5th Volunteer Unit. According to a copy of the minutes of the Łódź Volunteer Fire Department Board meeting dated 9 November 1927, Dr Mieczysław Marx was recommended to the Fire Department Association of the Łódź Province for decoration for 20 years of service [26]. His name also appears in the institution's report for 1934, where he is mentioned as a member of the medical committee and the committee of the fund for widows and orphans of fallen firefighters [27]. On 30 October 1937, the Main Board of the Fire Department Association of the Republic of Poland awarded him the Silver Medal of Merit 'for his merits in the field of firefighting' [28].

His name is not included in the appointment letters of the Volunteer Fire Department available in the State Archive in Łódź [29]. In September 1939, he was Sanitary Chief of the League of Air and Antigas Defence (Polish: *Liga Obrony Powietrznej i Przeciwgazowej*, LOPP) in Łódź. Displaced in the autumn of 1939, he settled in Warsaw, where he kept

Figure 4. Mieczysław Marx, c. 1949 [7].

a private practice during the Nazi occupation. Throughout the Warsaw Uprising, he cared for the wounded and sick in the hospital in Milanówek. In October 1944, Marx moved to Radom [8]. After the war, he returned to Łódź, as he is included in the address book of the City of Łódź for the year 1948/1949 (Fig. 4) on the list of doctors of the Medical Chamber residing in the city [30]. Finally, in 1946, he accepted a job at the Social Security Hospital in Łódź. He lived at 40 Kopcińskiego St [31].

Figure 5. In June 2022, the grave of Col. Mieczysław Marx was renovated through the efforts of the author, the family and the Łódź Branch Office for Commemorating the Struggle and Martyrdom of the Institute of National Remembrance.

Mieczysław Marx died on 30 November 1953 and was buried at the Evangelical Augsburg Cemetery at Ogrodowa Street in Łódź (sector 29_G1, row 9, grave number 23). The service awards he received included [10]: Order of Saint Stanislaus, 3rd and 2nd class, Order of Saint Anne, 3rd and 2nd class, Order of Saint Prince Vladimir 4th class, Gold Cross of Merit [32], Commemorative Medal for the 1918-1921 War, and the Medal of the Centenary of Regained Independence.

Mieczysław Marx's life story shows that he had a passionate spirit and was committed to his profession, while his social attitude was a prime example of the civic participation exhibited by military physicians of that time. Through the efforts of the article's author, the grave of Mieczysław Marx (Fig. 5) was entered in the burial register of veterans who fought for freedom and independence kept by the Institute of National Remembrance.

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REPORT OF THE XVII CONGRESS OF THE POLISH NUCLEAR MEDICINE SOCIETY

Sprawozdanie z XVII Zjazdu Polskiego Towarzystwa Medycyny Nuklearnej

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Abstract: The 17th Congress of the Polish Society of Nuclear Medicine was held in Białystok on 26-28/05/2022. The opening lecture, "Current and future development of nuclear medicine at the Medical University of Białystok", was delivered by the rector, Prof. A. Krętowski.

The congress was attended by 450 participants from Poland and abroad, professional scientists, specialists, clinicians and representatives of all professional groups associated with nuclear medicine centres. The Congress of the Polish Society of Nuclear Medicine is the largest Polish event addressed directly to this community.

The leading theme of the Congress was nuclear theranostics, that is personalised isotope therapy. In addition to the innovative application of nuclear medicine in oncology, endocrinology, cardiology, neurology or endocrinology, the agenda also included important sessions on the role of artificial intelligence in radioisotope diagnostics and therapy, modern radiopharmaceuticals and preclinical nuclear imaging methods as a major tool for developing molecular therapies.

Streszczenie: XVII Zjazd Polskiego Towarzystwa Medycyny Nuklearnej odbył się w Białymstoku w dniach 26-28.05.2022r. Wykład inauguracyjny pt.: „Rozwój medycyny nuklearnej w Uniwersytecie Medycznym w Białymstoku dziś i jutro" wygłosił rektor białostockiej uczelni prof. Adam Krętowski.

W zjeździe uczestniczyło 450 osób z kraju i zagranicy: pracowników nauki, specjalistów, klinicystów oraz przedstawicieli wszystkich grup zawodowych związanych z ośrodkami medycyny nuklearnej. Zjazd Polskiego Towarzystwa Medycyny Nuklearnej to największe w kraju wydarzenie skierowane bezpośrednio do tego środowiska.

Wiodącym tematem spotkania była teranostyka nuklearna, czyli spersonalizowana terapia izotopowa. Oprócz innowacyjnego zastosowania medycyny nuklearnej w onkologii, endokrynologii, kardiologii, neurologii czy endokrynologii, ważne miejsce w programie zajmowały także sesje dotyczące roli sztucznej inteligencji w diagnostyce i terapii radioizotopowej, nowoczesnej radiofarmacji oraz przedklinicznych metod obrazowania nuklearnego, jako głównego narzędzia do opracowywania terapii molekularnych.

Key words: congress Polish Nuclear Medicine Society.

Słowa kluczowe: zjazd Polskie Towarzystwo Medycyny Nuklearnej.

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The 17th Congress of the Polish Society of Nuclear Medicine was held in Białystok from 26 to 28 May 2022 under the honorary patronage of the Podlasie Province Governor and the Mayor of the City of Białystok.

The opening ceremony took place in the auditorium of the Branicki Palace, and the opening lecture, "Current and future development of nuclear medicine at the Medical University of Białystok", was delivered by the rector, Prof. A. Krętowski. The Mayor of the City, Tadeusz Truskolaski, honoured the ceremony with his presence and speech.

The congress was attended by 450 participants: professional scientists, specialists, clinicians and representatives of all professional groups associated with nuclear medicine centres. The Congress of the Polish Society of Nuclear Medicine is the largest Polish event addressed directly to this community.

Distinguished lecturers with global reputations, including P. Słomka and A. Kalinowski from the United States, Markus Luster, K. Hermann, and W. Brenner from Germany, Christer Haldin from Sweden, J. N. Talbiot from France, and Arturo Chiti from Italy, were invited to participate in this elite event along with local experts, such as National Consultant in Nuclear Medicine, Prof. Leszek Królicki and President of the Polish Nuclear Medicine Society, Prof. Bogdan Małkowski.


XVII Zjazd
Polskiego Towarzystwa
Medycyny Nuklearnej


XVII Zjazd
Polskiego Towarzystwa
Medycyny Nuklearnej
Białystok 2022 26-28 maja
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The leading theme of the Congress was nuclear theranostics, that is personalised isotope therapy. In addition to the innovative application of nuclear medicine in oncology, endocrinology, cardiology, neurology and endocrinology, the agenda also included important sessions on the role of artificial intelligence in radioisotope diagnostics and therapy, modern radiopharmaceuticals and preclinical nuclear imaging methods as a major tool in developing molecular therapies. The congress programme also included sessions from the Polish Academy of Sciences and the National Centre for Radiation Protection. Award-winning works published between 2017 and 2021 were presented at a session of the "PTMN – Nuclear Medicine Review" journal, whose editor-in-chief is Col. Prof. Grzegorz Kamiński MD, PhD.

The congress was organised with a two-year delay due to the pandemic and was therefore a great opportunity for those who wanted to finally attend much-awaited meetings, share experiences and have fun together.

THE PATHOMORPHOLOGY REPORT AS THE BASIS FOR ONCOLOGICAL TREATMENT

Raport patomorfologiczny to podstawa leczenia onkologicznego

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Abstract: Modern pathomorphology is a key medical field, and treating neoplastic diseases would hardly be possible without it. It has an impact not only on saving patients, but also affects the quality of their lives. A pathomorphology report provides a formal basis for initiating oncological treatment, as it contains the information necessary to plan a therapy that is both safe and effective for the individual patient. To make this possible, a pathomorphologist needs access to the complete medical data, oncological history and type of treatment the patient has previously received. Unfortunately, the data that the pathologist receives is quite often incomplete, which prolongs the tests and increases their cost. Therefore, adequate communication between the pathologist and the clinician is necessary, as well as standard procedures for each step in the processing of tissue or cytology samples collected for pathomorphological testing.

Streszczenie: Współczesna patomorfologia jest kluczową dziedziną medycyny, bez której leczenie chorób nowotworowych byłoby praktycznie niemożliwe. Ma wpływ nie tylko na ratowanie, ale również na jakość życia pacjentów. Formalną podstawą rozpoczęcia jakiegokolwiek leczenia onkologicznego jest raport patomorfologiczny zawierający wiele informacji koniecznych do ustalenia leczenia, które będzie skuteczne i jednocześnie bezpieczne dla danego pacjenta. Aby to było możliwe, patomorfolog musi mieć dostęp do kompletnych danych medycznych pacjenta, jego przeszłości onkologicznej oraz typu zastosowanego wcześniej leczenia. Niestety dość często otrzymuje dalece niekompletne dane, co skutkuje zarówno wydłużeniem czasu, jak i zwiększonymi kosztami takich badań. Dlatego niezbędna jest właściwa komunikacja między patologami i klinicystami oraz wystandaryzowanie każdego elementu postępowania z materiałem tkankowym bądź cytologicznym pobieranym do badania patomorfologicznego.

Key words: pathomorphology, pathomorphology report, molecular diagnostics, immunohistochemical testing

Słowa kluczowe: patomorfologia, raport patomorfologiczny, diagnostyka molekularna, badania immunohistochemiczne

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Interview with Col. Szczepan Cierniak MD, PhD, Head of the Department of Pathology at the Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine.

Pathology is a fairly young field in the medical sciences. When did it first begin to develop?

It appeared first in the 18th century, when it was known as anatomical pathology, having evolved from the few centuries-older anatomy. Initially, the primary scope of research in pathology was the confrontation of ante- and post-mortem clinical diagnoses, which is still preserved today in the form of post-mortem examinations when, despite the use of modern diagnostic techniques, the cause of an in-hospital death cannot be clearly established. The post-mortem examination has had an enormous impact on the progress of medicine and has provided an educational input to the clinical experience of doctors in many medical disciplines. Further advances in pathology have enabled studies on ante-mortem collected tissues. These were initially just microscopic descriptions of lesioned tissue, as there was no

Col. Szczepan Cierniak MD, PhD, Head of the Department of Pathology, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine.

Figure 1. *Artisan Link Pro Special Staining System*

classification of diseases. It was not until the 19th century that the first categories were created, though at first only concerning causes of death. Major advances in the classification of diseases, injuries and causes of death were only made in the second half of the 20th century, when the first International Classifications of Diseases were established by WHO. What is interesting in the beginning they were also based on pathological research.

What were the main breakthroughs in the development of pathology?

Over the past few decades, the development of pathology has been mainly related to the improvement of endoscopic techniques, which now offer the possibility of obtaining very small tissue fragments from the affected area without the need for debilitating surgical procedures. They are collected with the aid of modern radiological tools, which significantly speeds up the diagnosis. Pathology has already entered the era of genetic testing, but the starting point for oncology treatment is still the diagnosis given by the pathologist.

The role of pathology in oncology treatment is invaluable. What makes it so important?

The formal basis for cancer treatment is the pathology report. As the complexity of pathology diagnosis increases, and new diagnostic techniques are introduced, the reports become increasingly complicated. In addition to a description of the basic macroscopic and microscopic changes, the pathology report contains a range of additional information, including: the stage of the disease, the histological maturity of the tumour and the presence of a number of prognostic and predictive markers, determined by immunohistochemical and molecular methods. The focus on the latter means that pathology reports are in fact becoming theranostic reports (a term coined by combining the words 'therapy' and 'diagnostic'), containing a wealth of highly relevant information to select effective yet safe targeted treatments for a given patient. This is the future of medicine.

Which cancers involve the most advanced use of such methods?

A classic example of the use of such biomarkers in oncology is the treatment of breast cancer. Additional immunohistochemical tests are now obligatory for tissue samples diagnosed with breast cancer by the pathologist. With these, the molecular subtype of the cancer is identified in terms of the expression of steroid receptors, that is oestrogen and progesterone receptors as well as HER2. If the result for this receptor is inconclusive, fluorescence in situ hybridisation (FISH) is performed to finally determine the clinical status. In this way, the pathologist can select patients who can benefit from systemic treatment with complementary anti-HER2.

Yet another example is the diagnosis of lung cancer, where it is now standard practice in patients with an advanced cancer other than squamous cell carcinoma to assess the EGFR, ALK and ROS1 genes in addition to the classic pathology test, to detect mutations in the EGFR gene and translocations in the ALK and ROS1 genes. This is relevant for selecting patients for targeted treatment with tyrosine kinase inhibitors. When the oncologist intends to provide treatment with immune checkpoint inhibitors, tests are performed in the pathology laboratory to assess PD-L1 expression. Molecular biomarker diagnosis is also the standard in the treatment of melanoma, colorectal cancer, endometrial cancer, gliomas, GISTs or haematological diseases such as lymphomas and leukaemias. Considering all this, modern pathology is a key medical field, and treating neoplastic diseases would hardly be possible without it. Even in clinically advanced cases with multiple metastatic lesions, when the spread of cancer is indisputable, specimens are collected to identify the type of cancer and its starting point. This is because we have to know whether the metastatic cancer is caused by renal cancer, melanoma, lymphoma or lung cancer. By discovering the type of cancer, we can at the same time understand its biology and sensitivity to potential systemic treatment.

Still, it must be remembered that any tissue, removed for any reason, should be examined by a pathologist. At times, a lesion that is accidentally spotted and removed for histopathologic examination during surgeries carried out for completely different reasons, such as weight-loss bariatric surgeries or trauma surgeries, may turn out to be a malignant tumour. In some cases, this allows cancer to be detected at a very early stage.

Figure 2. *Autostainer Link 48 Immunohistochemistry Staining System*

Figure 3. *BenchMark ULTRA system – a fully-automated immunohistochemistry and in situ hybridisation system*

It could then be said that, because of this, pathology not only saves lives, but also has an impact on the quality of life?

I couldn't agree more, despite the old joke about a surgeon, an internist and a pathologist, where the latter 'knows everything and can do everything – but 24 hours too late.' Thankfully, this is now history. We can see this on a daily basis, as patients want us to give them the 'result' within a few days of the procedure. Unfortunately, this is not possible because the specimen must be fixed properly and undergo additional immunohistochemical tests, although it's extremely difficult to get this across to patients and to some doctors. Most importantly, the outcome of our work is not a 'result', but a 'pathology report' based on an intellectual interpretation of the microscopic image and an evaluation of the additional histo- and immunohistochemical tests performed. This fundamentally differentiates the laboratory result from the pathology report. A pathology diagnosis is a kind of medical consultation, similar to those provided in hospitals by doctors from other specialities. The pathologist must therefore have access to the patient's complete medical data, oncology history, and treatment used (chemotherapy, radiotherapy, hormonal treatment, etc.). Sadly, referrals very often contain incomplete data, which results in a tedious search for the missing data in hospital systems and ultimately increases the time and cost of the pathology test. This is why we're constantly working on proper communication with clinicians and have made good progress in this area.

Do you remember any particular pathology cases?

Working as a pathologist gives me a lot of satisfaction despite the lack of personal contact with patients. For me, pathology is an extremely interesting discipline, because almost every case is different, with sometimes surprising, if not spectacular, diagnoses. I do remember the case of a young man with gastric cancer diagnosed outside the Military Institute of Medicine from a core needle biopsy sample, that is from a small piece of the stomach collected during gastroscopy. The patient was admitted to our hospital for pre-operative neoadjuvant chemotherapy before a planned gastrectomy. At the same time, the clinician asked us to re-evaluate the histology specimens before the planned extensive surgery. During the microscopic examination, we saw a tiny fragment of cancerous tissue, which led to the diagnosis of cancer, even though it was located in the middle of a much larger fragment of normal mucosa. Equipped with the necessary diagnostic capabilities, we decided to investigate whether both tissue fragments (the healthy mucosa and the cancerous piece) came from the same person. We carried out genetic identification of the two pieces and found that they came from two different people. So in this case, cross-contamination with foreign material occurred during the technical processing, which is very rare, but unfortunately cannot be eliminated at the current technological level. I will always remember the moment when the patient came in to collect the report with his wife and a small child. I can still see the great excitement of the patient and his family when it became clear that he did not have to undergo the mutilating gastrectomy because we had actually ruled out cancer.

From your point of view, what is the most important aspect of a pathologist's job?

The final outcome of a pathologist's work is influenced by a large number of factors. The correct collection and fixation of material is considered to be the first step in pathology diagnosis. This moment is particularly important for core needle biopsies (collection of small tissue fragments by endoscopic methods). It is the experience of the endoscopist that determines the quality of the material provided for testing. Too sparse or damaged material (dried out or mechanically damaged) is often insufficient to make a pathology diagnosis. In such cases, the material has to be re-sampled, which means that some potentially costly medical procedures must be

Figure 4. *Idylla system for the detection of genetic mutations in colorectal cancer, melanoma and lung cancer, among others.*

repeated. Once the material is delivered to the Department of Pathology, virtually all stages of technical processing are important. The specimen cannot stay in the formalin for more than 72 hours, as longer fixation adversely affects the immunohistochemical and molecular diagnostic capabilities, reducing the reliability of such testing.

All of this means that every part of the handling of tissue or cytological material, including technical processing, should be standardised at every stage of the procedure. This is what the ongoing accreditation process for Pathology Departments in Poland, supervised for example by the Polish Society of Pathologists (PTP), serves to achieve. The project has developed some organisational standards and standards of conduct. Only departments which strictly adhere to these standards can be accredited by the PTP, ensuring that pathology testing in these units is performed at the same level of reference, in a reproducible and reliable manner. The ministry is planning to introduce refinancing of research only in those units that receive the appropriate quality certification within PTP.

The Department of Pathology at the** Central Clinical Hospital of the Ministry of National Defence **of the Military Institute of Medicine is a complete and modern pathology laboratory. What resources does it have at its disposal?

Our pathology diagnostic team consists of twelve experienced expert pathologists, five resident doctors and four laboratory diagnosticians, supported by a group of experienced technicians.

The structure of the Department encompasses all the laboratories required by the organisational standards, including the Histopathology and Cytology Laboratory, the Immunohistochemistry and Special Staining Laboratory and the Molecular Pathology Laboratory. We have state-of-the-art dissecting facilities where we can carry out autopsies, including forensic medical examinations for the Garrison Military Prosecutor's Office. For more than four years, the department has had a comprehensive IT service system, purchased under an equipment grant from the Ministry of Defence and fully integrated with the hospital's IT network. The system supports registration, technical processing, ordering of immunohistochemical and genetic tests, virtual documentation of microscope specimens with remote analysis and online consultation of difficult cases. In addition to equipment for ongoing histopathological diagnosis, our department is equipped with a high-speed scanner for microscope specimens that allows virtual specimens to be transferred to the PATARCH system and a microdissection microscope, using laser beam energy to enable the acquisition of single cells or their homogeneous populations from a heterogeneous pathologically altered tissue material. This allows us to extract well-defined cellular structures at the microscopic level for further testing. The Molecular Pathology Laboratory of the Department of Pathology has equipment like the Cobas unit for diagnosing EGFR, BRAF, KRAS, NRAS and PIK3CA gene mutations, the Idylla unit with panels for detecting mutations in colorectal cancer, melanoma and lung cancer, and the Applied Biosystems sequencer for de novo sequencing, comparative sequencing, resequencing, SNP detection and forensic human identification.

As you can see from this rather rough list of equipment and diagnostic possibilities, the days of diagnosing solely on the basis of microscopic images are definitely over. Today, pathology is a highly complex field that requires a large amount of interdisciplinary knowledge, encompassing pathophysiology, genetics, immunology, histology, medical analysis (e.g. in haematopathology) and, at least in part, clinical science, which is why I am very pleased that we have so many people in our department willing to do this difficult and sometimes unrewarding work.

MEET ZOFIA NIBUŻANKA,

A YOUNG DOCTOR WHO HAD JUST JOINED THE UJAZDOWSKI HOSPITAL IN WARSAW

NEW RELEASE
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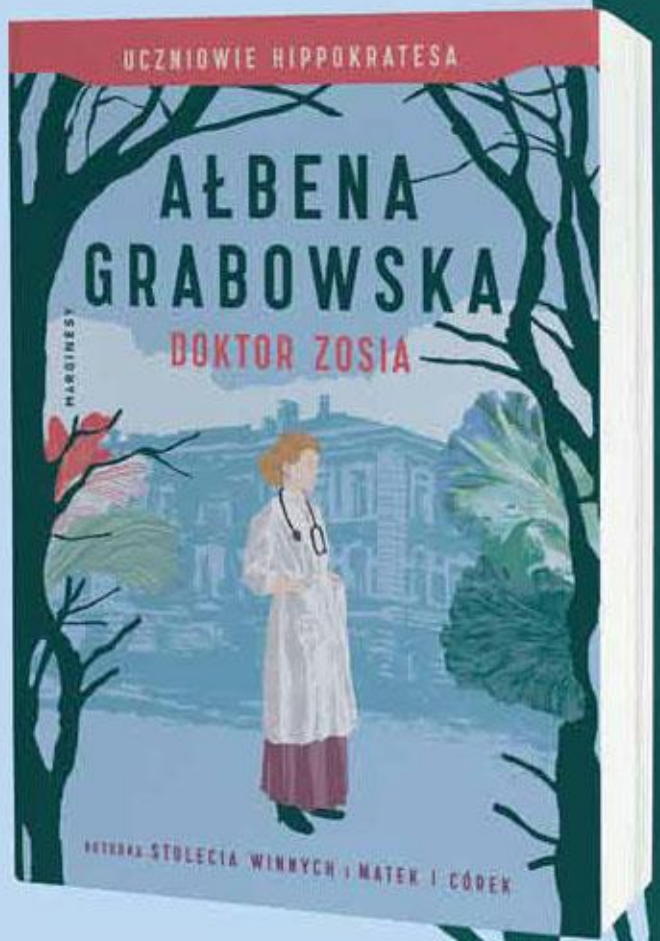
When Dr Zofia Nibużanka was offered a job at the Ujazdowski Hospital in Warsaw, she did not hesitate for a moment. The military hospital welcomed female doctors with open arms, and placed them on par with men. For Zofia, this was an opportunity to expand her knowledge and skills in the many thriving medical departments and modern laboratories. She learned the ins and outs of radiology, neurology, haematology and other specialities likely to help her become an excellent paediatrician in the future, even though she secretly dreamt of surgery.

Her work, alongside some of the most eminent specialists of the time, was interrupted by the outbreak of war. The Republic of Ujazdow – as the medics call their hospital – operated under the Hague Convention, but its regulations were ruthlessly violated by the occupying forces, and the staff, especially the doctors and nurses involved in the underground movement, experienced the unimaginable cruelty of war. The officers were deported to the east, and disappeared without a trace – the world will not hear about the Katyń massacre for many years to come. Some doctors were killed in bombings, others taken to concentration camps, locked up in the ghetto or tortured in the Gestapo's torture chambers. The survivors, including Dr Zofia, were trying to save patients despite the degrading conditions. It was all the more difficult for the young doctor as her husband became involved in underground activities and she was constantly hit by bad news about the fate of her loved ones. And yet, the worst would only come with the outbreak of the Warsaw Uprising.

The novel brings pre-war Warsaw to life – the fates of fictional characters are intertwined with real events involving prominent artists, politicians and scientists of the inter-war period. Similar to the previous parts of the series, the novel features real-life giants of medicine, such as Sigmund Freud, Alois Alzheimer and Kazimierz Funk.

Doktor Zosia is the final part of the *Uczniowie Hippokratesa* series, combining a fictional storyline with ground-breaking events from the history of medicine.



The Military Institute of Medicine in Warsaw is the heir to the traditions of Ujazdowski Hospital.