LEKARZ WOJSKOWY

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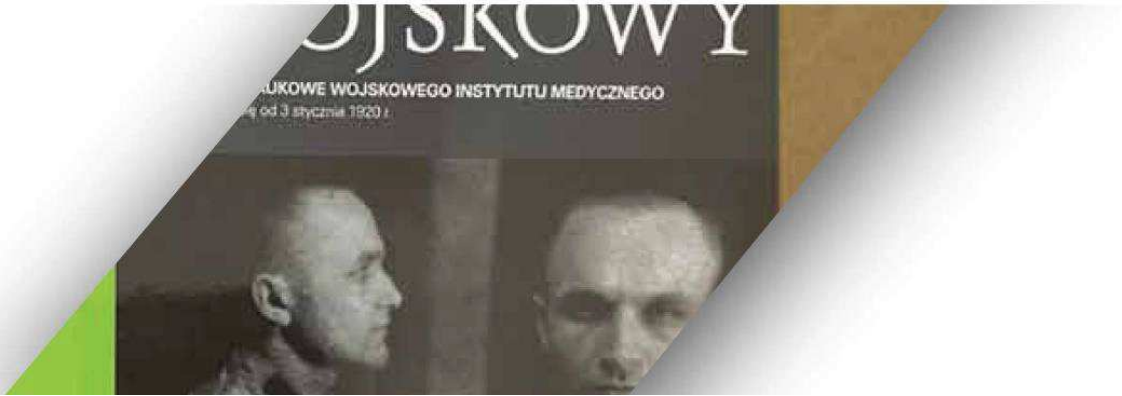
- Post-exposure prophylaxis of tetanus in cases of injury – rules of conduct
- Security above freedom? Compulsory vaccinations against COVID-19 as a controversial measure of ensuring health security
- Impaired autophagy as an etiological factor of various disease entities
- Mucormycosis and COVID-19



WOJSKOWY INSTYTUT MEDYCZNY

Informacje dla autorów

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

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   Books:
   Rudzki E. Alergia na leki: z uwzględnieniem odczynów anafilaktycznych i idiosynkrazji. Lublin, Wydawnictwo Czelej, 2002: 338–340
   Chapter of a book:
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   2) 'Good practices in review procedures in science' (developed by the Team for Ethics in Science, which advised the Minister of Science and Higher Education in 2009–2010);
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      b) in justified cases, immediately inform the relevant scientific institutions, as well as the appropriate law enforcement authorities about these practices;
   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

Before you is the first issue of the 100th volume of *Military Physician*. For a hundred years, the journal was changing its graphic design, and number of issues per year, but it persevered even in the worst periods in our tumultuous history, and it survived. *Military Physician* has published articles by outstanding Polish scientists and physicians, not only those wearing uniforms. I hope this will not change. We would like to invite all colleagues, including those living abroad, scattered around the globe, to collaborate with us.

A new chapter is being opened. Having introduced a range of changes (new graphic design and website, assigning DOI numbers to articles, electronic system for typesetting and editing), we started publishing the 100th volume of the journal. *Military Physician* is included in the list of ranked scientific journals of the Ministry of Science and Higher Education; therefore, authors will receive 20 points for an article published in our journal. The entire editorial team was involved in the preparation for the above changes. I would like to express my gratitude to everyone engaged in this work and to those who kept their fingers crossed for us.

In the first issue, as promised, you will find reviews, original articles, case reports, an interview, a conference report and a letter to the editor. The range of issues discussed is very broad: from articles on basic research to clinical aspects and problems regarding safety.

Noteworthy are the articles on post-exposure prophylaxis of tetanus – a problem still present in the work of Hospital Emergency Departments and in military medicine, impaired autophagy, and the course of tick-borne encephalitis based on a case report. The problem of the COVID-19 pandemic is present in the article discussing the approach of the governments in various countries to vaccination.

I hope you will find the graphic design and the website attractive. I can assure you that the editorial team will strive to ensure that the articles published in *Military Physician* are of practical use for our colleagues, and doctors, and that they meet the constantly rising standards.

Prof. Bolesław Kalicki MD, PhD

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CONTENTS

POST-EXPOSURE PROPHYLAXIS OF TETANUS IN CASES OF INJURY – RULES OF CONDUCT

Profilaktyka poekspozycyjna tężca w zranieniach – zasady postępowania

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Abstract: This article presents the management of injuries aimed at preventing tetanus. The epidemiology and pathomechanism of tetanus, clinical forms and symptoms, and non-specific and specific post-exposure prevention principles are discussed. A management algorithm supplements the article.

Streszczenie: W artykule przedstawiono postępowanie w zranieniach mające na celu zapobieganie rozwojowi tężca. Omówiono epidemiologię i patomechanizm tężca, postacie i objawy kliniczne oraz zasady profilaktyki poekspozycyjnej nieswoistej i swoistej. Artykuł uzupełnia algorytm postępowania.

Key words: immunisation, vaccine, wound infections, *Clostridium tetani*, tetanus antitoxin.

Słowa kluczowe: szczepienia, szczepionka, zakażenia przyranne, laseczka tężca, antytoksyna.

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Introduction

Tetanus is a life-threatening neurological disease caused by a potent neurotoxin produced by anaerobic *Clostridium tetani* rods. It can be effectively prevented by vaccination. Therefore, tetanus is found in unvaccinated populations, primarily in poor countries in Asia, Sub-Saharan Africa and South America, frequently in the form of neonatal tetanus. According to the World Health Organization, in 2015, 36,806 people and 19,937 neonates died due to tetanus worldwide [1, 2]. Based on the most recent data from 2018, 15,103 cases of tetanus were reported globally, including 1,803 in neonates [3]. Due to widespread vaccination, the incidence of this disease has been very low for years in well-developed countries. According to the data of the National Institute of Public Health – National Institute of Hygiene, in Poland 17 cases in 2019, and only 2 cases in 2020 of wound tetanus were reported (the annual incidence was 0.01 and 0.04/100,000 people, respectively); no cases in neonates were observed [4, 5].

Resistant to environmental conditions spores of tetanus rods are commonly present in the environment, including gastrointestinal systems of humans and animals. The spores may contaminate wounds and the umbilical stump. In most cases, tetanus is caused by small cuts and abrasions of the skin.

The excellent epidemiological situation in developed countries is due to widespread vaccination and effective post-exposure prophylaxis. Wound tetanus threatens unvaccinated and elderly people with weakened post-vaccination immunity. Other risk groups comprise intravenous drug users and immunosuppressed patients. Mortality due to generalised tetanus is 10 to 70%, depending on the age of the patient and access to treatment at an Intensive Therapy Unit. Recovered patients may suffer neurological complications for a long time.

Clinical forms of tetanus

Tetanus usually develops as a result of small skin injuries and abrasions and, in small children, as a result of chronic otitis media, so in 20 to 50% of cases the entry point of infection cannot be identified. The clinical course of the disease is probably determined by the amount and rate of toxin production, and its severity is highest in puerperal women, patients with deep wounds and intravenous drug users [6]. Following the prodrome period, one of four characteristic, different clinical forms of tetanus develops. Localised forms are characterised by muscle stiffness in the area of the wound that is the entry point of infection. However, local symptoms may forecast generalised tetanus – the most common, classic form of the disease, found in the majority of cases (80%). Its incubation period is 3 to 21 days, and the symptoms develop gradually, usually for a week, starting with the jaw muscles. Therefore, the first symptom is trismus. Then muscle spasms occur in a descending pattern, and

they may persist for a few weeks. Their tension increases, and paroxysmal, strong and painful contractions of large muscle groups, triggered by various sensory stimuli, occur. It leads to the typical clinical signs, such as hyperextension of the dorsal muscles (*opisthotonus*) and wince due to the spasm of facial muscles (*risus sardonicus)* which are, characteristically, not associated with consciousness disorders [6, 7]. The spasms are accompanied by the symptoms of autonomous nervous system impairment: heart rhythm disorders, disturbed thermoregulation and variations in arterial pressure. Contractions of the laryngeal muscles (epiglottis) or diaphragm may result in quick death. The rarest clinical presentation, cerebral tetanus, develops within 1–2 days as a result of head trauma or chronic otitis media, and it affects the muscles supplied by the cranial nerves. A special form of the disease is neonatal tetanus. A severe generalised form develops typically within 3 to 7 days after birth, usually due to infection of the umbilical stump [8]. The typical symptoms of the disease include difficulties with feeding, impaired suckling and swallowing reflexes and excessive crying of the neonate. Both localised and cerebral tetanus may be complicated by generalised tetanus [7].

The type of the wound largely determines the risk of tetanus. Small and clean injuries with good blood supply, without necrotic tissue occurring at home are associated with low risk. Whereas risk factors for the development of tetanus include:

- crush wounds, deep wounds, puncture wounds, shot wounds, wounds containing a foreign body, wounds that are considerably contaminated with soil, faeces or saliva, slaughterhouse waste or aerobic bacteria (they consume oxygen, thus supporting the anaerobic bacteria), wounds associated with shock (ischaemia), burns or frostbite,
- wounds that have not been treated within 24 hours,
- injuries occurring during work in soil (especially enriched with natural manure), e.g. while gardening, growing vegetables, taking care of farm animals (especially horses) and injuries caused by tools contaminated with soil,
- intravenous drug use,
- obesity (due to weakened response to vaccination).

Pathophysiology of tetanus

Clostridium tetani rods are non-invasive, anaerobic, Gram-positive bacteria commonly found across the world, particularly in soil contaminated by animal faeces, especially horses (saprophytes in the gastrointestinal system). They create spores that can survive dozens of years, and are resistant to environmental factors, high temperatures and disinfectants.

Tetanus is a wound infection, limited to the place of entry. Typically, the bacteria enter the body through a damaged skin. In anaerobic conditions, the spores transform into a vegetative form and produce a potent, polypeptide neurotoxin (tetanospasmin) which causes the symptoms. The toxin blocks the release of acetylcholine and inhibitory neurotransmitters in the spinal cord. The development of fully symptomatic tetanus is preceded by a prodrome period, characterised by patient anxiety, feeling unwell, minor increase in muscle tone, increased sweating, headache, insomnia, as well as pain and paraesthesias in the wound area. The incubation period of generalised tetanus is 3 to 21 days (a mean of 8 days), and in rare cases it may extend to a few months. Shorter incubation usually is associated with a more severe course of the disease and worse prognosis [9].

Due to the mentioned pathophysiology, tetanus patients do not pose a threat to others, as the disease is not transmitted between people, but on the other hand, population immunity cannot develop.

Post-exposure tetanus prophylaxis

Post-exposure tetanus prophylaxis consists in wound debridement (non-specific prophylaxis) and using a specific anti-tetanus immunoglobulin (antitoxin), as well as vaccination. It should be introduced as soon as possible. The principle applies both to the specific and non-specific prophylaxis.

1. Non-specific prophylaxis

Regardless of the history of vaccinations, each injury requires non-specific prophylaxis, i.e. wound care. The wound should be cleaned immediately, and if necessary, surgically debrided to remove the damaged or necrotic tissues and foreign bodies. It should be emphasised that extensive debridement may have adverse consequences in the case of deep puncture wounds [9]. Subsequently, depending on the risk of tetanus, specific prophylactic measures should be applied.

2. Specific prophylaxis

Specific prophylaxis consists in post-exposure use (active prophylaxis) of tetanus toxoid (tetanus anatoxin) or a vaccine combined with a tetanus component (toxoid) or human anti-tetanus immunoglobulin (anatoxin – TIG – passive prophylaxis). The decision regarding the use of specific prophylaxis and its type (active or active-passive) is determined by two main factors: the anti-tetanus immunity status of the exposed person (interview related to the vaccination history) and the risk of developing the disease (type of wound and time from the injury). The general immunity status of the exposed patient is also an important factor. The basic principles of specific post-exposure prophylaxis of tetanus are presented in Table 1 along with the enclosed algorithm with a check list.

2a. Active prophylaxis

It consists in administration of a single dose of a vaccine containing tetanus toxoid (deactivated toxin). The toxoid dose is the same, regardless of the patient's age.

Unvaccinated patients, those with incomplete vaccination or without documented vaccination, continue to receive vaccination from their family doctor. The following products are available on the Polish market: monovalent tetanus toxoid vaccines (T) and combined vaccines containing tetanus toxoid and diphtheria toxoid (Td), vaccines against diphtheria, tetanus and pertussis (DTP and dTpa – a capital D or P in the abbreviation refer to a higher dose of diphtheria toxoid or pertussis antigens, respectively, and a lowercase d and p denote lower doses), typhoid and tetanus vaccine (against tetanus and typhoid – TyT), as well as multi-combination vaccines 4-in-1, 5-in-1 and 6-in-1

for infants and young children. All of these vaccines contain similar doses of tetanus toxoid. According to the current Polish Protective Vaccination Programme for 2021, T and Td vaccines are of key importance in the post-exposure prophylaxis of tetanus. However, both the American CDC (*Center for Disease Control and Prevention*) and AAP (*American Academy of Pediatrics*) recommend to use preferentially the products that contain not only tetanus toxoid but also a pertussis component, to offer protection against whooping cough [10].

Table 1. Post-exposure prophylaxis of tetanus

Patient's vaccination history	Risk of tetanus infection	
	Low	High
Unvaccinated or incompletely vaccinated patients, or those with uncertain vaccination history	Tetanus and diphtheria or tetanus vaccine, then continue basic immunisation (0; 1; 6 months)	Tetanus and diphtheria or tetanus vaccine and antitoxin (TIG 250/500 IU), then continue basic immunisation (0; 1; 6 months)
Basic or booster immunisation – last dose more than 10 years ago	Tetanus and diphtheria or tetanus vaccine – one booster dose	Tetanus and diphtheria or tetanus vaccine – one booster dose and antitoxin (TIG 250/500 IU)
Basic or booster immunisation – last dose 5–10 years ago	Tetanus and diphtheria or tetanus vaccine – one booster dose	Tetanus and diphtheria or tetanus vaccine – one booster dose
Basic or booster immunisation – last dose less than 5 years ago	Not required	Not required In particularly high-risk cases, administration of one dose of tetanus and diphtheria or tetanus vaccine should be considered

Check list and explanation of the algorithm of "Specific post-exposure tetanus prophylaxis"

Qualification for specific prophylaxis has two stages. First, the patient's immunity against tetanus at the moment of exposure (previous vaccination) is assessed, as current vaccination allows specific prophylaxis to be omitted in immunocompetent patients. Then, in stage two, the risk of tetanus development is evaluated, based on the circumstances and type of wound, and the decision regarding the type of specific tetanus prevention is made.

1. Assessment of the tetanus vaccination status and of general immunity

- Did the patient receive a full course of tetanus vaccine ?
- When did the patient receive the last booster dose?
- Is the vaccination documented or highly probable (e.g. based on military service, surgically treated injury)?
- Which group does the patient belong to?
  - Lack of tetanus vaccination, unvaccinated or incompletely vaccinated patients, or those with uncertain vaccination history.
  - Basic or booster immunisation – last dose 5–10 years ago.
  - Basic or booster immunisation – last dose less than 5 years ago

Assessment of general immunity:

- Is the patient's immunity significantly compromised (HIV or SCID infection, severe antibody deficiency)?
  - **If yes, the risk is high –** administration of TIG is required after every injury

2. Assessment of the risk of tetanus based on the wound

- Is the wound clean, with good blood supply or is it a small and clean superficial wound that occurred in a domestic environment and does not contain necrotic tissue?
  - **If yes** – the risk of tetanus is low.
- Is it a crush wound, a deep wound, a puncture injury, a shot wound, does it contain a foreign body, is it contaminated with soil, faeces or saliva, slaughterhouse waste or infected by aerobic bacteria?
  - **If yes** – the risk of tetanus is high.
- Was the patient in the state of shock during or after the injury?
- Does the wound result from a burn or frostbite?
- Was the wound treatment delayed by more than 24 hours?
- Did the injury occur while working in soil, e.g. growing flowers or vegetables, taking care of farm animals (especially horses)?
- Was the wound caused by a tool contaminated with soil?
- Is the patient an intravenous drug user?
  - **If yes** – the risk of tetanus is high.

Table 2. Vaccines with a tetanus component registered in Poland that can be used in post-exposure tetanus prophylaxis.

Type of vaccine		Commercial name	Comments
Tetanus vaccine	T	Tetana	Routinely used
Tetanus and diphtheria vaccine	Td	Clodivac	Routinely used
		Td-pur	In a pre-filled syringe
Diphtheria, tetanus and pertussis vaccine	dTap	Adacel	For children from 4 years of age and adults, including pregnant women
		Boostrix	For children from 4 years of age and adults, including pregnant women
		Tdap – SSI	For children from 4 years of age and adults, including pregnant women
Diphtheria, tetanus and polio vaccine	dT-IPV	Dultavax	For children from 7 years of age and adults, including pregnant women
Diphtheria, tetanus, pertussis and polio vaccine	DTPa-IPV	Tetraxim	For infants from 2 months to children 12 years of age
	dTpa-IPV	Boostrix-Polio	For children from 3 years of age and adults, including pregnant women
Typhoid and tetanus vaccine*		Ty T	For children from 6 years of age and adults up to 60 years of age. Practically not used in post-exposure prophylaxis.

*Packaging of 20 doses

It applies to post-exposure prophylaxis following injury in children aged 5 to 7years and adolescents, as well as adults who were not vaccinated in the recent years (usually 5) against pertussis and demonstrate no contradictions preventing this vaccination [11]. Depending on the manufacturer's recommendations, the vaccine is administered by a deep subcutaneous or intramuscular injection. Table 2 presents the vaccines registered in Poland for use in tetanus prevention [12–18]. The table does not include the multi-combined preparations used in children up to 3 years old. When selecting a vaccine, it is important to consider the summary of product characteristics regarding the age groups for which the product is approved.

2b. Passive specific prophylaxis

It consists in the administration of hyperimmunised immunoglobulin containing specific antibodies binding the tetanus toxin. The antitoxin (TIG) is injected deeply into the muscles at a dose of 250 IU or 500 IU, at a different anatomical site than the previously administered vaccine. The dose does not depend on the patient's age or body weight, but is determined by the risk of tetanus infection. If the wound is infected and cannot be surgically treated within 24 hours, the injury is deep, the access to oxygen is restricted, and in certain types of injuries, e.g. caused by animals (e.g. bites, stings) or by foreign bodies (e.g. shot wounds), a higher TIG dose (500 IU) should be used, following the relevant SPC. If a wound is associated with a lower risk of tetanus infection, half of that dose (250 IU) will be sufficient [19]. When TIG is not available, normal human immunoglobulin or equine tetanus-specific immunoglobulin may be used (the product is not available in Poland) [9]. Following CDC recommendations, normal human immunoglobulin (IVIG) should be administered at a dose of 0.2–0.4 g/kg b.w.; however, it is worth mentioning that the FDA (Food and Drug Administration) has not approved such treatment, and it has not been included in the Polish Protective Vaccination Programme [10, 20]. If there are any indications for using tetanus-specific immunoglobulin, it should be administered as soon as possible. It is also used in patients who come to the doctor with a delay, regardless of the time from the injury. This is due to the therapeutic properties of the immunoglobulin (it is also used to treat tetanus) and a potentially long period of tetanus incubation.

3. Prophylactic antibiotic therapy

Routine antibiotic therapy is not recommended in tetanus prevention. However, wound monitoring is advised, as well as selection of appropriate antibiotic therapy in case the wound area becomes infected [20].

Conclusions

Due to common protective vaccination against tetanus, improved sanitary conditions, widespread access to healthcare and routine post-exposure tetanus prophylaxis, in developed countries – including Poland – tetanus is only occasionally observed. However, despite the favourable epidemiological situation, we should bear in mind that tetanus spores are common in the environment, and in the case of tetanus infection, the mortality rate in Poland is up to 30%. Moreover, recovered patients often suffer from chronic complications that significantly reduce the quality of life [21]. After exposure, routine management should include both an effective, non-specific post-exposure prophylaxis, i.e. wound treatment, and specific prophylaxis: passive – administration of TIG antitoxin, or active – administration of a vaccine containing tetanus toxoid. Post-exposure tetanus prophylaxis should be introduced as quickly as possible, immediately after the risk assessment. As part of post-exposure prophylaxis, patients who were vaccinated against tetanus should continue the tetanus immunisation, following the recommendations in the current Protective Vaccination Programme.

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REVIEW ARTICLE

IMPAIRED AUTOPHAGY AS AN ETIOLOGICAL FACTOR OF VARIOUS DISEASE ENTITIES

Zaburzona autofagia jako czynnik etiologiczny zróżnicowanych jednostek chorobowych

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Abstract: Autophagy is a conservative process of lysosomal digestion of damaged cell organelles, pathogens and nonfunctional proteins, which determines the maintenance of cellular balance. This process is an alternative source of energy for the cell under stress conditions induced by starvation, chemical factors or hypoxia. In recent years, the interest in autophagy has increased, and its dysfunctionality is considered to be one of the factors contributing to the development of various disease entities. The likelihood of diseases such as cancer, cardiovascular diseases or neurodegenerative diseases increases with age, and the process of autophagy is inhibited in an ageing body, which further indicates the involvement of impaired autophagy in the pathogenesis of many diseases. Therefore, activities aimed at modifying the pathways related to autophagy are indicated as a potential therapeutic tool. In this review, we present selected diseases, the causes of which are believed to be disturbed autophagy, indicate potential therapeutic possibilities and emphasise the dichotomous role of autophagy, especially in the neoplastic process.

Streszczenie: Autofagia jest konserwatywnym procesem polegającym na lizosomalnym trawieniu uszkodzonych organelli komórkowych, patogenów i niefunkcjonalnych białek, co warunkuje utrzymanie równowagi komórkowej. Proces ten stanowi alternatywne źródło energii dla komórki w warunkach stresowych indukowanych głodzeniem, czynnikami chemicznymi czy niedotlenieniem. W ostatnich latach wzrosło zainteresowanie autofagią, a jej dysfunkcjonalność uznawana jest za jeden z czynników sprzyjających rozwojowi zróżnicowanych jednostek chorobowych. Prawdopodobieństwo występowania chorób, takich jak nowotwory, choroby układu sercowo-naczyniowego czy choroby neurodegeneracyjne wzrasta wraz z wiekiem, a proces autofagii ulega hamowaniu w starzejącym się organizmie, co dodatkowo wskazuje na udział upośledzonej autofagii w patogenezie wielu chorób. W związku z tym, działania ukierunkowane na modyfikację szlaków związanych z autofagią wskazywane są jako potencjalne narzędzie terapeutyczne. W niniejszym przeglądzie prezentujemy wybrane choroby, których przyczyn upatruje się w zaburzonej autofagii, wskazujemy także potencjalne możliwości terapeutyczne oraz podkreślamy dychotomiczną rolę autofagii, szczególnie w procesie nowotworzenia.

Key words: autophagy, autophagy-related diseases, impaired autophagy.

Słowa kluczowe: autofagia, choroby związane z autofagią, upośledzona autofagia.

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Introduction

Autophagy is a conservative process occurring in all eukaryotic cells: from yeasts, where it was first observed and described, to human cells [1, 2]. The name comes from Greek and it means “self-eating” [3]. Autophagy consists in lysosomal degradation of damaged and misfolded proteins, cellular organelles and pathogens [2]. In this process, cellular components are separated from the cytoplasm, surrounded by a membrane and bound in a vesicle called an autophagosome or autophagic vacuole [4]. As a result of the fusion between an autophagosome and a lysosome, its content is degraded by digestive enzymes to amino acids, sugars, fatty acids and nucleotides that can be used as alternative energy sources for the cell in stress conditions or provide building material for the synthesis

of new structures [5, 6]. Autophagy is activated in cellular stress conditions that may be induced by starvation, chemical stress or hypoxia (insufficient oxygen supply) [7]. Autophagy was first described in the 1960s, and further intensive studies on the process brought a Nobel Prize for Yoshinori Ohsumi in 2016 for research on the mechanism of autophagy. At present, autophagy, a process of cellular self-cleaning, is considered a determinant of health and longevity. Recently, an increasing number of scientific reports have demonstrated the relationships between impaired autophagy and various diseases, resulting in growing interest in the process itself and the methods of inducing it.

Classification of autophagy

Previously, three main types of autophagy were described: microautophagy, chaperone-mediated autophagy and macroautophagy [8]. This classification is based on the manner in which the elements intended for degradation are delivered to the lysosomes [9]. The simplest type of autophagy is microautophagy, which involves a direct absorption of the material to be digested by the lysozyme. Chaperone-mediated autophagy (CMA) is characterised by the presence of a specific amino acid sequence (KFERQ, Lys-Phe-Glu-Arg-Gln) in a substrate molecule [10]. This pentapeptide in damaged proteins interacts with chaperone proteins Hsc 70 (heat shock cognate 70 kDa) and only in the form of this complex is delivered to the lysosome, where it binds with a LAMP 2A (lysosome associated membrane protein type 2A) receptor, to be moved and hydrolysed [11]. Macroautophagy is the type of the process most frequently defined as autophagy [12]. It essentially involves four phases: initiation, elongation of the phagophore, maturation of the autophagosome, fusion between the autophagosome and lysosome and degradation of the content by proteolytic enzymes [11]. Autophagy is controlled antagonistically by AMPK (AMP-activated protein kinase) and mTOR (mammalian target of rapamycin), which act as cellular indicators of nutrients [13]. Ulk1 phosphorylation by AMPK activates autophagy, while mTOR inhibits the process [14]. The entire process is controlled by specific Atg proteins [15]. The key factors in the initiation of autophagy and creation of autophagosomes are beclin 1 (a homologue of the yeast Atg 6 protein) and PI3K class III (phosphoinositide 3-kinase class III). In subsequent phases, beclin 1 activates other Atg proteins, resulting in elongation of the vesicle [14]. One of the more important stages of autophagy is conversion of cytosolic LC-3 (LC3-I; microtubule-associated protein 1 light chain 3) to a form conjugated with the inner membrane of the autophagic vesicle, LC3-II, which is considered the principal marker of autophagy [14, 16].

Diseases associated with impaired autophagy

All diseases associated with impaired autophagy share a common characteristic: accumulation of damaged cellular organelle and/or dysfunctional proteins, which disturbs cellular homeostasis. These elements may accumulate as a consequence of impaired final phases of autophagy, observed in microscopic images as an accumulation of the structures specific for this process: autophagic vacuoles (AV), inclusion bodies (IB) or multi-vesicular bodies (MVB) [17, 18]. Progress in the research on autophagy was supported by genome-wide association studies (GWAS), which allowed for identification of genes associated with autophagy [19]. In recent years, an increasing number of diseases associated with autophagic dysfunction has been found. They include among others inflammatory bowel diseases, cardiovascular diseases, neurodegenerative conditions, diabetes, obesity and neoplasms [1, 20].

Inflammatory bowel diseases

Inflammatory bowel diseases (IBD) are chronic gastrointestinal conditions characterised by periods of exacerbation and remission [21]. The most common non-specific inflammatory bowel diseases are Crohn's disease (CD) and ulcerative colitis (UC) [22]. CD presents as non-specific inflammation of the gastrointestinal wall and may affect any section of the digestive tract[11], while UC affects the final fragment of the digestive tract [23]. Sometimes, when the inflammation affects the colon, differentiation and diagnosis is impossible; in such cases we talk about unclassified colitis (IBDU) [11]. Aetiology of inflammatory bowel diseases is varied, but the most commonly identified causes include environmental and genetic factors, impaired autophagy and dysbiosis [11, 24]. The development of GWAS contributed to the progress in IBD diagnostics. The genes associated with autophagy, whose mutations contribute to IBD, include *ATG16L*, *IRGM* and *LRRK2* [25]. Atg 16L protein plays a crucial role in the process of autophagy, as it participates in the creation of autophagosomes [26]. The best known modification associated with dysfunctional autophagy in the course of IBD is a single nucleotide polymorphism (SNP) in which threonine is substituted for alanine at position 300 (T300A), which doubles the risk of CD [27, 28]. This mutation disturbs the activity of Paneth cells and goblet cells, resulting in impaired autophagy dedicated to pathogen elimination, known as xenophagy [29, 30]. Apart from disturbed pathogen elimination, mutation in the *ATG16L* gene increase the secretion of proinflammatory cytokines by Paneth cells, and increase the secretion of interleukin-1β (Il-1β), interleukin-18 (IL-18) and reactive oxygen species (ROS) by macrophages due to the activity of lipopolysaccharide (LPS) [31]. Therefore, *ATG16L* mutations contribute to exacerbated inflammation. Another gene related to autophagy and the development of IBD is IRGM which codes the M protein (immunity-related GTPase family M protein, IRGM) [32]. This protein is responsible for the maturation of autophagosomes and participates in

pathogen elimination from mammalian cells. Previous studies demonstrated inconsistent results regarding the relationship between polymorphisms of this gene and CD phenotype [33, 34]. However, a correlation was found between mutations in the *IRGM* gene and incidence of UC [34]. Regarding the next gene, *LRRK2* (leucine-rich repeat kinase 2), it has been demonstrated that its polymorphism is related to the occurrence of CD [35]. An increased expression of this gene was observed in patients diagnosed with CD [36]. Interestingly, compared to other genes associated with autophagy, the expression of LRRK2 is observed in the leukocytes present in the lamina propria, not in the intestinal epithelial cells [37].

Cardiovascular diseases

The continuity of the cardiac function is maintained by the energy (ATP) synthesised in mitochondria. A selective type of autophagy, involving degradation of these structure, is known as mitophagy, and its impairment is associated with various disorders of the heart muscle function [38, 39]. A particular role of autophagy was found in heart failure, proteinopathy, ischaemia and reperfusion, in which proteins are damaged due to oxidative stress [14, 40]. Studies on mice revealed that deficits of the Atg 5 protein contribute to the accumulation of polyubiquitinated proteins, mitochondria, increased endoplasmic reticulum stress, changes in the structure of the sarcomere and apoptosis of the cardiomyocytes [39]. Accumulation of the p62/SQSTM1 protein and polyubiquitinated proteins have been correlated with atherosclerosis, and the findings were based on murine models, as well as on studies involving patients diagnosed with atherosclerosis [41]. Another study demonstrated a relationship between autophagy/mitophagy and heart failure or aortic stenosis. Initially, the processes were activated, but due to reduced effectiveness of mitochondrial function and progressive heart failure, they were inhibited [42]. A therapeutic role of autophagy in various cardiovascular diseases has also been established. For instance, cardiomyocyte hypertrophy in the course of cardiac hypertrophy was reduced following treatment with sophoricoside that activated the AMPK/mTORC1 pathway, inducing the autophagy process [43]. Another example is the use of metformin which, by blocking the pathway activating autophagy regulated by AMP-activated protein kinase, reduced the development of heart failure [44].

Neurodegenerative diseases

Probability of neurodegenerative diseases increases with age, due to changes such as oxidative stress, mitochondrial damage, energy deficits, hyperactivation of glutamate receptors and disturbed homeostasis [45]. The majority of neurodegenerative diseases is due to accumulation of specific proteins, characteristic for a particular disorder [46, 47]. This accumulation is caused by the impairment of the processes of protein degradation that progresses with age, including autophagy [48]. Protein accumulation may lead to disturbed transmission of neural impulses between synapses, and even to the death of nerve cells [46, 47]. The most frequently observed neurodegenerative diseases include Alzheimer's disease (AD) and Parkinson's disease (PD). In their course, accumulation of autophagosomes and damaged proteins is observed [49]. Alzheimer's disease involves a progressive loss of synapses in the cerebral cortex and in the hippocampus, resulting in memory disorders and impairment of the cognitive functions [50]. The aetiology of this condition is not fully understood. The most common explanations point to the accumulation amyloid-β (Aβ) and tau protein [51, 52]. Amyloid-β accumulates in the form of amyloid plaques, while tau builds up in the form of intraneural aggregates, creating neurofibrillary tangles [53]. Impaired autophagy is indicated as the principal cause of aggregation of these structures; therefore, strategies to activate autophagy are being explored as a therapeutic option in the treatment of Alzheimer's disease [54]. For instance, it has been demonstrated that using rapamycin (mTOR kinase inhibitor, activator of autophagy) blocked the aggregation of amyloid-β and tau protein, and improved cognitive functions; however, this effect was only observed in early stages of the disease [55, 56]. Parkinson's disease is caused by the accumulation of α-synuclein and degeneration of dopaminergic neurons [57]. The main symptoms include impaired motor function, sleep disorders, mood swings and reduced cognitive function [58]. Although the mechanisms behind the disease are not fully understood, GWAS made it possible to identify numerous genes associated with impaired autophagy and development of Parkinson's disease [59].

Diabetes

Diabetes, despite the differences between type I and type II, is characterised by a lack of glucose homeostasis, due to insufficiency of pancreatic β-cells [60]. Simplifying, the pancreas produces less insulin, which causes hyperglycaemia. The impaired function of β-cells is due to endoplasmic reticulum stress and oxidative stress [61]. Autophagy plays a key role in the function of pancreatic β-cells [62]. The correlation between inhibited autophagy and impaired β-cell function was demonstrated in a study using *Atg7* knockout mice [63]. Reduced insulin secretion and impaired glucose tolerance were observed in the cells of the knockout mice, which clearly points to the role of dysfunctional autophagy in the pathogenesis of diabetes. Another study, using obese diabetic mice, demonstrated impaired autophagy and death of pancreatic β-cells [64]. Following intermittent fasting, autophagy was activated and the course of obesity-induced diabetes was milder. Demonstration of the relationship between inhibited

autophagy and diabetes led to the development of methods aimed at induction of autophagy in the treatment of diabetes. One of effective methods of controlling the course of diabetes is diet modification. It was demonstrated that the fast-mimicking diet (FMD) supports regeneration of pancreatic β-cells in the murine model of type I and type II diabetes [65]. Highly effective in the treatment of diabetes is e.g. metformin, an insulin-mimetic agent. It was demonstrated to activate autophagy in β-cells and to inhibit apoptosis under lipotoxicity in an in vitro model [66]. What is interesting, in relation to diabetes, a varied effect of rapamycin was observed. On the one hand, it was demonstrated that this autophagy activator helps to reduce body weight growth and blood glucose levels in rodents receiving a high-fat diet [67, 68]; on the other hand, increased insulin resistance and impaired pancreatic function were observed, even when autophagy was activated [69].

Obesity

Obesity and its consequences, i.e. increased risk of diabetes, arterial hypertension, cardiovascular diseases and neoplasms, are a global problem [70]. Excessive fat content localised outside of the fatty tissue, e.g. in hepatic cells or skeletal muscles, may injure these tissues or induce systemic lipotoxicity due to a high concentration of free fatty acids in the blood serum [71, 72]. One of the factors activating autophagy is hunger, so excessive caloric intake, characteristic for the diet of obese patients, impairs this process. Studies demonstrated that excessive caloric intake may contribute to the inhibition of autophagy due to stimulation of its negative regulator, mTOR kinase [73]. Studies on mice demonstrated that in obese mice, autophagy is inhibited due to reduced expression of the genes related to autophagy: *ATG5* and *ATG7* [74]. On the other hand, there are numerous scientific reports demonstrating the accumulation of autophagosomes in the liver and adipocytes of obese mice and humans, which potentially points to the activation of autophagy [75]. Obesity is indicated as one of the factors inducing endoplasmic reticulum stress in the liver, and ER stress activates autophagy. Therefore, it is possible that autophagy is induced to restore the homeostasis disturbed by excessive body weight [74, 76]. However, effective autophagy should result in elimination of autophagic substrates, such as lipid droplets and protein aggregates, while many studies reveal accumulation of these elements in cells and tissues [75, 77]. Increased production and accumulation of autophagosomes points to the activation of autophagy, but also to its reduced efficiency [78]. The unclear problem of autophagy in the adipose tissue was addressed in studies on the function of lysosomes and proteases using *in vitro* and *in vivo* models [79]. The authors demonstrated that in the pathological adipose tissue, production of autophagosomes was accelerated, but at further stages the autophagic flow was inhibited, which resulted in accumulation of autophagosomes. The obtained results suggest an ineffective autophagy process in the adipose tissue.

Neoplasms

In the context of neoplasms, autophagy arouses the greatest controversy. On the one hand, it is a crucial process in cell growth and neoplastic transformation; on the other hand, it contributes to the death of neoplastic cells [80]. First reports regarding the role of autophagy in the neoplastic process date back to 1999, when the activity of beclin 1 was demonstrated to suppress tumour growth [81]. Studies revealed that deletion of the beclin1-coding gene was correlated with the development of neoplasms in the breasts, ovaries and prostate, while reduced expression of the gene was observed in neoplasms of the breasts, ovaries and brain [81, 82, 83]. Research demonstrated that mutation in the beclin-coding gene inhibited autophagy and increased susceptibility to neoplasms [84, 85]. Other studies showed that p62 protein (a selective autophagy protein) participated in the control of the neoplastic process [86]. In the murine model, aggregation of p62 was found to impair autophagy. Unclear is the role of autophagy in the development of colonic neoplasms. On the one hand, it was demonstrated that in advanced stages of the tumour, LC3-II (autophagy marker) is overexpressed, which indicates high activity of the process [86], but other studies showed reduced expression of *ATG 5*, a gene that activates autophagy [87]. A study on pancreatic tumours revealed that increased autophagy supports the development of cancer cells, not only providing the energy necessary for the progression of the neoplastic process, but also supplying substrates, such as proteins, nucleic acids and lipids that make increasing the biomass of the neoplastic cells possible [88]. It appears that the role of autophagy in the neoplastic process is determined by the stage of the disease. Initially, autophagy degrades the damaged organelle and proteins, preventing the development of a neoplasm, but in advanced stages autophagy enables the tumour to adapt to adverse conditions, such as hypoxia, and allows the disease to progress [89, 90].

Methods of autophagy activating

Effective autophagy is considered a determinant of good health. Elimination of the damaged cellular organelle and dysfunctional proteins supports homeostasis and prevents diseases, which helps also to delay the ageing process. General systemic effects promoting longevity were proven in mice, worms and flies [91], but in recent years there has been growing interest in methods of activating this process also in humans. One of the factors inducing autophagy is fasting stress, so various dietary models based on caloric restrictions are gaining popularity. Proautophagic effects of energy deficits consists in antagonistic activity of AMPK/mTOR, the cellular sensors of the availability of nutrients [13]. For

autophagy to be activated, the glycogen stored in the liver and muscles must be used, so the time necessary to induce the process is considered 72 hours [92]. However, three-day fasting is too challenging for consumers, so different fast-imitating nutritional models have been developed [93]. The most popular protocol is intermittent fasting (IF), involving periods of fasting and so called "eating windows". The most common IF schedule comprises 16 hours of fasting followed by an 8-hour period when eating is allowed [94]. Other nutritional strategies based on alternating fasting and eating include ADF (alternate days fasting), FMD (fast-mimicking diet), and TRD (time restriction diet) [95, 96]. An example of dietary activation of autophagy can be obtained by ketogenic diet (KD), in which daily carbohydrate intake is limited to approximately 5–10% of the total caloric intake or if their amount is less than 50 g a day [97]. With glucose deficits, fats are metabolised, resulting in ketosis, in which the main sources of energy are ketone bodies, used by the organism also during fasting [96]. The relationship between ketogenic diet and induction of autophagy was demonstrated e.g. in a study on mice in which an increased expression of LC3-II and beclin 1 was observed in animals on a high-fat diet, indicating that autophagy had been activated [98]. Due to the growing interest in autophagy, biologically active substances that can affect the process have been identified. They include among others curcumin and resveratrol. The role of curcumin in the activation of autophagic pathways was demonstrated e.g. in studies on human colon cancer cells (HCT116) and mouse embryonic fibroblasts (MEF) [99]. Resveratrol was shown to contribute to the degradation of amyloid plaques in mice, demonstrating a potentially therapeutic effect in Alzheimer's disease [100]. Physical activity also appears to stimulate autophagy. There are reports from studies assessing the effect of endurance training on the activation of autophagy in mice, depending on whether the training animals were fasting or after a meal. Based on the increased levels of autophagy markers, the study revealed that autophagy was activated in both cases. It should be emphasised that autophagy was more marked in the animals that were training in a fasted state [101].

Conclusion

Growing interest in autophagy in recent years results from its role in aetiopathogenesis of a broad spectrum of diseases, including among others inflammatory bowel diseases, cardiovascular diseases, neurodegenerative diseases, diabetes, obesity or neoplasms. Autophagy, as a process of cellular self-cleaning and recycling, maintains homeostasis in the organism, and elimination of harmful or defective components, such as pathogens and dysfunctional proteins, ensures normal function of cells and tissues. It reduces the risk of diseases associated with ageing. Since autophagy decreases with age, methods of activating the process are sought. Autophagy itself is considered to be a process that inhibits ageing and promotes longevity. The behavioural methods of inducing autophagy include nutritional restriction, such as reduction of the caloric intake, intermittent fasting and reduced carbohydrate supply. Autophagy is also promoted by physical activity, as well as by certain groups of products rich in biologically active compounds, such as curcumin and resveratrol. Although autophagy is believed to have a range of health-promoting properties, it should be emphasised that the process is dichotomous; therefore, both its impairment and excessive activation have an adverse impact on health.

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PHARMACOTHERAPY NOT ONLY IN CHILDREN

Farmakoterapia u dzieci i nie tylko

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Abstract: The study presents the factors that can affect the response to drugs at various stages of a child's development, thus determining the effectiveness and safety of pharmacotherapy. Based on the presented developmental changes, methods of calculating doses were established to enable extrapolation of adult dosing to the paediatric population. Moreover, the article demonstrates other potential tools (therapeutic drug monitoring, pharmacogenetics) that may be used to optimise drug dosing in children.

Streszczenie: W pracy przedstawiono czynniki, które mogą wpływać na odpowiedź na leki w poszczególnych stadiach rozwoju organizmu, warunkując tym samym skuteczność i bezpieczeństwo farmakoterapii. W oparciu o przedstawione zmiany rozwojowe opracowano sposoby obliczania dawek, które umożliwiają ekstrapolację dawkowania u dorosłych na populację pediatryczną. Wskazano również inne potencjalne narzędzia (terapia monitorowana stężeniem leku, farmakogenetyka), które mogą służyć do optymalizacji dawkowania leków u dzieci.

Key words: medicine, dose, children, pharmacokinetics, pharmacodynamics.

Słowa kluczowe: lek, dawka, dzieci, farmakokinetyka, farmakodynamika.

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Introduction

Dosing medicines in children in most cases is based on the clinical data established in an adult patient population , thus unfortunately, as a result, a number of variables specific for the developmental age are disregarded. This thesis was formulated over 100 years ago by the father of American paediatrics, Dr Abraham Jacobi, who said: "Paediatricians do not deal with miniature women and men who need reduced doses of drugs for diseases occurring in a smaller organism, but (...) with patients who require a proper dosing regimen". Since then, a lot of factors that modify the response of a paediatric patient to treatment, especially those affecting the pharmacokinetic properties of drugs, have been identified. Unfortunately, the pharmacokinetics (including interactions) and effects (including adverse effects) of many medications used in daily clinical practice are not directly verified; therefore, their dosing, indications and adverse effects in the individual developmental periods of a child have not been established. It is associated with the need to use medications inconsistently with the recorded indications (off-label) or to administer medications in a way different than recommended by the manufacturer (unlicensed use). It is estimated that in the European Union approximately 50% and even up to 90% (depending on the source) of medications administered to children are used off-label [1, 2]. Therefore, the agencies regulating the marketing of drugs (e.g. European Medicines Agency [EMA] and Food and Drug Administration [FDA]) encourage manufacturers to conduct studies on medications that provide sufficiently high quality in the paediatric population, via initiatives such as the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) or by establishing advisory bodies, e.g. Paediatric Committee (PDCO) that specialise in the use of medications in children and adolescents. Hopefully, with a growing body of knowledge regarding developmental changes that determine the effectiveness and safety of pharmacotherapy, appropriate therapeutic guidelines, considering various stages in the development of the organism, will be established.

Pharmacokinetics

Development of the organism is associated with a number of functional changes that significantly affect the fate of medications in the body, i.e. pharmacokinetics, which include the following processes, represented by the acronym ADME: drug

absorption, distribution, metabolism i.e. biotransformation, and excretion. Optimisation of medicine dosing in children requires understanding and finding relationships between ontogenesis and the pharmacokinetic data.

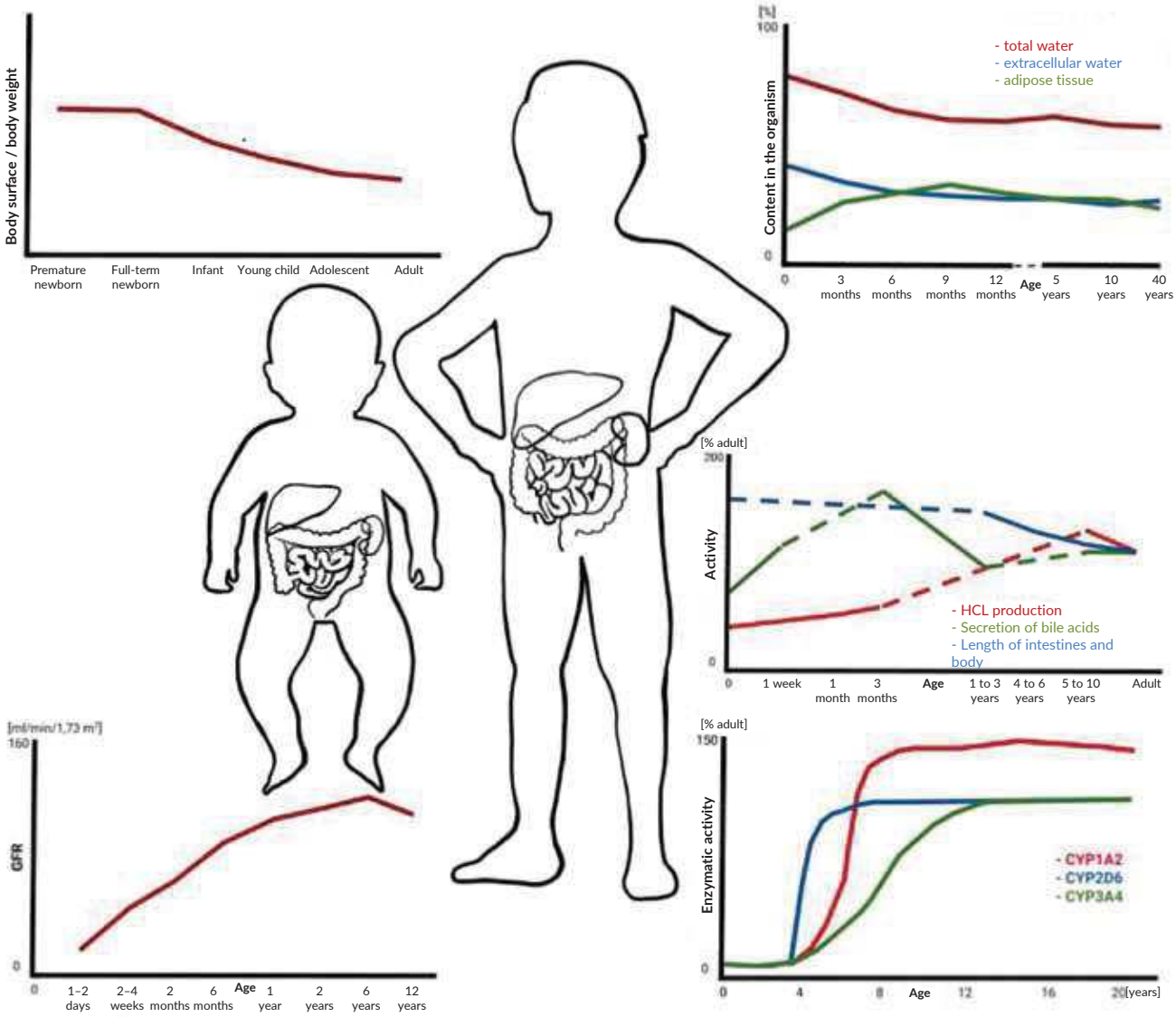
Drug absorption is affected by a number of mechanical, biological and physicochemical factors that determine substance penetration through biological barriers that have different characteristics in paediatric population. The first factor is pH, which changes in different parts of the digestive tract, affecting the level of drug ionisation and stability, as well as the function of drug transporters in the enterocyte membrane [3]. After birth, the pH in the neonate's stomach is higher than in adult, and is usually 4–6. This results in higher bioavailability of medications that degrade in an acidic environment (amoxicillin, erythromycin) in neonates compared with older children, as well as in a reduced absorption of weak acids (paracetamol, phenytoin, phenobarbital), whose ionisation increases in a more alkaline environment. Other differences include longer gastric emptying time, 6–8 hours (1–3 hours in an adult), which may lead to delayed drug absorption, e.g. the maximum concentration of paracetamol is delayed and is higher due to reduced drug clearance. The pharmacokinetics of the drug is also affected by the frequency, amplitude and duration of propulsive contractions that increase with age, as well as by a gradual maturation of the processes of passive and active drug absorption, which are fully active in the fourth month of life. Due to the above phenomena, the bioavailability of paracetamol in neonates and infants (up to two months of age) is 10 times lower than in older feverish children. Summing up, the absorption rate of most medications is lower in infants and younger children than in the older population, and the time to reach maximum concentration is longer [4].

Another important factor affecting the bioavailability of a medication is the varying activity of the intestinal enzymes participating in drug metabolism, which may determine the absorbed quantity of the medicine. Previous studies demonstrated that the activity of cytochrome P4501A1 increases and the activity of glutathione S-transferase decreases with age. Changes in bile secretion, affecting the bioavailability of lipophilic medicines through modification of their solubility, also appear to be significant.

Absorption of medicines administered via routes other than oral may also differ between children and adults. In neonates and younger children, after rectal administration, the bioavailability of drugs metabolised in the liver may be significantly higher, primarily due to the immaturity of the enzymatic systems. In prematurely born children, full-term newborns and younger children, transdermal absorption is increased, probably due to a thinner epidermal corneal layer, higher water content and increased blood flow through the skin (compared to the adult population). Therefore, the amount of medicines absorbed through the skin (glucocorticosteroids, antihistamines, disinfectants) may exceed the desired therapeutic values and result in adverse effects. Studies demonstrated that local treatment of nappy rash for approximately two weeks may lead to dysregulation of the hypothalamic-pituitary-adrenal axis, resulting in iatrogenic Cushing's syndrome. In clinical practice, the use of steroids should be limited exclusively to cases where it is necessary, with a possibly short time of treatment (products characterised by a low transdermal penetration should be chosen).

Drug distribution describes the location of medicines in the organism. It is illustrated by distribution volume (the hypothetical volume of body fluids in which the medicine, following a balanced distribution in the organism, would reach the same concentration as in the blood). Having reached systemic circulation, the medicine is distributed in the blood, tissues and organs. This process is determined by a number of patient-specific factors, i.e. the level of blood supply, permeability of membranes and pH differences between tissues and blood plasma, as well as drug-dependent factors, i.e. the degree of binding with plasma proteins and tissues, molecule size and its physicochemical properties. Drugs with large distribution volume (lipophilic, non-polar) are characterised by a low capacity to bind with plasma proteins, they bind strongly to peripheral tissues and have low molecular weight. The higher total water content in organisms of newborns (compared to adults) results in lower plasma concentrations of hydrophilic medicines dosed per body weight unit. In addition, a higher water-to-lipids ratio in the adipose tissue of newborns contributes to this situation. An important factor affecting the distribution, but also metabolism and activity of medicines, is the degree of their binding to plasma proteins, as only the unbound fraction of the drug may penetrate to tissues. Therefore, changes in the quantity or composition of plasma proteins (especially of albumin and acidic α1-glycoprotein) may affect the distribution volume of medicines characterised by high binding. Newborns have foetal albumin and higher concentrations of endogenous substances that can displace medicines from protein-bound molecules (including bilirubin and free fatty acids), and that contribute to the increase of the biologically active free drug fraction with high affinity to albumin (a clinically significant degree of binding: 90–95%). Factors other than age, important for neonatologists and paediatricians, may also affect the degree of drug binding to plasma proteins: pathological conditions that increase the unbound drug fraction, i.e. hypoalbuminemia in cystic fibrosis, malnutrition, kidney or liver diseases or conditions increasing the concentration of acidic α1-glycoprotein, i.e. injuries, postoperative condition, burns, inflammatory processes and neoplastic diseases, contribute to a higher degree of binding of alkaline medicines (lidocaine, propranolol).

Figure 1. Developmental changes affecting pharmacokinetics.



Another group of pharmacokinetic processes characterised by age-dependent variability depends on the activity of the enzymes that metabolise drugs. Metabolism/biotransformation of medicines typically occurs in two phases. Phase I reactions include oxidation, reduction and hydrolysis, while phase II reactions include conjugation with glucuronic acid, sulphuric acid, glutathione or amino acids and acetylation and methylation of drugs or their metabolites resulting from phase I reactions.

The main goal of the processes above is biotransformation of lipophilic compounds into hydrophilic compounds, which demonstrate a considerably lower ability to penetrate through biological membranes and can be eliminated with urine. The principal site of drug metabolism is the liver. The enzymatic system found in its microsomal fractions (cytochrome P450 isoenzymes) catalyses over 90% of the drug oxidation reactions. The most important isoenzymes in the fraction include: CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CY-P3A4. At birth, especially in premature newborns, the activity of certain metabolic pathways is reduced. After the birth, the activity of CYP2E1 and CYP2D6 increases significantly, while the activity of CYP3A7 decreases (it is present in foetuses and neonates, providing a protective role through the metabolism of dehydroepiandrosterone sulfate and the teratogenic derivatives of retinoic acid), to be replaced by CYP3A4. In the first week of life, the activity of CYP2C9 and CYP2C19 can be observed, and CYP1A2 occurs from first to third month. The most important (considering drug biotransformation) isoenzyme of P450 cytochrome is CYP3A4. Its expression is reduced in neonates and infants, which affects pharmacokinetics, including the medicines used in the early period of postnatal life. As a result of this lower activity, the substrates of CYP3A4 (cisapride, macrolide antibiotics, amiodarone, glucocorticosteroids) are slowly metabolised and

eliminated from the organism, which may result in frequent adverse effects in young children. Among the most serious ones is *torsade de pointes*, polymorphic ventricular tachycardia following the use of cisapride. In older children and adolescents, the activity of CYP3A4 is higher than in adults, so medicines are metabolised and eliminated faster, e.g. the increased clearance of carbamazepine is observed. In medical practice, it is recommended to increase the dosing of these medicines in order to obtain therapeutic concentrations. The immaturity of CYP2C9 and CYP2C19 (to a lesser degree) results in an extended half-life of drugs, e.g. phenytoin: in preterm newborns it is approximately 75 hours, in full-term neonates it is approximately 20 hours. The rate of phenytoin metabolism decreases with age: in the neonate period it is approximately 14 mg/kg/day and at puberty it is 8 mg/kg/day. The activity of CYP2D6 increases considerably after birth, reaching 20% of the adult values in 28-day-old infants. Clinical studies demonstrate that these correlations must be considered and neonates and infants need to be treated as slow metabolisers. It is assumed that in children aged approximately 10 years old the activity of CYP2D6 is comparable to that in adults. The metabolic activity of CYP1A2, of which theophylline is a substrate, increases gradually after birth and in 6-month-old children it can exceed the values observed in adults. The adult levels of activity are achieved in puberty. In clinical practice, higher doses of theophylline should be used in children.

The ontogenesis of the enzymatic systems catalysing the reactions in phase II of drug metabolism is much less known. It appears that the activity of phase II enzymes is also lower at birth than in adults. Therefore, medicines that require glucuronidation will have a longer half-life, and may undergo modifications via different metabolic pathways than in adults. In neonates and younger children, a reduced paracetamol glucuronidation capacity is observed, due to the lower activity of the UDP-glucuronosyltransferase (UGT) isoforms: UGT1A6 and UGT1A9 (to a lesser extent). The activity of UGT2B7 (morphine glucuronidation) is found in premature neonates as young as 24 weeks of gestation, and it increases gradually until 28–40 weeks of gestation. Therefore, newborns and infants cannot synthesise sufficient amounts of an active morphine metabolite (morphine-6-glucuronide), so they require higher doses of the drug. Reduced activity of the enzymes that catalyse glucuronidation causes hyperbilirubinaemia in neonates. Using phenobarbital as a UGT inducer increases the efficiency of bilirubin conjugation and its further elimination. Contrary to the glucuronidation reactions, in neonates, infants and young children a considerably higher efficiency of conjugation with sulphuric acid is observed, which enables partial conjugation of paracetamol with sulphuric acid (which in adults undergoes only glucuronidation), thus improving the medicine's safety [4, 5].

Drugs are eliminated from the organism in an unchanged form or as metabolites produced as a result of the transformations presented above. Most medicines are eliminated with urine through the kidneys, but some may also be eliminated with bile through the liver, with faeces through the digestive tract, with saliva through the salivary glands, with sweat through the sweat glands, with the air exhaled through the lungs and with milk through the mammary glands.

The elimination process is typically described using clearance (i.e. the volume of plasma that was cleared from the drug in a unit of time) and half-life (i.e. the time in which drug concentration in blood is reduced by half compared to the initial value). Drug clearance is largely determined by the function of the kidneys and liver, so physiological developmental changes in these organs, as well as any pathological conditions, will be reflected in the pharmacokinetic parameters. The glomerular filtration rate in full-term neonates is approximately 2–4 ml/min/m^2 of body surface area (0.6–0.8 ml/min/m^2 in premature neonates) and it increases gradually, until 8–12 months of age, when it approaches adult levels (90 ml/min/1.73 m^2). In this time, the permeability of the filtration membrane and renal blood flow increase, which improves glomerular filtration. Similarly develops tubular transport, reaching maturity in the first 12 months of age. However, due to the uneven rate of renal development (filtration and tubular transport), significant caution should be exercised when administering drugs eliminated through the kidneys to children, especially in the 1–2 week of age. A considerable extension of the aminoglycoside half-life in children up to 6 months of age (due to reduced glomerular filtration) was observed clinically. The immaturity of the tubular transport until at least 7 months of age may impair the elimination of drugs dependent on its activity: cephalosporins, digoxin, thiazide diuretics and furosemide [6–9].

Pharmacodynamics

Unfortunately, little is known about the effect of developmental changes in the organism on pharmacodynamics, i.e. the response to medications associated with their effect in the target sites (e.g. receptors, enzymes). Therefore, children are sometimes referred to as "pharmacodynamic orphans". For instance, a relationship was found between age and the effect of famotidine, i.e. a more pronounced inhibition of hydrochloric acid production in children. Other studies demonstrated different pharmacodynamic responses to medicines based on their effect on receptors (ciclosporin) or the relation between their blood concentration and the clinical effect (midazolam as a sedative), an increased frequency of paradoxical responses to diphenhydramine, an increased frequency of obesity during treatment with antipsychotics and increased hepatotoxicity of the valproic acid (decreasing with age) [9, 11].

Table 1. Examples of different half-lives (hours) according to age (adapted from [10]).

Isoenzyme	Drug	Neonate	Infant	Child	Adult
CYP1A2	Theophylline	24–36	7	3	3–9
CYP 2C9	Phenytoin	30–60	2–7	2–20	20–30
CYP2C19	Phenobarbital	70–500	20–70	20–80	60–160
	Diazepam	22–46	10–12	15–21	24–48
CYP3A	Carbamazepine	8–28	–	14–19	16–36

Pharmacotherapy

The above pharmacokinetic and pharmacodynamic dissimilarities occurring in the developmental age and absence of direct studies in the paediatric population make selecting a proper dose (or even a medicine) difficult in daily clinical practice. Due to the above differences between adults and children at various developmental stages, a direct extrapolation of the clinical use of a drug used in adult patients is not always appropriate and which was many times the cause of numerous adverse effects in children (e.g. thalidomide – teratogenic effect; chloramphenicol – grey baby syndrome; tetracyclines – teeth discolouration).

Due to an incomplete knowledge of the factors affecting drug pharmacokinetics and pharmacodynamics, the developed dosing regimens, especially in children under 8 years old, are imperfect. Doses are usually estimated based on a child's body weight, which is the easiest, but not necessarily the most accurate method. It is accepted that in children up to 10 years old, dosing based on body surface area is more appropriate. In 6-month-old infants, a dose based on body weight is underestimated by approximately 56%, whereas when the dose is established based on body surface area, it is underestimated by approximately 22%. Dose underestimation is primarily due to the relatively higher renal clearance per kilogram of body weight in children, which may lead to ineffectiveness of treatment. However, it should be mentioned that the therapeutic index of most medicines exceeds 50%, which minimised the clinical manifestation of dose underestimation. The above difficulties related to appropriate dosing result from an assumption that the relationship between body weight and surface area is linear. However, the processes of growth and maturation are not always linear, due to age-dependent variations in body composition and development of the organs that change dynamically, especially in the first decade of life.

Body surface area is commonly included as the parameter to calculate drug dose, but – as mentioned above – it is not free from flaws. To calculate body surface area, a range of nomograms are used (also taking into account other variables), which have certain disadvantages. The original nomogram for determination of body surface area, developed by DuBois and Du Bois uses a standard surface area of 1.9 m^2. Therefore, the resulting clearance values are appropriate only for children whose body weight is over 7 kg. Using 1.73 m^2 as a standard body surface area (in the above model), typically results in clearance overestimation by approximately 10% (this is associated with the varying development of the area of the skin, intestines, pulmonary alveoli and filtration membrane). The presented two models are most frequently used in daily clinical practice, but they are not perfect. Their limitations are most visible in neonates, infants and young children (e.g. using body surface area to calculate a dose results in its underestimation by approximately 22% in 6-month-old infants, whereas dose calculation using body weight is associated with underestimation by 56%).

Other calculation methods that enable adult dose extrapolation are not free from flaws either. They use age, body weight or surface area and the adult dose as the basis for calculations (Table 2).

Table 2. Paediatric dose calculation methods.

Method	Paediatric dose
Fried's equation (for children under 2 years of age)	age (months) / 150 x adult dose
Young's equation (from 2 to 12 years of age)	age (years) / age (years) + 12 x adult dose
Clark's equation	body weight (pounds) / 150 pounds x adult dose
Formula based on modified body weight	body weight (kg) / 50 kg x adult dose
Formula based on body surface area	Body surface area (m^2) / 1.73 m^2 x adult dose
Gowling's equation (over 12 years of age)	adult dose x age (years) / 24

The above formulas do not take into consideration developmental changes, which makes them imperfect. They are not equally appropriate for children in individual age groups. Summing up, the formulas based on body surface area are the most appropriate for children up to 2 years of age. They become less suitable for patients as they grow older. The formulas based on modified body weight (i.e. assuming that adult body weight is 50 kg) appear to be the best available methods of dose calculation in children over 10 years. The above formula appears to be more appropriate than the one

that uses 68 kg (150 pounds) as the adult body weight (Clark's equation). The last formula uses a body weight that is closer to the real mean body weight adapted when establishing adult doses (i.e. 70 kg). However, dosing based on the actual body weight of adult patients results in administration of too low doses in children, due to the increased drug clearance (per kilogram of body weight) in paediatric patients. Therefore, when calculating paediatric doses, using 50 kg as a referential body weight is appropriate. The above methods of dose calculation seem to be adequate at the beginning of pharmacotherapy, but may appear to be inadequate for long-term medication, when age-specific differences, especially regarding pharmacokinetics, should be considered. To optimise drug dosing in children, ontogenesis must be considered with relation to the parameters that describe the fate of medications in the organism and their effects. The most appropriate method consists in using the dosing range established in clinical studies involving children of the relevant age, but the availability of such data is limited. In older children and adolescents, no significant differences are found in the functioning of the organism compared to young adults (except the age-dependent differences in bioavailability) [12, 13].

Options for optimising pharmacotherapy

Therapeutic drug monitoring – in the case of certain medicines, particularly those with a narrow therapeutic index (i.e. drugs characterised by a small difference between the therapeutic dose range and a potentially toxic concentration), it is possible to adjust the dosing based on measurement of the drug concentration in the blood plasma/serum/full blood. For the measurement, a blood sample is usually collected in steady-state concentration, i.e. the state of dynamic equilibrium between the processes of absorption and elimination, established after approximately 5 half-lives of a given medication. Such management of pharmacotherapy makes it possible to adjust the dosing regimen to obtain therapeutic concentrations of the drug. The need for individualised therapy occurs more frequently in children than in adults, due to the differences in pharmacokinetics and uneven functional development of various organs. Recommendations for paediatric clinical practice include monitoring of blood concentrations of aminoglycoside antibiotics (amikacin, gentamicin), vancomycin, theophylline, digoxin, methotrexate and antiepileptics (carbamazepine, valproic acid, phenytoin) [14, 15].

Pharmacogenetics is another option for treatment optimisation. It makes it possible to select a medicine or its dose based on the patient's genetic profile. Multiple genetic variants have been described in the literature, especially regarding drug-metabolising enzymes, and the information regarding the effect of genetic factors on the response to medications is presented in Summaries of Product Characteristics for approximately 80 medicinal products. Regarding medications used in the paediatric population, it is recommended (but not required) to determine the polymorphism of the thiopurine methyltransferase gene (TPMT) to calculate doses of drugs that are substrates of this enzyme, i.e. azathioprine (AZA), 6-mercaptopurine (6-MP) and 6-thioguanine, in order to prevent a myelotoxic effect in slow metabolisers. Based on the genetic data, the initial dose of 6-MP or AZA in slow metabolisers can be established at 5–15%, and in patients with intermediate metabolism at 70% of the standard therapeutic dose. Determination of the polymorphism of the CYP2D6-coding gene also has clinical implications, as the enzyme catalyses the conversion of codeine and tramadol to active metabolites, morphine and M1, respectively; genetic information may help to prevent respiratory depression (in ultrafast metabolisers) or the lack of an analgesic effect (in slow metabolisers) [16, 17].

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LEKARZ WOJSKOWY
MILITARY PHYSICIAN

REVIEW ARTICLE

MUCORMYCOSIS AND COVID-19

Mukormykoza i COVID-19

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Abstract: This article presents the current situation regarding the spread of mucormycosis. Since mucormycosis is a very poorly known disease in Poland, we present here only the most important facts and observations regarding the relationship of this mycosis with COVID-19. We are dealing with a wave of infections, mainly in India, caused by the so-called black fungus. The increase in the number of infections and their spread, including outside of India, is directly related to the COVID-19 pandemic, and more specifically to the use of drugs containing corticosteroids or anti-interleukins, such as tocilizumab, which suppress the patients' immune system. Some specialists voicing warnings against underestimating mucormycosis and related mycoses, such as aspergillosis, and calling for more research on these diseases to find effective treatments and eventually preventive measures.

Keywords: mucormycosis, COVID-19, immunodepression, mycoses, aspergillosis.

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Rapid increase in the number of cases in India in 2021

Mucormycosis, which is a severe and often fatal invasive fungal infection, achieved wider public awareness during the COVID-19 outbreak in India in early 2021 [1,2]. The rapid increase in mucormycosis cases followed the second wave of the COVID-19 pandemic in India caused by the SARS-CoV-2 delta variant. This increase was noticed especially in the COVID-19 survivors and in diabetic patients. Mucormycosis is caused by fungi of the order *Mucorales*. The most common species is *Rhizopus oryzae*, but in tropical countries, there are many different species, belonging to the genera *Rhizopus*, *Apophysomyces*, *Mucor*, and *Lichtheimia*, which can also cause mucormycosis [3]. However, the precise identification of the species in patients is very difficult. Spores and mycelial fragments are found in the soil, and therefore also in the ubiquitous dust scattered everywhere in the air. Mucormycosis is not a new disease to India, but before the COVID-19 pandemic, it occurred sporadically in the immunocompromised people. The COVID-19 pandemic has caused a significant increase in the number of such patients. For this reason, mucormycosis, next to COVID-19, has become the second epidemic in this country [4].

Mucormycosis is an extremely fatal disease with a mortality rate of 50%. The fungus enters the human body through the mucosa during breathing. That is why it attacks the nasal sinuses so often. But it can also pass through wounds in the skin, or the circulatory system to the rest of the body. Because it is ubiquitous, the fungus easily attacks those COVID-19 patients with weakened immune systems.

Additional risk factors for mucormycosis are: ketoacidosis occurring in cases of poorly treated or untreated diabetes (which is also an increased risk factor for COVID-19) as the fungus grows particularly well in the acidified tissues, patients dialysed and undergoing deferoxamine therapy for kidney diseases, patients with extensive wounds or burns, and malnutrition, which is very common in overpopulated India.

India has been struggling with the COVID-19 pandemic during 2021. The SARS-CoV-2 virus delta variant has proven to be particularly deadly in this densely populated country that often lacks high-quality healthcare. The situation became even more complicated with the emergence of new mutations of the delta variant, called delta plus. But the mucormycosis accompanying the COVID-19 pandemic has proven to

be a particularly gruesome scourge. The SARS-CoV-2 infection itself greatly weakens the body and immune system. In addition, treatments of patients suffering from COVID-19 with drugs containing corticosteroids or anti-interleukins reduces the activity of the patients' immune systems to such an extent that their state resembles the immunosuppression applied, for example, in the transplant recipients to prevent acute transplant rejection [5]. This is how the patients recovering from COVID-19 infection often come to suffer from mucormycosis.

Mucormycosis manifests with tissues turning black when affected by mycosis, hence the common name of the disease: the black fungus. The disease is usually localised in the tissues of the sinuses, eyes, lungs, or the skin around the wound. But it can also take the form of an infection spread throughout the body which is called the disseminated form. This happens when the fungus travels around the body in the bloodstream. In the case of eye or paranasal sinus infections, mucormycosis can easily spread to the brain, which is always associated with a fatal prognosis for the patient. Therefore, in such cases, the eye or sinus areas are surgically removed. Obviously, such a drastic medical intervention causes enormous injuries to the face and head. This is why local people fear mucormycosis so much – it is not only deadly but also disfigures many of those who survive COVID-19 infection.

Spreading beyond India

To date, the vast majority of reported cases of mucormycosis in the world have occurred in India. The incidence of mucormycosis is 70 times higher in India than in the other parts of the world [3]. So, it is not surprising that the particularly rapid increase in the number of infections in connection with the COVID-19 pandemic happened in India. However, the spread of mucormycosis to India's neighbouring countries is very worrying. Many cases are reported not only in neighbouring Pakistan but also in the countries east and north of India such as Nepal, China, Bangladesh, Malaysia, and even Indonesia [7]. In the latter, mainly in Java and Bali, a particularly high level of infections with the delta variant of SARS-CoV-2 was recorded, and consequently, a greater number of cases of mucormycosis followed. The COVID-19 pandemic also lead to an increase in the incidence of mucormycosis in South America, mostly in Brazil [8,9].

This new epidemic is of great concern to the Indonesian authorities. The health authorities started a campaign to spread knowledge about mucormycosis and its prevention [10]. Of course, an early diagnosis of mucormycosis gives better chances for its treatment. For this reason, the media are reporting the typical symptoms of this disease, which are unfortunately initially not very specific. These include fever with a cough, chest pain, and shortness of breath that do not improve with standard treatments. In cases of infection through the intestinal mucosa, abdominal pain, nausea, vomiting, and gastrointestinal bleeding occur. Particular attention is also paid to infections of skin wounds, e.g. after surgery or burns, where black blisters or ulcers appear. The population is warned of disseminated forms of mucormycosis, which can spread to internal organs, including the brain, spleen, and heart, and which manifests itself as a severe disease with specific symptoms that are difficult to recognise. The disease can also cause coma and changes in mental status.

Due to global warming, mucormycosis can also reach our latitudes. The fungi that cause mucormycosis can also be brought to the western countries along with dust containing spores or mycelial fragments. The first reports of mucormycosis have already appeared in Poland, especially in patients with poorly treated diabetes. However, for now, aspergillosis is probably the greater threat in Poland. It is a mucormycosis-like mycosis caused by aspergillus, a fungus of the genus *Apergillus* and *Candida sp*. Aspergillosis and candidosis also occur most frequently in immunocompromised individuals, such as AIDS patients, and also significantly increased as a consequence of COVID-19 pandemic [11]. These patients are either treated with amphotericin B, itraconazole, or voriconazole, and surgical treatment is also used if necessary.

Urgent need for more research on mucormycosis and related mycoses

In the August 2021 issue of Lancet Microbe, published online in June 2021, three researchers, Neil Stone, Nitin Gupta, and Ilan Schwartz, of the Hospital for Tropical Diseases, University College London, Kasturba Medical College in Manipal, India, and the University of Alberta in Edmonton, Canada, called for increased efforts to improve the diagnosis and treatment of mycoses such as mucormycosis and aspergillosis [12]. They argue that these diseases, which until now were considered to be secondary because they were restricted to a small group of particularly susceptible patients, may now pose a threat to everyone. The COVID-19 pandemic should also change the approach to this type of forgotten but extremely dangerous disease.

They point out that the most often used antifungal treatment is amphotericin B, a nephrotoxic polyene antifungal that has been in use since 1958. Liposomal formulations, preferred because of their reduced toxicity, are often too expensive or even unavailable in many poor countries. The few alternative medications, such as posaconazole and isavuconazole, are even more expensive and therefore out of reach for poor populations.

The mucormycosis epidemic in India, but also in Indonesia and Brazil, has made it clear how huge the problem of fungal infections is and how poor the state of medical research is, which is necessary for the correct

prevention, diagnosis, and cheap and efficient treatment in the countries threatened by this scourge.

This major global warning should stimulate action to tackle the many problems associated with this disease. There is a need to better understand the risk factors that contribute to the current epidemic. It is very important to develop fast, reliable and non-invasive or minimally invasive diagnostics for mucormycosis, to increase access to existing treatments and to improve therapeutic measures.

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REVIEW ARTICLE

SIMULATION TRAINING BASED ON REAL CLINICAL CASES

Trening symulacyjny oparty na rzeczywistych przypadkach klinicznych

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Abstract: Advanced functionalities of medical simulation tools can be used in the improvement of medical personnel skills. This applies in particular to complicated clinical situations involving patients in serious or life-threatening condition. Difficult and rare clinical cases can be the background for the preparation of simulation scenarios. Performing them in practice and discussing during the debriefing session helps to prepare doctors to make similar procedures in a real clinical environment. The method of problem-based and case-based learning is especially valuable. It enables active participation in the didactic process, focussing attention on a given issue in a holistic approach. The knowledge of the rules of conduct and the practical ability to act in such events increases the safety of treated patients. The simulation training based on real clinical cases can also be used to train medical personnel of the Polish Armed Forces.

Streszczenie: Zaawansowane funkcjonalności narzędzi symulacji medycznej mogą być wykorzystywane w doskonaleniu personelu medycznego. Dotyczy to skomplikowanych sytuacji klinicznych u pacjentów w stanie ciężkim lub z zagrożeniem życia. Trudne i rzadkie przypadki kliniczne mogą służyć do przygotowania scenariuszy symulacyjnych. Praktyczne ich przećwiczenie oraz omówienie w trakcie sesji debriefingowej pozwala na przygotowanie lekarzy do realizacji podobnych procedur w rzeczywistym środowisku pracy. Szczególnie cenna jest metoda nauczania problemowego oraz opartego na przypadkach klinicznych. Pozwala ona aktywnie uczestniczyć w procesie dydaktycznym, skupiając uwagę na zagadnieniu w ujęciu holistycznym. Znajomość zasad postępowania oraz praktyczna umiejętność działania, w tego typu zdarzeniach, niewątpliwie podnosi bezpieczeństwo leczonych pacjentów. Technika doskonalenia symulacyjnego oparta na przypadkach klinicznych może być również wykorzystywana do szkolenia personelu medycznego Sił Zbrojnych RP.

Key words: medical simulation, simulation training, clinical case.

Słowa kluczowe: symulacja medyczna, trening symulacyjny, przypadek kliniczny.

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Introduction

Medical simulation for over 50 years has been establishing its role as a didactic tool. In many countries, including Poland, it is used in university training, allowing students to improve their practical skills without risk to the health of real patients [1, 2]. Using various simulation tools makes it possible to develop practical and interpersonal skills, filling in the gap between theoretical knowledge and clinical practice. Improving students' skills in the controlled environment of simulation centres becomes a standard in teaching, completing the classical training at the patient's bed under master's supervision.

Advanced functionalities of medical simulation tools can also be used effectively to improve the skills of experienced medical personnel. This applies in particular to complicated clinical situations involving patients in a serious or life-threatening condition [3]. In these cases, a high risk of complications and balancing on the verge of therapeutic failure does not leave any room for mistakes. Therefore, it is necessary to find alternative methods of gaining experience in procedures that are dangerous or associated with unusual or rare situations, for which practice has the greatest value [4]. In these cases, the proper combination of the traditional forms of

teaching, the simulation-based improvement of skills and the actual experience in patient care is challenging.

Tools and environment of medical simulation

Depending on the educational purpose, medical simulation offers various tools: trainers, phantoms, advanced patient simulators, virtual reality and even simulated patients [5–14]. Their functionalities allow learners to practice practical and interpersonal skills and to use the acquired competences in clinical practice. In order to achieve a high degree of realism, the combination of different types of tools is possible via hybrid simulation [3]. It makes possible to imitate procedures as closely as possible to real life. Implementation of simulation scenarios in the controlled conditions of a simulation room or in a real work environment (*in-situ simulation*) additionally increases the sense of reality, increasing the didactic value of the training process [15, 16]. Medical simulation allows participants to move beyond the traditional learning methods by offering them the ability to perform selected procedures in practice, in a safe simulation environment or in a real clinical setting. The controlled simulation environment creates the conditions for practical learning through acting and independent decision-making; it provides exposure to rare situations that may be challenging in daily practice, often posing a direct threat to a patient's health and life [17]. It allows to gradually develop the experience-gaining process, from a basic level to proficiency in a given procedure, before it is performed in a real clinical setting.

Problem-based learning

In the classical approach, the process of gaining knowledge and practical skills in medicine involves a step-by-step transition from theory to practice. In some countries, the Problem-Based Learning (PBL) approach, based on solving clinical problems, is gaining advantage [18–20]. This is due to the need to confront one's knowledge and experience with the disease symptoms presented by a patient [20, 21]. In this sense, the participant must switch from the role of a learner, passively receiving information, to an active participant in the learning process. It allows learners actively participate in the didactic process from the beginning, and focus on a given issue via a holistic approach. PBL is based on the concept of learning through the analysis of complex situations resulting from practice[19]. It requires from participants integration of knowledge from various areas and a high level of activity and engagement. Characteristic for the method is a team-based approach to problem-solving, whose goal is full engagement of all participants in achieving the planned educational purposes [19–20]. The process is supervised by an experienced mentor, but independent problem-solving by participants is promoted. Independence in decision-making is an important element of this method, as it allows learners to develop valuable skills, show their strengths and discover their own talents and predispositions. Problem Based Learning is associated with a similar concept of Case Based Learning (CBL) which uses real-life examples, adding reality to the didactic process [18, 20–26]. CBL is defined as a structured educational experience in which realistic clinical cases are used to solve or explore a clinical problem [25, 26]. Didactic sessions are realised under the guidance of an experienced teacher. Compared to PBL, advantages of CBL include a higher level of focusing on the didactic objectives and the potential for deeper learning due to the acquired critical thinking skills [26]. This methodology is widely used in medical teaching, allowing learners to gain also experience in the areas that are not encountered in everyday practice or are challenging due to their complexity or difficulty of the problem [20]. It helps to prepare personnel professionally for the implementation of newly learnt procedures in a real-life work environment.

Simulation-based medical education

High-fidelity simulations, including hybrid simulations, are advanced didactic techniques that ensure effective implementation of the teaching process and professional training [3–6]. Simulation sessions in which scenarios are based on real-life cases offer the most advanced level of practical education. Due to the complexity of the problems presented, they are intended for participants with clinical experience. They are excellent for postgraduate education, in particular to achieve competence and expertise to perform procedures that pose a challenge in daily clinical practise. To successfully complete a simulation session, participants must know how to operate medical equipment and devices, and demonstrate a general understanding of the organisation of treatment and the course of the practised procedures. Familiarity with the environment is also required, especially when simulation takes place in a real-life facility (Emergency Room, operating block, ICU, endoscopy unit, etc.). For an effective session, knowing the simulation environment, the principles of interaction with the simulation tools, and understanding their natural limitations is also important.

A simulation session allows participants to interact with a simulator imitating a real patient and clinical situation. It forces them to act and take therapeutic and organisational decisions, according to learner's knowledge and competences [6–10]. During the session, depending on the goal of the scenario, participants are confronted with situations that could happen in real life. It allows them to identify areas for performance improvement in their future daily work environment. A simulation session is followed by a debriefing session, the most valuable element in the didactic process [27–29]. In the debriefing, the team participating in the simulation together with an experienced teacher discuss the course of the exercise and analyse the problems identified during the simulation. Positive aspects of the

performance, as well as the identified potential errors are indicated. This is a time for reflection, discussion on the proper line of action in a given case and solution of the clinical problem, as well as for group work on solutions that could prevent similar problems in the future [27]. Simulation-based learning helps to improve critical thinking and to use knowledge and experience in the therapeutic process, initially in a simulated, and finally in a real-life clinical setting. It also allows participants to make mistakes and learn about their consequences in controlled conditions, without any risk to a real patient.

Simulation scenarios based on clinical cases

Practising medicine requires constant self-improvement. It applies to all specialties, but in particular to those that involve dealing with life-threatening medical emergencies on a daily basis. Typical for these situations is the need to act quickly, under time pressure; the need for coordinated team-work; the risk of disturbed situation awareness and, often, limited personal and technical resources. In unfavourable circumstances, these factors may lead to incorrect action, adversely affecting the treatment outcome. A lack of practice in the implementation of complex procedures may also be related to work in lower-reference centres that have limited experience in treating patients in a life-threatening conditions. Moreover, their condition may be due to a particularly rare casuistic pathology. All that will negatively affect the safety of treated patients. In order to prevent failures, in the light of the above limitations, forms of training other than daily practice need to be found. Simulation of difficult cases, including training in the principles of crisis management and communication in a simulated environment or in a real-life clinical setting, may provide an effective method of gaining expertise in various procedures [15, 16, 30].

An example of a real event used as a model for creating a training programme was the tragic case of Elaine Bromiley, described in the literature [31]. The 37-year-old patient died as a result of errors made by the medical team while anaesthesia for a planned laryngology surgery. The inadequate management of the unexpected difficulties with ensuring respiratory patency (CICV – *can't intubate, can't ventilate*), apnoea, extreme hypoxia and the dramatic consequences of this situation provided the background for a discussion regarding the necessary change in the approach to the management of crisis situations and implementation of a range of procedures and simulation trainings in *Anaesthesia Crisis Resource Management* (ACRM).

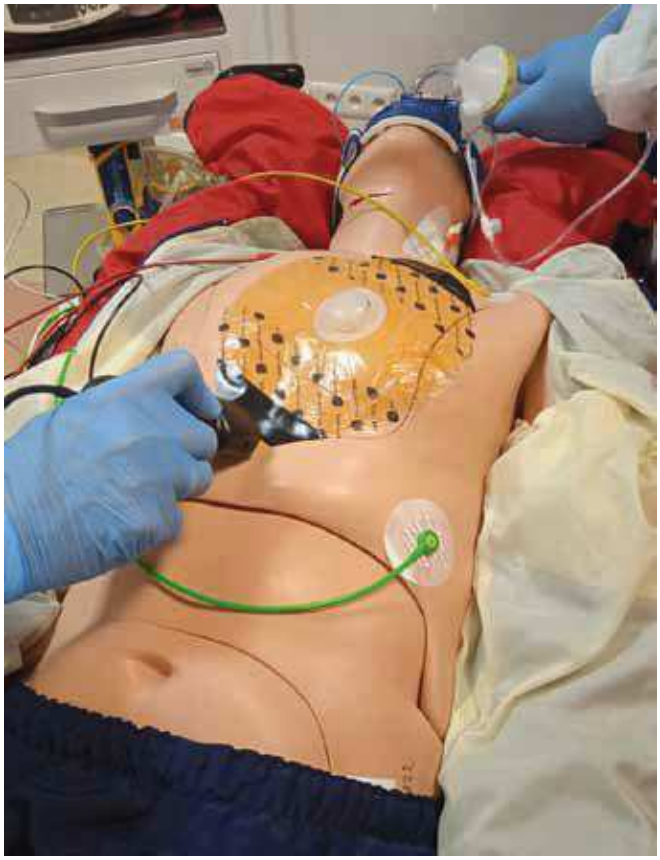

Fig. 1. *Multiorgan injuries*

It was possible due to the determination of the patient's husband, Martin Bromley, an airline pilot, whose initiative and actions allowed doctors to learn from the mistakes made in case of his wife. It increased the awareness of the importance of the human factor in healthcare. Similar actions were undertaken by D. M. Gaba and A. De Andy (*Department of Anesthesia, Stanford University School of Medicine, Palo Alto, California*). They created the Comprehensive Anaesthesia Simulation Environment (CASE), which they used to test the skills of anaesthesiologists in critical situations occurring during anaesthesia [33]. Their studies provided the basis for the principles of ACRM, and of the simulation-based learning programme for anaesthesiologists [33–36]. With time, the principles of ACRM were adopted in leading medical centres across the world. The ACRM-based approach was extended to many other medical specialties characterised by complexity and dynamism, such as emergency medicine, traumatology, surgery and intensive care [37–43]. These rules are used in practical training of rapid response teams and resuscitation teams [37, 38]. Maintaining a high level of services requires constant training. Such trainings, based on the CRM principles, are expected to become a standard in many healthcare facilities across the world, improving the safety of patients treated by multidisciplinary medical teams [42].

Fig. 2. *Airway burns*

Apart from practical skills, medical simulation also helps to improve interpersonal competences [44]. Literature data demonstrate that numerous preventable medical errors result from dysfunctional teamwork and poor communication [45–49]. To improve the status quo, the American Agency for Healthcare Research and Quality, and the Department of Defense together developed Team Strategies and Tools to Enhance Performance and Patient Safety (TeamSTEPPS) [50]. Simulation-based trainings with the use of this system are intended to improve patient safety by educating healthcare workers on communication and teamwork skills [50]. In the light of reports demonstrating that effective teamwork enhances treatment outcomes [51, 52], the principles of teamwork are incorporated in training programmes [53, 54]. Most of them use active learning methods, including simulations of critical incidents and scenarios based on real clinical cases [55, 56]. Many teachers agree that alternative methods of teaching teamwork and communication skills need to be developed [51–53]. There is evidence that adults learn best by active participation, self-reflection and using multi-modal learning strategies [57]. Improvement through experience is an effective approach in adult education [57]. Simulations combined with a structured summary not only allow participants to acquire the desired knowledge and practical skills, but may also increase the chances that they will be able to use these competences when confronted with real cases in a clinical setting [58].

Simulation training based on real clinical cases –-own experiences.

The authors have their own experience in providing trainings using simulation scenarios based on clinical cases. In our centre, they are used as elements of practical continuous training of doctors specialising in e.g. emergency medicine. Performing simulation scenarios in practice allows doctors to prepare for conducting similar procedures in a real clinical setting. They practice practical understanding of applicable guidelines, the methods and order of performing individual procedures, but also the specificity of the decision-making process and interpersonal skills. It takes place in a controlled simulation environment, without exposing real patients to a risk of complications. The discussed simulation scenarios involve e.g. procedure in the case of unexpected difficulties with ensuring airway patency, as a result of a thermal inhalation injury and management of massive intraperitoneal haemorrhage in trauma patient. During simulation sessions, participants improve their skills in ensuring airway patency following the Difficult Airway Society (DAS) guidelines and following the Damage Control procedures in multiorgan injuries (Fig. 1.) (Fig. 2.). Knowledge of the rules of conduct in these cases, the awareness of potential consequences of faulty decisions and the practical ability to respond to such incidents undoubtedly enhances the safety of patients treated in a real clinical setting. It allows also participants to maintain or regain lost competences in situation when they do not deal with similar cases in their daily professional practice. Recreating realistic situations in a safe simulation environment creates the opportunity to improve teamwork and communication, necessary in the management of a multidisciplinary medical team in a crisis situation [44]. In the future, such simulations, conducted in a real or virtual work environment, can be used to assess the qualification of personnel for work in the most demanding areas, thus minimising the risk of adverse events resulting from inadequate actions due to so called human factor [1, 2, 11–13].

Simulation-based training for military medical personnel

The continuous development of simulation technologies allows us to move beyond the traditional training methods not only in the civilian setting, but also in the training of medical personnel in the Polish Army. Due to the unique features of a combat setting, new methods of training need to be sought, both regarding the procedures conducted in the theatre of war, and during the individual stages of medical evacuation. The functionalities of medical simulation enable learners to practise simple practical skills (evacuation, maintaining airway patency, decompression of tension pneumothorax, stopping haemorrhage, etc.) [59], and to improve on complicated medical procedures performed as part of prolonged field care [60] and at the higher

levels of medical evacuation, including 2nd and 3rd level facilities [60]. The nature of operations in these areas requires from the personnel proficiency in performing procedures relevant for saving the lives of injured and ill patients. Medical simulation tools allow us to practise the procedures whose knowledge is essential during evacuation and treatment of the injured and ill patients in a combat setting [60]. To adjust the training process to the conditions typical for combat field medicine, most modern simulation equipment must be used. It is possible due to the solutions used in the civilian setting, including extensive teleinformatic infrastructure, using trainers and advanced patient simulators, as well as advanced technologies for creating virtual and augmented reality. These solutions, the most advanced achievements of medical simulations, allow learners practise scenarios based on real clinical cases in a simulation environment that reflects an actual tactical environment. The objective is to create in the participants the impression that they are working with real patients and to achieve a high level of training before performing tasks in a real tactical setting.

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SECURITY OVER FREEDOM? COMPULSORY VACCINATIONS AGAINST COVID-19 AS A CONTROVERSIAL METHOD GUARANTEEING HEALTH SAFETY

Bezpieczeństwo ponad wolność? Przymusowe szczepienia przeciwko covid-19 jako kontrowersyjny środek gwarantowania bezpieczeństwa zdrowotnego

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Streszczenie: Celem artykułu jest przybliżenie kontrowersji, związanych ze stosowaniem przez władze poszczególnych państw środka gwarantowania bezpieczeństwa zdrowotnego, jakim są przymusowe szczepienia. Dopuszczalność przyznania szczepieniom przeciwko zakażeniu wirusem SARS-CoV-2 statusu obowiązkowych rodzi pytanie, jakie są dopuszczalne granice ingerencji w sferę wolności jednostki. Problem ten tym samym związany jest zarówno z systemami ochrony praw człowieka, jak i postrzeganiem istoty bezpieczeństwa przez władze publiczne. Wskazano, że istota problemów i kontrowersji, związanych z ewentualnym ustanowieniem obowiązkowych szczepień, ma nie tyle charakter sporu o podłożu prawnym, lecz dotyczy politycznego i społecznego, a nawet kulturowego wymiaru sprawy.

Abstract: The aim of the article is to present the controversy related to the use by authorities of individual countries compulsory vaccination as a measure for guaranteeing health safety. The admissibility of granting mandatory status to vaccines against SARS-CoV-2 virus infection raises the question of the permissible limits of interference in the sphere of individual freedom. This problem is therefore related to both human rights protection systems and the perception of the essence of security by public authorities. It was pointed out that the essence of the problems and controversies related to the possible introduction of compulsory vaccinations is not so much a legal dispute, but concerns the political, social and even cultural dimension of the case.

Key words: COVID-19, bezpieczeństwo zdrowotne, przymusowe szczepienia, SARS-CoV-2, pandemia.

Słowa kluczowe: COVID-19, health security, compulsory vaccinations, SARS-CoV-2, pandemic

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There is no doubt that the SARS-CoV-2 pandemic has affected virtually every aspect of modern life – economic, medical, political, social, as well as legal. The pandemic has not only resulted in more than four million deaths and nearly 190 million cases worldwide [1]. It is also difficult to estimate the economic losses and – as will be discussed in the article – significant changes in the legal systems of individual countries. What happened during the pandemic was a kind of reevaluation of the idea that by means of global health management mechanisms, particularly by the international community imposing tasks on the World Health Organization (WHO), both the outbreak and spread of epidemic could be effectively counteracted. While only the coming years will provide an answer about whether, and to what extent, the countries will actually redefine the tasks and mechanisms of action of the WHO – which will undoubtedly be a long process given the way in which changes in international law are implemented – it can already be said that we are witnessing a transformation of legal systems in individual countries. The apparent redefinition of the regulations aimed at ensuring collective security in individual countries, on the one hand axiologically contradicts previous development of international human rights law, that places the individual at the centre, which has been accompanied for decades by a progressive process of positivisation of human rights. On the other hand, it is characterised by conviction that the security of societies can be guaranteed to the greatest extent through laws and efficient legislation. Moreover: "It seems reasonable to conclude that the pandemic period is a unique test for the mechanisms of democracy, since often state authorities, motivated by

the intention to ensure the effectiveness of protective measures taken to protect the security of citizens, will take actions both *praeter legem* and *contra legem*" [2].

The aim of this article is to present the issue of compulsory vaccination against SARS-CoV-2 infection, and to highlight the problems and controversies that arise from the decisions of particular countries which have decided to implement this measure. Due to the methodology of this study, the author will focus on selected legal conditions related to the analysed issue, in particular the issue of consistency of the human rights system with mandatory vaccination.

The SARS-CoV-2 pandemic, which began on 11 March 2020, has caused significant economic and social disruption in almost all countries around the globe and has permanently transformed the modern world. These changes have also occurred within the limits of the law. We need to remember that previous efforts aimed at limiting the spread of the virus were based on the belief that it is up to the individual to decide whether or not to get vaccinated. However, in some countries, workers in selected sectors, most often health care, have been obliged by law to undergo mandatory vaccination. If they refused to get vaccinated, they were to face sanction in the form of termination of their employment contract. In June 2021, the world saw photos depicting health care workers having been fired and forced to resign from their jobs at hospitals belonging to Houston Methodist in Texas. Its authorities announced on 1 April 2021 that all employees who wish to keep their jobs at Houston Methodist-affiliated hospitals must get vaccinated. While 24,972 employees were vaccinated, more than 150 were either fired or resigned as a result of the employer's decision [3]. 117 of these unvaccinated employees brought a lawsuit; however it was dismissed by federal district court judge Lynn Hughes. In the justification for her decision, the judge pointed out that the employer's position is not coercive, and Houston Methodist "[...] is trying to save lives by not infecting them [the employees – author's note] with the SARS-CoV-2 virus. This choice is aimed at ensuring the safety of staff, patients and their families. Bridges [a plaintiff – author's note] is free to choose whether or not to undergo the COVID-19 vaccination; however, if she refuses, she will simply have to work elsewhere" [4]. Despite the controversy caused by this process in the United States, the University of Pennsylvania Health System has also announced that all hospital staff must be vaccinated by the end of September this year. Employees, including medical staff, who choose not to be vaccinated will have to leave their jobs [5].

For the sake of complementarity of considerations, we need to emphasise that apart from the United States, where President Biden's administration imposed the vaccination requirements on employees and federal contractors in September 2021, vaccination of selected social groups is already mandatory in such countries as: United Kingdom: compulsory vaccination has applied since October 2020 to people working in care homes, France: compulsory vaccination of medical personnel, including volunteers by 15 September 2021, Russia, Greece, Hungary, Italy – from March 2021, and Kazakhstan. It should also be mentioned that, in the United States, the vaccination mandate also applies to employees of medical institutions that receive federal funds. At the same time, unvaccinated employees do not have access to free testing. In addition, the authorities of some states have already decided to introduce mandatory vaccination for health care workers. We further need to keep in mind that different states have different legal regulations against COVID-19. Interestingly, in contrast to unitary countries, federal ones often put public health legislation in the hands of the states and territories *vide* Australia [6].

In Italy, the introduction of mandatory COVID-19 vaccination was explained by the government as a desire to ensure "the greatest possible protection of both medical and paramedical personnel, as well as individuals in environments that may be at greater risk of infection" [7].

Some countries, such as Tajikistan and Turkmenistan, on the other hand, have introduced mandatory universal vaccination. In both countries, vaccination is mandatory for all citizens over 18 years of age, and the pandemic approach of the authorities is the most restrictive in the world [8]. There are also countries where a vaccination requirement has been established for those who intend to visit or work in certain places: such policies have been implemented in Saudi Arabia and Pakistan. Saudi Arabia implemented a "no vaccination, no work" policy, which applies to both the state and private sectors of the economy. There is also the fourth and largest group of countries, including Poland, in which an individual makes a sovereign decision whether or not to get vaccinated.

When faced with reports of increasingly contagious strains of SARS-CoV-2, such as the Delta variant, an increasing number of researchers are wondering whether implementing mandatory vaccination is justified and what the implications of this very controversial remedy would be.

Undoubtedly, public authorities in most countries around the world, particularly in democracies, avoid implementing this measure that interferes with the personal rights of an individual, aimed at reducing the risk of infection. Objections result both from an individualistic approach to human rights in some democratic countries and from political and religious beliefs of citizens. As a counterpoint, we should emphasise that the views of some researchers considering the introduction of mandatory vaccination are based on the belief that the more people get vaccinated, the faster herd immunity will be achieved.

In doctrine Daniel Graeber, Christoph Schmidt-Petri and

Carsten Schöeder point out that an argument for mandatory vaccination is the presence of "free riders", i.e. individuals who take advantage of the reduced risk of disease achieved by other people's vaccination, but do not wish to vaccinate themselves. The above-mentioned researchers emphasise that those who have decided to get vaccinated "have incurred personal costs in the form of discomfort or money" [9]. According to the authors, a mandatory vaccination policy could prevent such behaviour. However, they recognise other factors that accompany vaccination, such as potential side effects and vaccine ineffectiveness.

An exemplification of the challenges faced by public authorities in most countries in deciding whether to introduce vaccination mandates, regardless of their scale, is represented in the words of Ryszard Piotrowski. He points out that when considering the use of compulsion in the sphere of health, in the Polish constitutional system, "[...] constitutional reservations would certainly arise, first of all whether the introduction of mandatory vaccination is necessary and whether it is proportional; in other words, whether the good that we are sacrificing, in this case freedom, is really less important than the good that we are, perhaps not very effectively, protecting in this way, that is, public health. Opinions on this issue would certainly be divided. Our Constitution defines personal liberty individualistically, not collectivistically. [...] Coercion is the worst argument, and it sets a precedent for creating totalitarian solutions. Control over the individual will greatly expand, and then we may find that human rights also become victims of the virus" [10].

It is interesting to note, however, the appearance of a polemic voice with the view expressed by Ryszard Piotrowski. According to Łukasz Korzeniowski, the introduction of mandatory vaccination against SARS-CoV-2 infection would not weaken the human rights system. He points out: "If someone were to argue that they are contrary to the Constitution of the Republic of Poland, they would thereby undermine legality of mandatory vaccinations against diphtheria, tuberculosis, whooping cough, mumps, rubella, which, after all, have been with us for quite a long time. [...] COVID-19 would become just another infectious disease covered by mandatory vaccination. Since we are obliged to vaccinate against mumps or tetanus, wouldn't it make sense to implement mandatory vaccination against COVID-19, a disease which has totally changed our lives in recent months, and which in Poland has caused the greatest number of deaths since World War II?" [11]. Following the proposed reasoning, the content of Article 2 of the Regulation of the Minister of Health of 18 August 2011 on Mandatory Preventive Vaccination should be amended and the list of infectious diseases subject to mandatory preventive vaccination should be expanded [12]. On the basis of the statutory authorisation contained in Article 17(10) of the Act of 5 December 2008 on the Prevention and Control of Infections and Infectious Diseases in Humans, it is the Minister of Health who determines [13] both the list of infectious diseases covered by the preventive vaccination mandate and persons or groups of persons obliged to undergo mandatory preventive vaccination against infectious diseases.

Referring to the very broad, long expanded catalogue of human rights, which in the form of many international agreements has been introduced into the legal systems of most countries in the world, we need to recall that one of the fundamental rights underlying the entire system is the right to the protection of individual health, stipulated in Article 12(1) of the International Covenant on Economic, Social and Cultural Rights. "The States party to the [...] Covenant recognise the right of everyone to the enjoyment of the highest attainable standard of physical and mental health" [14]. Robert Tabaszewski wrote about the significance of Article 12 of the ICESCR, pointing out that "Article 12 in Part III of the ICESCR establishes social rights to health, which consist of a number of specific rights, including the right to health care and the right to participate in a universal health insurance system. Thus, for the first time, the right to health care has been included *expressis verbis* in the catalogue of conventionally protected human rights" [15].

The right to health care defined in this way is an emanation of human dignity, as well as one of the fundamental rights of an individual included in the model of a democratic state under the rule of law. According to Article 2 of the said article, the states are obliged to fully guarantee this right, and in order to achieve it, the actions of the states "[...] shall include measures necessary to: [...] c) prevent epidemic diseases [...]" [14].

In the approach proposed by Ryszard Piotrowski, mandatory vaccination of citizens is equivalent to restriction of freedom. It is worth to recall the words of English philosopher and economist John Stuart Mill, according to whom "[...] the sole end for which mankind are warranted, individually or collectively, in interfering with the liberty of action of any of their number, is self-protection. The only purpose for which power can be rightfully exercised over any member of a civilised community, against his will, is to prevent harm to others. His own good, either physical or moral, is not a sufficient warrant" [16]. Adam Plichta, referring to this very well-known view of John Stuart Mill, points out that: "John Stuart Mill made it clear that living in a society, the individual has specific duties. He points out that society must be repaid through obeying the law, working, and making sacrifices to defend it. Moreover, society can enforce fulfilment of these duties" [17].

At this point, we must note that although the Convention for the Protection of Human Rights and Fundamental Freedoms, which is very important for the

European culture, guarantees the right to respect for private and family life, it also contains a reservation that "No restrictions shall be placed on the exercise of these rights other than such as are prescribed by law and are necessary in a democratic society in the interests of national security or public safety, […] for the protection of health […]" [18]. It should be noted that some researchers clearly indicate that Article 8 of the Convention can provide a basis for the establishment of mandatory vaccination. For example, according to Anja Krasser: "Interferences within the scope of Article 8 CPHRFF can, however, be justified provided that the benefit to the community outweighs the burden on the individual" [19].

In Poland, this rule is stressed by Mateusz Paplicki, according to whom: "The statutory obligation to undergo vaccination is not a violation of constitutionally guaranteed human freedoms, because these freedoms are not absolute and must take into account the rights of others, including the right to live in a society free from contagious diseases […]" [20].

For the sake of clarity, we need to recall that, in contrast to the views of researchers who argue against mandatory vaccination, Julian Savulescu states in the doctrine, that the introduction of compulsory vaccinations should be considered, under the condition that a total of four premises are met. These are: occurrence of a serious threat to public health, the vaccine being safe and effective, mandatory vaccination offering a better cost-benefit profile compared to other alternatives, and finally, the level of coercion should be proportional [21].

Perhaps we should also consider whether resorting to any form of coercion by public authorities in the realm of pandemic control will be effective. Numerous studies have shown that coercion may bring about effects that are completely different from those intended. We need to note the position presented by Lawrence Gostin, Daniel Salmon, and Heidi Larson, according to whom, coercion can "[…] undermine public support, generating opposition and even decreasing vaccine uptake" [22].

Not without significance in undermining the idea of mandatory vaccination, both sectoral and universal, is the fact that some of the countries whose authorities have chosen to arbitrarily establish vaccination mandates are non-liberal countries. For example, the aforementioned authoritarian Turkmenistan is ranked infamously second last on the list of countries compiled by *Freedom House* which positions countries in terms of their human rights access [23]. According to the *Freedom House* index, Turkmenistan observes only two civil rights, while Poland is credited with the presence of 34 political rights and 48 civil liberties.

It seems that the essence of the problems and controversies related to possible implementation of mandatory SARS-CoV-2 vaccination is not so much in the nature of a dispute with a legal basis, because, as has been shown, the legal systems of individual countries are able, in accordance with the convention obligations, to establish such a mandate, but concerns the political and social, and even cultural dimension of the issue. Not without significance for consideration of the legitimacy of mandatory vaccination is also the fact that the coronavirus pandemic concerns a new health threat and, associated with it, the presence of newly produced vaccines and distrust in their effectiveness on the part of citizens. These negative processes are aroused by the enormous amount of false information circulating in the media. Finally, the noticeably reduced credibility of the World Health Organization is important for the effectiveness of actions taken from March 2020 to limit the reach and impact of the coronavirus. It has been accused by the authorities of countries such as Japan and the United States of not providing enough effective information on the scale of the threat posed by the coronavirus. Hence, perhaps the words formulated by Italian researchers: Paola Frati, Raffaele La Russa, Nicola Di Fazio, Zoe Del Fante, Giuseppe Delogu and Vittorio Fineschi, remain true. In their opinion "as the vaccination program continues, social norms about COVID-19 vaccines will become more deep-rooted, people will see that their friends, colleagues and loved ones have been vaccinated and are fine. Levels of hesitancy are then likely to decrease" [24].

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THE COURSE OF TICK-BORNE ENCEPHALITIS BASED ON A CASE REPORT

Przebieg kleszczowego zapalenia mózgu na podstawie opisu przypadku

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Streszczenie: Kleszczowe zapalenie mózgu jest najczęstszą wirusową chorobą przenoszoną przez kleszcze w Polsce. Dokładna liczba przypadków jest znacznie niedoszacowana z powodu rzadko wykonywanych badań w tym kierunku podczas diagnostyki chorób infekcyjnych wskazujących na zajęcie ośrodkowego układu nerwowego. Objawy kleszczowego zapalenia mózgu są niespecyficzne. Badanie stężenia przeciwciał w surowicy krwi w kierunku kleszczowego zapalenia mózgu należy rozważyć w sytuacji wystąpienia choroby w okresie czerwiec-październik oraz dodatniego wywiadu w kierunku ukłucia przez kleszcza. Lepsza wykrywalność zakażenia wirusem kleszczowego zapalenia mózgu pozwoliłaby na redukcję liczby wykonywanych badań oraz stosowanego leczenia farmakologicznego, w tym zbędnej antybiotykoterapii.

Abstract: Tick-borne encephalitis (TBE) is the most common viral disease transmitted by ticks in Poland. The exact number of cases is significantly underestimated due to the fact that patients presenting with infectious diseases and signs of the involvement of the central nervous system are rarely tested for TBE. The symptoms of tick-borne encephalitis are non-specific. Determination of the blood serum concentration of TBE antibodies in patients who develop the disease in June–October and have a positive history of tick bite should be considered. Better detection of TBE infection would make reduction of the number of tests performed and the amount of pharmacotherapy applied possible, including unnecessary antibiotic therapy.

Słowa kluczowe: neuroinfekcja, kleszczowe zapalenie mózgu, choroby odkleszczowe, wirus kleszczowego zapalenia mózgu.

Key words: neuroinfection, tick-borne encephalitis, tick-borne encephalitis virus, tick-borne diseases.

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Introduction

Tick-borne encephalitis (TBE, Lat. *encephalitis ixodica*) is a disease caused by Central European encephalitis virus. It belongs to the *Flaviviridae* family, which consists of RNA viruses. It is introduced into the human body via a bite by an infected tick. In Poland, the TBE virus is transmitted by the castor bean tick (*Ixodes ricinus*). The virus reservoir are small rodents and ticks themselves [1, 2]. The infection is also spread by the oral route through consumption of thermal untreated milk from infected animals, mainly goats and sheep and less frequently cows, in the viraemic phase. The virus becomes inactivated during pasteurisation [3, 4, 5]. There is no possibility of human-to-human transmission [1].

In 2019, according to the data of the National Institute of Public Health – National Institute of Hygiene, the incidence of TBE in Poland was 0.69 cases/100,000/year [6]. According to the WHO definition, TBE-endemic areas are districts where more than 5 cases/100,000 persons/year are detected [7]. In our country, this definition is met only by the Podlaskie province. The actual number of cases is probably higher due to rare TBE testing, because the incidence is higher in most of Poland's neighbouring countries [8, 9]. For this reason, the entire area of Poland should be considered to be threatened by the occurrence of TBE. The highest TBE incidence in Poland occurs from May to October with a characteristic increase in July followed by October [10, 11].

Table 1. Comparison of the frequency of tick-borne diseases in Poland. Status as of 2017 [13].

Tick-borne diseases in Poland (number of cases)				
Lyme disease	**TBE**	**tularaemia**	**anaplasmosis**	**babesiosis**
21,516	282	30	4	1

Ticks are transmitters of various diseases. In Poland, these include Lyme disease, TBE and occasionally tularaemia, anaplasmosis and babesiosis [12] – Table 1.

The TBE virus initially multiplies in the skin and surrounding lymph nodes. It is delivered with the lymph to the cells of various organs. This is the phase of primary viraemia, which is responsible for the symptoms of the first phase. Then, cytotoxic lymphocytes eliminate the virus from the body. In some cases, the body's response is inadequate and secondary viraemia occurs. As a result, the virus enters neurons and glial cells through the endothelium of blood vessels in the brain [1].

The incubation period is 4–28 days, with an average of 7 days. In endemic areas, it is estimated that 70–95% of persons passes the infection subclinically or completely asymptomatically. Most often, the disease occurs suddenly and has two phases [1, 8, 10]:

- **First (prodrome) phase**: flu-like symptoms lasting up to 7 days: malaise, weakness, apathy, fever (usually not exceeding 38°C), upper respiratory tract inflammation, headache, muscle and joint pain, vomiting, nausea, diarrhoea. In laboratory tests: leukopenia, thrombocytopenia and slightly elevated transaminases.
- **Second (neurological) phase – neuroinfection**: symptoms of central nervous system involvement, such as fever up to 40°C, malaise, vomiting, nausea, headache and dizziness, meningeal symptoms, convulsions, consciousness disorders, focal signs, unilateral hearing loss, tinnitus – Table 2.

Table 2. Comparison of the frequency of occurrence of particular symptoms in patients with TBE in the group of adults and children. Own compilation based on [14].

Prevalence of symptoms in adults and children		
Symptom	**Adults**	**Children**
Headache	98%	90%
Vomiting	50%	60%
Fatigue	90%	40%
Malaise	83%	15%
Muscle pains	38%	10%
Joint pains	27%	0%
Dizziness	47%	10%
Photophobia	55%	10%
Fever > 38°C	98%	100%
Meningeal symptoms	85%	90%
Tremor	50%	25%
Paresis	3%	0%

The neurological phase can take the form of the following medical conditions [8, 10, 14, 15]:

- **meningitis** (45–49% of adults, 69–78% of children): occurs most often and is the mildest form. It develops with typical manifestations of lymphocytic meningitis: fever, headache, nausea, vomiting.
- **meningoencephalitis** (45% of adults, 21–30% of children): with a more acute course and symptoms of encephalitis. The most common manifestation is ataxia as a result of cerebellar involvement. In addition, symptoms such as impaired consciousness and cranial nerve palsy may occur.
- **meningoencephalitis + myelitis** (5% of adults, 1% of children): the most severe form. In addition to the symptoms listed above, there are symptoms of injury to the anterior horns of the spinal cord and flaccid paralysis of the limbs. Prognosis is worse in the case of involvement of the medulla oblongata and brainstem. The most severe complication of this form is respiratory muscle paralysis.
- **meningoencephalitis + myelitis with spinal nerve root involvements** (5% of adults): characterised by meningeal symptoms and focal damage of the CNS, nerve roots and peripheral nerves. In most cases, brachial plexus injury occurs, causing paresis of the upper limb, which regresses slowly and is not always completely relieved.

Criteria for the diagnosis of TBE are presented in Table 3.

There is no specific treatment for TBE. Despite ongoing research on an antiviral drug against TBE, no product has been registered to date [15, 17].

The prognosis in most patients is good, with complete resolution of symptoms. In severe cases of encephalomyelitis, pareses, sensory disturbances and impairment of intellectual functions, such as focussing attention and memory, may persist for several months [1, 8]. Mortality in adults in Europe is estimated at 1–4% [18], in Poland at less than 2% [11].

Prophylaxis of tick-borne encephalitis involves, first of all, protection against tick bites by avoiding the areas of increased risk of TBE, the use of repellents (preferably containing DEET or permethrin) and appropriate clothing with long sleeves and legs, hats, high shoes and socks. Light-coloured clothing is recommended. After returning from a forest or meadow, the skin of the whole body should be inspected each time. In the case of a tick bite, the tick should be mechanically removed as soon as

possible, because the virus is contained in its salivary glands and infection can occur within minutes after the bite [1, 2].

Table 3. Criteria for the diagnosis of TBE according to the National Institute of Public Health (PZH) [16].

Criteria for diagnosis of TBE	
Clinical criteria of TBE	symptoms of CNS inflammation
Epidemiological criteria	exposure through the same source (non-pasteurised dairy products)
Laboratory criteria for a confirmed case	• presence of serum IgM- and IgG-specific antibodies • presence of serum IgM and IgG antibodies in the cerebrospinal fluid • seroconversion or a 4-fold increase in the titre of TBE-specific antibodies in two serum samples • detection of TBE virus nucleic acid in clinical specimens • isolation of the virus from clinical specimens
Laboratory criteria for a probable case	detection of TBE-specific IgM antibodies in a single serum sample

Probable case of TBE: clinical criteria and at least one of two criteria, epidemiological or laboratory criteria of a probable case.
Confirmed case of TBE: clinical criteria and one of the five criteria for a confirmed case.

The most effective way to avoid infection is to undergo preventive vaccinations. It is recommended for people living in endemic areas or planning to travel to these regions (in such a case a vaccination cycle should start several months beforehand). There are two inactivated vaccines available in Poland, that provide protection for several years. Both can be administered to children from the age of one. They are administered in two doses, 4–12 weeks apart, followed by a third dose after 9–12 months. A booster dose is recommended after three years [8, 11, 19, 20].

Case study

A 5-year-old boy with autism and allergy was admitted to the Department of Pediatrics, Nephrology, and Paediatric Allergology of the Military Institute of Medicine in July 2021 because of low-grade fever, weakness, headache lasting a week, and decreased appetite over the previous month. A tick bite was observed in early June. In mid-June 2021, the child was hospitalised in another hospital for mild acute myositis in the course of a viral infection accompanied by fever and signs of upper respiratory tract infection. At that time, tests showed leukopenia and elevated creatine kinase values. Symptomatic treatment was administered and improvement was achieved. Two weeks after hospitalisation, fever recurred, accompanied by headache and vomiting. Sinusitis was suspected on an outpatient basis and cefuroxime axetil was introduced.

On admission to the Department of Paediatrics, the child was in good general condition, no significant abnormalities were found. On neurological examination: meningeal signs, Romberg's test and finger-nose test were negative. Muscle strength in the upper and lower limbs was normal. On examination of the visual organ, the eye movements were normal, the pupils were equal, round and responsive to light. Somaesthesia was preserved. The 5th nerve outlets were not painful.

In laboratory tests, inflammatory markers were not elevated (CRP <0.1mg/dl, ESR 11 mm, leukocytes 10,120). Serum electrolyte and water balance were normal (sodium 134 mmol/L, potassium 5.0 mmol/L). Blood count showed no significant abnormalities (WBC 10,120, RBC 4.62 million, HGB 12.5 g/dl, HCT 36%, MCV 78fL, PLT 378,000, LYMPH 25.8%, NEUT 61%, MONO 9.5%, EO 2.8%, BASO 0.5%). Liver and kidney function tests were normal (ALT 16 U/l, AST 28 U/l, ALP 129 U/L, urea 34 mg/dl, creatinine 0.5 mg/dl). Creatine kinase CK-MB concentration was elevated (32 U/l). Other markers of myocardial damage were not elevated. Serology (ELISA method) excluded *Borrelia*, *Yersinia enterocolitica* and *Mycoplasma pneumoniae* infections. No signs of infection were detected in the urine test. No abnormalities were seen on chest radiography. The ultrasound examination of the abdominal cavity showed single reactive lymph nodes up to 8.5 mm in size, otherwise without any abnormalities. Parasitic infestation of the gastrointestinal tract was excluded. The PCR test for SARS-CoV-2 was negative.

A contrast magnetic resonance (MR) scan of the head was performed. Focal lesions in the brain, cerebellum and brainstem and features of increased cerebrospinal fluid pressure were excluded. The only abnormality detected on MR was thickening of the mucosa of the left nasal concha. Because of the lack of abnormalities on imaging examinations and in the presence of symptoms and positive history of tick bite, a serum antibody test for tick-borne encephalitis virus was performed after consultation with a neurologist. A positive result of IgM class antibodies against tick-borne encephalitis [4.4 Ratio (>1.1)] was obtained.

After a seven-day hospitalisation and symptomatic treatment, the complaints reported on admission subsided. The boy was discharged home in good general condition with recommendations for further multispecialist care.

Discussion

In many respects, the presented case fits a typical picture of tick-borne encephalitis. In 90% of children, the disease has a biphasic course [8]. In the patient, the first phase of the disease began in June with flu-like symptoms, fever and leucopenia. The time between the first and second phase in children is on average 6–14.5 days. The second phase began after about two weeks, which also corresponds with the typical picture of the disease [8, 14]. The symptoms of the second phase coincide with those most commonly reported by patients: low-grade fever, weakness, lack of appetite, headache, vomiting.

In addition, the time from the tick bite to the first symptoms of the disease in the described patient also fits the typical picture of the disease. In children, the average TBE incubation period is 12 days [8, 14].

The course of tick-borne encephalitis in children is usually milder than in adults; however, severe forms develop in one third of cases [8, 10, 14]. The most common form in children is asymptomatic, meningitic or meningoencephalitic [21]. In the past, the disease was considered benign due to rare cases of acute complications, death or significant disability. More recent studies indicate that only a proportion of children are completely cured [8].

In children, the infection often presents non-specifically with malaise and fever, which makes diagnosis difficult. We should keep in mind that children may suffer from that disease as early as in the first year of life, which also complicates the diagnosis due to limited communication. The youngest reported case of a child suffering from TBE is a 17-day-old infant in Austria [22]. A case of a child with atypical severe course in the form of epileptic seizures and productive symptoms has also been described [21]. The heterogeneity of the clinical picture should make physicians particularly vigilant when diagnosing paediatric patients. It is estimated that 10% of meningitis cases in children in endemic regions are caused by the TBE virus [22].

Complications in the paediatric population tend to be cognitive-behavioural, in contrast to adults with predominating neurological complications [23]. Cognitive dysfunction and subjective complaints have been proven to occur one year after the illness [24]. Parents of children who have contracted TBE note fatigue, headache, irritability and memory impairment in long-term follow-up [22]. Studies have also shown that children who have suffered from TBE have poorer psychomotor performance and impaired attention, which may translate into poorer school results [24, 25, 26]. Younger children may have difficulty describing their symptoms. After-effects of TBE in children and adults are summarised in Table 4.

Table 4. Incidence of complications post-TBE infection in adults and children [8].

Complications in adults and children %		
Complication	**Adults**	**Children**
Chronic headache	10.8–22.6	11–14
Palsies	2.6–11	no data/not tested
Ataxia and tremor	2.4–14.5	<1
Post encephalitic Syndrome (PES)	40–50	no data/not tested
memory disorders	10.8–19.7	50
concentration disorders	8.4–15.4	26–43
mood disorders	18.8	45
cognitive disorders	11	12–69
fatigue	21.7	45
hearing loss	2.4	no data/not tested
sensory impairment	2.4	no data/not tested
hypersensitivity to sounds and light	1.2	3–11

Because of possible long-term complications, a child with TBE should be placed under paediatric, psychological, and otolaryngologic care to monitor their psychological development and possible hearing loss.

A serum test for specific antibodies to the TBE virus is a relatively simple and inexpensive test. Therefore, it should be performed in the differential diagnosis of neuroinfection. This is especially true when accompanied by the characteristic history of TBE: typical symptoms, biphasic nature of the disease, onset of the disease in June–October, spending time in a heavily forested area, and tick bite. It should be kept in mind that 1/3 of the patients do not remember a tick bite [8].

A positive test result can reduce the number of procedures and examinations performed, shorten the time until diagnosis and prevent the patient from being exposed to unnecessary pharmacological treatment. Such management undoubtedly improves patient comfort and reduces the cost of diagnostics and treatment.

The best solution is universal application of the principle: prevention is better than cure. Children – as young,

developing organisms exposed to complications in the form of neurological developmental disorders – should be covered by vaccine prophylaxis. Both vaccines available in Poland can be used in children from the age of one. The vaccine protects also against food-borne infection [20]. Data from reports from sanitary and epidemiological stations in 2015–2019 in Poland show an increasing number of vaccinated people among both adults and children, but the vaccination rate in Poland still remains low [11].

Conclusions

In case of characteristic symptoms and history indicating a tick bite, TBE needs to be excluded. This may contribute to a reduced number of unnecessary procedures, lower treatment costs, and implementation of appropriate care aimed at diagnosing and treating complications of TBE.

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REGARDING THE ARTICLE BY STANLEY W. RACZEK – REFLECTIONS OF A "TRAITOR", PUBLISHED IN THE 2/2021 ISSUE OF VOL. 99

Dotyczy artykułu Stanley'a W. Raczka – Refleksje „zdrajcy", opublikowa nego w wydaniu 2/2021 vol . 99

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Streszczenie: Informacje uzupełniające do kariery zawodowej dr. Raczka

Abstract: Additional information about Dr. Stanley Raczek

Słowa kluczowe: dr Stanley Raczek, polonijno-polska współpraca psychiatryczna.

Key words: Dr Stanley Raczek, trans-Atlantic psychiatric collaboration.

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It is good that the article about the professional activity and success of Staszek Raczek MD was published while he is still alive. Also very valuable is his own perspective on his trials and tribulations, describing and complementing the achievements of just one Polish-born U.S. citizen, whose fate sent him to the other side of the Atlantic. The predominantly "uniform" aspect only adds the flavour of the "adventure at command" and his personal *companion article* has special significance for me as I was often an active participant in many of the activities of Staszek, who is my "colleague".

Stanisław Raczek MD was (and despite his formal retirement still is) the initiator and social soul of all Polonia psychiatric meetings. He himself concentrates on the military aspect, because this was his everyday work. He describes establishing first contacts and official cooperation with Polish military psychiatrists since 1993. But it all originated in 1987, when at the annual meeting of the American Psychiatric Association (APA) in Chicago many of us attended a lecture held by prof. Andrzej Piotrowski on alcohol problems in Poland. When they heard Polish speech in the dark conference room, this group of participants spontaneously decided to invite prof. Piotrowski to meet privately over tea and coffee. At a large, round (!) table, it turned out that each of us knew several other Polish psychiatrists working in the USA or neighbouring Canada. At this meeting, the "initiative group" decided to formalise somehow at the next APA convention in Montreal, Canada, in 1988.

And so it happened. During the year, we drafted the statutes of our organization "Association of Polish Psychiatrists and Neurologists in America" and established the membership fees. We elected the first authorities and the APP-NA Newsletter, initially published 3–4 times a year in the "samizdat" system, was now a fact. As an affiliated organisation, we operated under the umbrella of the APA, since most of us belonged to it and the annual meetings held in large cities always attracted thousands of psychiatrists from all over the world. Usually at these conventions you could always run into someone else who spoke Polish. We also agreed that during APA conventions, we would gather every Tuesday evening for a formal organisational meeting, always ending with a good dinner for all participants and their families.

Shortly thereafter, the long-awaited transformation of the political system in Poland, which was being forced on the communist authorities, began. It was natural for us to get involved in this process. In order to familiarise ourselves with the needs and expectations of our Polish colleagues-psychiatrists, we organised two trips to Poland with the support of the Upjohn pharmaceutical company, then having its headquarters in my home state of Michigan. In 1992, "Staszek & Staszek" were joined by paediatric psychiatrist, prof. Maria Paluszny (who lived in Michigan, but who worked in Toledo, Ohio) and we made a tour of large Polish psychiatric hospitals: Tworki, Kędzierzyn, Kochanówka and Abramowice. During our next trip, in 1993, we were joined by Elżbieta Wirkowska MD, a psychiatrist and neurologist from New York. We visited the academic centres of Polish psychiatry: Poznań, Krakow, Warsaw, Gdańsk, Lublin, Łódź, and Szczecin. At that time, I also conducted a formal survey among the participants of all of our meetings, in order to

gain a degree of objectivity and to establish a ranking of psychiatric needs, which at first were very numerous.

We also had a chance to meet at Congresses of the Medical Polonia from around the World, organised on average every three years, including the first, spontaneously organised one in Częstochowa on 19–23 June 1991 (Photo 1.). To date, there have been ten such Polonia Medical Congresses organised in large cities in Poland.

The contribution and personal chapter of Staszek Raczek MD in the "History of Medicine and Military Healthcare" is a good beginning. The period after World War II that Poland went through and aspirations of psychiatrists who somehow managed to escape the omnipotent control of the imposed system is certainly an underdeveloped topic, which is a pity! One of the first leaders of our organisation was Roman Orłowski MD, unfortunately, a deceased Polish military psychiatrist from Łódź, who left Poland with his wife after the memorable events of 1968. After having his medical degree recognised, Roman Orłowski MD worked in the Michigan State Penitentiary in Jackson until his retirement.

The imposition of martial law in Poland is yet another historical aspect that changed the fate of thousands of Poles (including mine) overnight. If you were a tourist outside of Poland before 13 December 1981, you woke up on that memorable Sunday to a completely different and unplanned reality that few were prepared for. But this is a topic for a separate study, perhaps after my own retirement in a few years.

The history of collaboration among Polish, Polonia, and Native American psychiatrists, both military and civilian, is "still alive" and being recorded on an ongoing basis. New communication technologies, including virtual ones (necessitated by COVID), provide other, almost instantaneous opportunities to share experiences. But nothing can replace personal, socialising interactions, conference presentations during congresses and medical conventions of all kinds, as well as those less formal, backstage and social ones during evening dinners, banquets or sometimes around a campfire outdoors, later transforming into long "night Polish talks". Modified military and medical (and psychiatric) cooperation is also possible, as the US military medical services still employ a large number of medical personnel with decidedly Polish roots.

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REPORT FROM 53RD ANNUAL MEETING OF EUROPEAN SOCIETY FOR PAEDIATRIC NEPHROLOGY

53. doroczna Konferencja Europejskiego Towarzystwa Nefrologii Dziecięcej

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Streszczenie: Artykuł dotyczy sprawozdania z Konferencji ESPN, która odbyła się w Amsterdamie w 2021 r.

Abstract: The article presents the report on the ESPN Conference in Amsterdam in 2021.

Słowa kluczowe: Konferencja, Europejskie Towarzystwo Nefrologii Dziecięcej, choroby nerek.

Key words: Conference, ESPN, renal diseases.

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The 53rd Annual Conference of the European Society for Paediatric Nephrology (ESPN) was held in a hybrid format on 16–19 September 2021. Lectures and live presentations were held at the congress centre in Amsterdam, while many of them were presented in an online format due to the SARS-CoV-2 pandemic.

The conference was devoted to the broad issue of kidney and urinary tract diseases in the paediatric population. Lectures and reports were presented simultaneously in four rooms. Poster presentations were a separate category.

A large group of lectures was devoted to chronic and end-stage renal disease and methods of renal replacement therapy. New and interesting papers on kidney transplantation were presented. A very interesting lecture entitled "*Infection – the price of no rejection?*" was presented by professor Priya Verghese from Ann & Robert H. Lurie Children's Hospital in Chicago. The topic concerned the optimisation of immunosuppressive treatment, which is now so advanced that the problem of transplant rejection seems to be less than the problem of the development of bacterial and viral infections associated with this treatment.

The very interesting lecture "*Retarding progressive kidney failure – what paediatricians can learn from adult nephrologists*" was given by professor Jürgen Flöge from University Hospital in Aachen, Germany. According to the professor, the use of the highest possible doses of RAAS blockers that are tolerated by the patient or allowed by the drug manufacturer should be taken into account when planning nephroprotective therapy in children and adolescents. Only such treatment, according to the professor, may be beneficial in inhibiting the progression of chronic kidney disease.

Interesting reports concerned the problems of urinary tract defects. In the polemic entitled "*Has the term CAKUT outlived its usefulness?*", Adrian Woolf and Nine Knoers presented different approaches to the term CAKUT (*Congenital Anomalies of Kidney and Urinary Tract*), which has been used also in Poland for many years. Professor Woolf expressed the opinion that the term was imprecise and misleading for urologists planning surgical correction of defects, whereas Professor Knoers defended the terminology as useful in the genetic diagnostics of diagnosed abnormalities. The lecture "*Prenatal programming of the kidney*" by professor Michiel Schreuder from Radboud University in Nijmegen, the Netherlands, closed the block. The lecturer emphasised the importance of environmental factors in the development of birth defects and compared them with genetic factors.

In the block devoted to hypertension, Professor Joseph Flynn of Northern Illinois University in Chicago presented the lecture "*Latest in BP Assessment and HTN Management in Pediatrics*". The presentation included considerations of the difficulty of establishing norms for determining normal BP values in a paediatric population, which is usually not threatened by cardiovascular complications. Hence, it is difficult to correlate blood pressure values with the incidence of stroke or myocardial infarction. It is worth mentioning that in the United States the upper limit of normal blood pressure values for 13-year-olds is now 130/80 mmHg, which is far from the European norms based on percentile grids.

Many reports concerned also the problems of glomerulonephritis, treatment of systemic lupus and progress in the therapy of hemolytic uremic syndrome, especially its atypical forms.

As usual in recent years, much attention was paid to markers that could facilitate the diagnosis of kidney and urinary tract diseases. This problem was addressed, among others, in the lecture of Professor Pierre Ronco from Hôpital Tenon, Paris, *"Serum and podocyte markers of membranous nephropathy"*. The professor is well known in the world of nephrology, so I do not have to add that the lecture was both interesting and delivered in a wonderful style.

The lecture "*Draining the oedema: something old, something new, something for you*" by Professor Detlef Bockenhauer from GOSH Hospital in London was devoted to methods of oedema therapy in patients with hypo- and hyper/normovolemia. Professor Bockenhauer stressed the necessity to avoid intravenous infusions of albumin, reminding that, depending on the type of dehydration, such management may lead to the risk of pulmonary oedema on the one hand and deterioration of renal function on the other. He also presented the unreliability of the method of determining the extraction fraction (EF) of sodium in a urine portion as an aid in distinguishing the type of dehydration, using the examples of two of his patients, in whom the calculation gave similar results, although each was a model example of a different type of problem. He recommended that the evaluation should be guided rather by parameters such as pulse rate and blood pressure. Finally, he mentioned the usefulness of the old method of water immersion in the fight against refractory oedema. What is new, however, is the attempt to administer a selective, competitive vasopressin 2-receptor antagonist, tolvaptan, in the treatment of oedema associated with nephrotic syndrome.

Several presentations, such as the report "*GFR estimation in children and adolescents – what is the optimal approach?*" by Professor Hans Pottel from the University of Leuven, concerned new and improved methods of estimating the glomerular filtration rate (eGFR).

The block of reports on ciliopathy included presentation of the preliminary results of tolvaptan treatment in children with renal cystic fibrosis. So far, the drug has been administered to adult patients, so the trials on the treatment of children finally provided hope for progress in the therapy of this defect, for which management has so far consisted of proper hydration and observation of patients. The results are encouraging in terms of inhibiting the growth of cyst size and counteracting the decrease of the glomerular filtration rate. No serious side effects were observed.

Several interesting lectures were devoted to the issue of patients with a single functioning kidney. Conclusions from long-term observations concerned both children with renal agenesis and those who lost an organ or its function due to trauma or disease. The authors of the presented papers unanimously emphasised that patients with only one functioning kidney should be included in long-term follow-up, as this condition poses a threat to their health. An example of such a report is the multicentre study "*Kidney injury in a large cohort of children with solitary functioning kidney*". Its authors (Groen et al.) showed that as many as one third of 982 observed paediatric patients (mean age 15 years) developed features of chronic kidney injury such as: proteinuria, hypertension and decreased glomerular filtration rate.

One of the leading topics of the Conference was devoted to genetically determined rare diseases. Among them, due to the interests of my Nephrology Department, I took particular interest in the issues of primary oxaluria type I. This disease is a rare disorder of glyoxalate metabolism characterised by accumulation of oxalate deposits, initially in the urinary tract and later in the parenchymal organs. It results from a deficiency of glyoxalate aminotransferase (AGT). The clinical picture can lead from symptomatic nephrolithiasis to nephrocalcinosis and end-stage renal failure with systemic symptoms. Only in recent years, promising new drugs based on the iRNA technique have emerged. They are currently in clinical trials. An entire block of topics was devoted to these exciting issues. The first lecture "*Illuminating the patient journey for children with PH1. Challenges, outcomes and unmet needs in the management of PH*" was presented by Professor Justine Bacchetta from the University of Lyon. The next, "*Identifying and managing PH1 in children*" was held by Professor Rezan Topaloğlu from Hacettepe University in Turkey, while new treatments were discussed by Dr. Sander Garrelfs from Amsterdam in his presentation "*Clinical trial updates in PH1*". We also heard a polemic entitled "*iRNA for ALL children with PH1?*", where different points of view were presented by Professor Justine Bacchetta and Professor Shabbir Moocchala from the University of Singapore.

In the block of reports devoted to urinary tract infections, Dr Kjell Tullus from GOSH hospital in London

presented the interesting lecture "*Indications for antibiotic prophylaxis in 2021*". According to the views of recent years, the recommendation was to reduce the use of prophylactic antibiotic therapy as a method with low effectiveness that leads to increasing drug resistance. The presentation of Dr Kavruk from Turkey, "*Is a different follow-up procedure necessary for infants with first febrile urinary tract infection caused by non-E.coli and ESBL producing bacteria?*", questioned, in turn, the necessity of treating an atypical aetiology of infection as an indication to perform micturition cystography. Such a procedure is currently recommended in most studies and diagnostic charts. Finally, in "*Uromodulin and vesico-ureteral reflux. A genetic study*", Dr Silvio Maringhini, showed the association between the rs4293393 genotype and scar formation in the renal parenchyma following urinary tract infection in patients with vesicoureteral reflux.

The posters presented at the Conference included two works by authors from the Department of Paediatrics, Nephrology and Pediatric Allergology from the Military Institute of Medicine in Warsaw. The first, entitled "*The assessment of the usefulness of selected markers in the prognosis of chronic kidney disease in children*", prepared by Agata Będzichowska and Katarzyna Jobs, showed the possible practical usefulness of two tubular markers, NAG and NGAL, in detecting early stages of kidney damage in patients with kidney disease and hyperfiltration. The second work, "*Renal cysts and diabetes syndrome (RCAD) – case report*", prepared by Małgorzata Placzyńska and Katarzyna Jobs, was a case report of a rare disease associated with an HNF1β gene mutation. Moreover, Dr Łukasz Obrycki presented his paper, "*Renal length normative values in children aged 0-18 years – multicenter study*", co-authored by Małgorzata Placzyńska, Małgorzata Sopińska, Katarzyna Jobs and Bolesław Kalicki. This multicentre work aimed at creating norms of kidney length in children from our geographical area. The fact that the work was accepted for publication in *Pediatric Nephrology* indicates that the intention was achieved.

Due to the number of reports and the necessity to select those that could prove most useful in clinical practice, I unfortunately did not manage to listen to all of the interesting presentations. For example, Dr Laura Massella from Rome, was the author of "*Hypertension in cystic kidney diseases*", and Dr Paul Winyard from GOSH Hospital in London presented "*Prenatal detection of cystic kidney disease – what can we tell families?*". The title of the report "*Fighting against kidney diseases with small interfering RNA: opportunities and challenges*" by Professor Bin Yang from the University Hospital of Leicester also suggested that interesting and novel issues were raised. We can only hope that the organisers, as they announced, will at least partially make the materials from the Conference available on the Conference website.

THE AMULET PROJECT – A NEW MODEL OF AMBULATORY TELECARE OF PATIENTS WITH HEART FAILURE

AMULET – nowy model teleopieki ambulatoryjnej nad chorymi z niewydolnością serca

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Streszczenie: Konsorcjum naukowe, którego liderem był Wojskowy Instytut Medyczny, zakończyło realizację projektu AMULET, którego celem było wypracowanie sposobu postępowania w poszpitalnej opiece ambulatoryjnej. Wyniki badań klinicznych modelu AMULET wykazały, że zwiększa on szanse pacjentów na regularną opiekę specjalistyczną i umożliwia wczesne wykrywanie objawów zaostrzenia choroby. Teleopieka realizowana w punktach opieki pielęgniarskiej, z wykorzystaniem szczegółowej oceny hemodynamicznej i wsparcia zdalnego kardiologów, wiązała się z 38-proc. zmniejszeniem liczby hospitalizacji z powodu zaostrzenia niewydolności serca w obserwacji rocznej. Również telemonitoring domowy z wykorzystaniem mobilnego rejestratora kardioimpedancyjnego okazał się dobrze akceptowany przez pacjentów i przydatny klinicznie. Kompleksowy model teleopieki stworzony w projekcie AMULET może być jednym ze sposób zwiększenia dostępu pacjentów z niewydolnością serca do wysokiej jakości opieki medycznej.

Abstract: The scientific consortium, led by the Military Institute of Medicine, completed the AMULET project, with the goal of determining the procedures for post hospital outpatient care. The findings from the clinical studies on the AMULET model demonstrated that it increases patients' chances of receiving specialist care and makes possible detection of early symptoms of disease exacerbation. Telecare provided in nursing care offices, including detailed haemodynamic assessment and remote support from cardiologists, was associated with a reduction of 38% in hospitalisations due to exacerbation of heart failure in one year of observation. Home telemonitoring with the use of a portable impedance cardiograph was also well accepted by patients, and demonstrated clinical usefulness. The comprehensive model of telecare developed in the AMULET project offers a method of increasing the access of patients with heart failure to high-quality medical care.

Słowa kluczowe: niewydolność serca, e-zdrowie, telemedycyna, badanie kliniczne, kardiografia impedancyjna.

Key words: heart failure, e-health, telemedicine, clinical trial, impedance cardiography.

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The scientific consortium, led by the Military Institute of Medicine, completed the AMULET project, with the goal of determining the procedures for post hospital outpatient care. The findings from the clinical studies on the AMULET model demonstrated that it increases patients' chances of receiving specialist care, and makes possible detection of early symptoms of disease exacerbation. Telecare provided in nursing care offices, including detailed haemodynamic assessment and remote support from cardiologists, was associated with a reduction of 38% in hospitalisations due to exacerbation of heart failure in one year of observation. Home telemonitoring with the use of a portable impedance cardiograph was also well accepted by patients, and demonstrated clinical usefulness. The comprehensive model of telecare developed in the AMULET project offers a method of increasing the access of patients with heart failure to high-quality medical care.

Interview with Col. Paweł Krzesiński MD, PhD, Professor of the Military Institute of Medicine, Head of the Department of Cardiology and Internal Medicine of the Central Clinical Hospital of the Ministry of Internal Affairs, Military Institute of Medicine, Poland, Head of the AMULET Project.

What problems in the care of patients with heart failure can the AMULET model that you developed help to solve?

The idea of AMULET project was created as an answer to the shortcomings of healthcare systems: shortage of medical staff and

Col. Paweł Krzesiński MD, PhD

low availability of effective tools for non-invasive haemodynamic monitoring of cardiac patients. Current guidelines for heart failure management indicate the importance of frequent and meticulous patient monitoring in ambulatory care. Meanwhile, a growing number of patients with heart failure in Europe, there are already about 1.4 million of them in Poland alone, requires increasing involvement of health care system resources. As a result, there is an increasing shortage of physicians, which significantly limits the possibility of conducting face-to-face visits with cardiologists with the intensity and quality that patients with heart failure require. These problems are known around the world and effective solutions have been sought for years. The AMULET model combines a number of proven components: involvement of nursing staff, advanced methods for assessing cardiovascular function, and telemedicine solutions that bridge the gap of space and time.

What does the AMULET model of care for patients with heart failure consist of?

In our model, after an episode of exacerbation of heart failure symptoms, the patient visits an outpatient clinic run by nursing staff according to a defined schedule. The visit schedule can, of course, change if, for example, due to their condition, a patient needs more frequent monitoring. A cardiologist is directly involved in the first visits, but later on the cardiologist holds remote consultations and performs a face-to-face examination only if absolutely necessary. This decision depends greatly on key indicators of patient assessment classified according to defined alerts generated by a decision support module. It should be emphasised that nursing assessment is complemented by a detailed assessment of the patient's haemodynamic conditions: their heart rate, blood pressure and hydration status with the use of bioimpedance methods (impedance cardiography and body composition assessment). It is on the basis of these parameters that patients at risk of deterioration are identified. Therefore, it is not an "ordinary" visit, but a thorough assessment of key vital parameters of heart failure. This is a significant innovation and added value to the diagnostic tools previously used in ambulatory care.

What did the results of the randomised, prospective, controlled clinical trial AMULET[1], which were published in the European Journal of Heart Failure, show?

First and foremost, AMULET had a positive primary outcome: in this model telecare reduced the risk of cardiovascular death or urgent hospitalisation due to heart failure symptom exacerbation by 31 percent. Analysis of secondary outcomes showed that this effect resulted from a significant reduction in hospitalisations, both first-time hospitalisations, by 38 percent, and overall hospitalisations, by 36 percent. The results of the study confirmed our assumption that the combination of good nursing care, modern methods of cardiovascular function assessment and remote cardiology consultations with the use of a telemedicine platform created according to clinicians' requirements is a better solution than the current management standard. I would like to emphasise the important role of the decision support module in formulating the medical recommendations – the recorded percentage of compliance in this regard was nearly 90%!

How significant are the results of this study for everyday clinical practice in the diagnosis, therapy, and care of patients with heart failure?

Publication of the AMULET trial results in such a renowned journal as the European Journal of Heart Failure is the proof of recognition of the advantages of this telecare model by the scientific community. One of the main goals of heart failure patient's care is to significantly reduce hospitalisations, and our solution has shown great potential in this regard. The ability to provide the patient with the most modern treatment methods, taking into account their individual needs, represents "tailor-made" care and use of the full potential of 21st century cardiology. I think that the reviewers also appreciated the pragmatic approach to creating such a solution. From the beginning, we were aware that our model cannot be too complicated and full of expensive technologies. The AMULET solution is relatively simple to implement. The clinical trial itself was a "mini implementation", because it was carried out in nine Polish centres. It involved telecare of nearly 300 patients, who attended over 1,500 visits. Undoubtedly, both the technological solutions and the trained nursing and medical teams passed the test. Patient satisfaction, and frequently their positive emotional attachment to this form of care, is another argument for widespread implementation of this model.

How significant is the potential for implementation of the AMULET model in Polish clinical practice?

The number of potential beneficiaries of the AMULET model in Poland is hundreds of thousands of Poles with heart

[1] Effects of an outpatient intervention comprising nurse-led non-invasive assessments, telemedicine support and remote cardiologists' decisions in patients with heart failure (AMULET study): a randomised controlled trial (wiley.com) DOI: https://doi.org/10.1002/ejhf.2358

failure, because, unfortunately, so many citizens of our country are hospitalised at least once a year due to exacerbation of heart failure symptoms. There is a profound need to prevent unplanned hospitalisations in this group of patients because of their negative clinical, social and economic consequences. In fact, it is a priority in outpatient care for patients with heart failure. The proposed solution is universal and can be implemented, for example, in primary care and other medical specialties. We have encouraging cost-effectiveness data. Of course, widespread application requires including this procedure in the range of public benefits or offering it as a medical service by private facilities. This is worth being done, because the results clearly show that implementation of the AMULET model reduces the workload of the cardiology specialist, who is involved only in the necessary activities related to remote issuance of medical recommendations, while maintaining the safety and accurate assessment of the patient. Moreover, the competence of nursing staff, whose central role in telecare is one of the trends of modern medicine, increases. The image value cannot be overlooked either. Implementation of the AMULET model can be a showcase of Polish development in the field of cardiology and e-health.

You have said a lot about telecare in nursing practice. But this is not the only aspect of the AMULET project. What are the results of work and research on the mobile device and the whole system of home telemonitoring?

The second main path of research was to produce and test the home monitoring system in a clinical setting. It should be emphasised that within the AMULET project, we did not create only a miniaturised version imitating stationary devices. We built a complex home telemonitoring system consisting of the following components: a recorder for non-invasive recording of bioimpedance signals compatible with Bluetooth-enabled devices (e.g., smartphone, tablet), a mobile application used to transmit the recorded signal between the measuring device and the electronic platform and to report symptoms, and finally a telemedicine platform where the data are integrated, analysed, and presented to the supervisory staff.

What are the implications of these results for the overall model and for patients?

The results are very promising. Analyses of the user surveys of the system showed a high level of acceptance from patients undergoing monitoring. Patients used the system efficiently and the percentage of examinations sent according to the schedule was very high. In general, no significant problems with the operation of the equipment were reported. In analyses of the results obtained, we found satisfactory consistency between the parameters measured with our device and the reference measurements. The possibility of home monitoring, especially of the chest fluid content, may guarantee even more effective identification of patients at risk of overhydration. With this solution, we bridge the "gap" between ambulatory visits. This is particularly useful in patients prone to rapid deterioration of their health and at particularly sensitive periods of the disease, such as just after an episode of hospitalisation due to symptom exacerbation.

The results of the AMULET project are the effect of several years of work of an interdisciplinary team of physicians, nurses, engineers, computer scientists, promotion and commercialisation specialists. The consortium consisted of units with complementary potential: Military Institute of Medicine, Military Clinical Hospital with the Polyclinic in Wroclaw, Medical University in Wrocław, Medical University of Gdańsk, Military University of Technology, Łukasiewicz Research Network – Institute of Medical Technology and Equipment and Infoscan SA and casusBTL Group businessmen. Within four years, we developed an advanced telemedicine platform, conducted a series of clinical trials and created prototypes of new types of devices.

The AMULET project was co-financed by the National Centre for Research and Development under the third edition of the STRATEGMED program (contract STRATEG-MED3/305274/8/NCBR/2017). The total value of the project was PLN 13,002,322.06.

Where people and institutions interested in the AMULET model can find more information about it?

First of all, the results of the AMULET project are included in the monograph "Ambulatory Telecare in Heart Failure", which is available for free download in electronic form at https://amulet.wim.mil.pl/pl/monografia. It summarises the state of knowledge about the current possibilities and future prospects for the use of telemedicine in the care of patients with heart failure. It presents the problems and needs of patients with heart failure and describes in detail the solutions developed in the AMULET project and the principles of interpretation of measurement results, including the use of the decision support module. It also presents the concept of future use of the AMULET solutions in a broader perspective of IT solutions in health care, taking into account already existing systems. A rich source of knowledge about the project can also be found on the website https://amulet.wim.mil.pl/, where we present a lot of substantive content and audiovisual materials.

Secondly, we want the knowledge about the project to reach a wide audience: medics, patients, business representatives and policymakers. Therefore, in September 2021, we organised an international scientific conference "Innovation in heart failure in telecare and therapy". It was actively participated by the project executors and other prominent Polish experts, including: prof. Przemysław Mitkowski, President of the Polish Cardiac Society, prof. Ryszard Piotrowicz, chairperson of the Informatics and Telemedicine Committee, executive board of the Polish Cardiac Society, and foreign guests: prof. Friedrich Koehler and Mario Klessascheck. We invited a wide range of stakeholders to the conference; 311 participants were registered. Videos were recorded and can be viewed on the conference website: https://amulet.care/.

5th Scientific Congress of the Polish Society of Medical Biology "Biology-Medicine-Therapy"

Will be held at:
Knowledge Transfer Centre of the John Paul II Catholic University of Lublin in Lublin
on 15–17.09.2022

The conference is the next cyclical meeting of distinguished Polish and foreign scientists. Its is aimed mainly at promoting achievements, exchanging experience and integration of scientific, clinical and diagnostic environments for the development of medical biology. Putting the motto of our conference into practice, we will try to make every effort to ensure that conference participants can meet as a group of people whose work contributes to the development of biological, medical and health sciences. They will be nationally and internationally recognised scientists and practitioners who will present the current state of knowledge, their research results and challenges for the future. As in previous years, you will not only listen to interesting lectures, but also have the opportunity to talk with the speakers, and the chance to network in a warm, supportive atmosphere.

More information about the event:
https://www.kul.pl/konferencja-quot-biologia-medycyna-terapia-2022-quot,110664.html

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