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Editorial
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HISTORY OF OTONEUROSURGERY AND SURGICAL TREATMENT OF MENIERE'S DISEASE

ISTORIJAT OTONEUROHIRURGIJE I HIRURŠKOG LEČENJA MENIJEROVE BOLESTI

Dragan DANKUC

Otoneurosurgery

The internal auditory meatus is, in a sense, the meeting point between the territories of the neurosurgeon and the otologist. Having been previously the exclusive zone of the neurosurgeon, the cerebellopontine angle became focus of interest of the otologist as well in the last third of the 20th century. The collaboration between neurosurgeons and otologists in diagnosis and in surgery has produced the best possible results for the patient.

In 1900 Carl Sternberg [1] (1872-1935) from Vienna compiled many of the reported examples of what had come to be called acoustic tumors, and by adding four of his personal observations he gave a very clear pathological description of the lesion, which he regarded a mixed tumor of gliomatous nature (gliofibroma). Based on the post-mortem appearances, he suggested that such lesions might be eligible for operative removal. In the same year, the Russian Constantin von Monakow [2] reported a case of tumor of the auditory nerve which had been correctly diagnosed and localized during life.

Fritz Hartmann [3] (1871-1937) from Graz, Austria, compiled 26 cases in the German literature in 1902 and gave an excellent description of the symptomatology of the tumors situated in what he called the "recessus acustico-cerebellaris". At the same time, the term "cerebellopontine-angle tumor" was introduced by Richard Henneberg [4] (1868-1962) and Max Koch from Berlin. During these early years of the 20th century, surgery of cerebellar tumors was in considerable disarray, largely due to the publication of Ernst von Bergmann's discouraging views on the subject. Nevertheless, the first operations on undoubted acoustic tumors in any considerable number began to be undertaken, and in 1903, Victor Horsley (1857-1916) apparently had a series of six cases and at least one of them made an unusually perfect recovery.

Charles Ballance removed a tumor from the posterior fossa successfully in 1894, but Harvey Cushing [5] (1869-1939) from Boston later doubted that the tumor had been an acoustic neuroma and thought that it was more likely to have been a me-

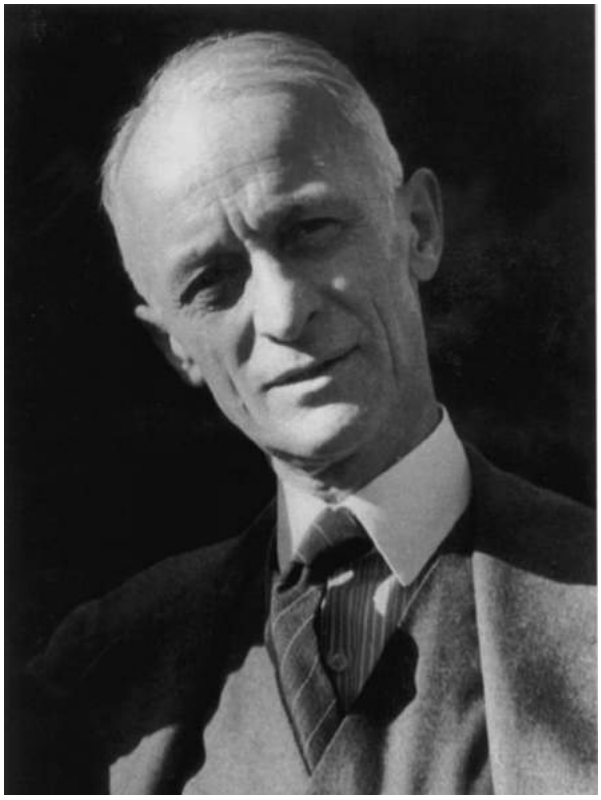

Figure 1. Harvey Cushing (1869-1939)
Slika 1. *Harvi Kušing (1869-1939)*

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Figure 2. Rudolf Panse (1863-1942)
Slika 2. *Rudolf Panse (1863-1942)*

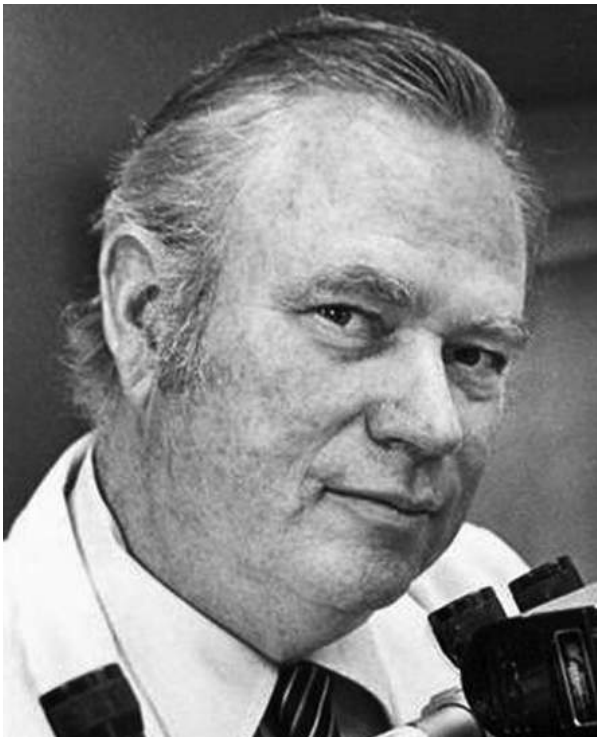

Figure 3. William F. House (1923-2012)
Slika 3. *Vilijam F. Haus (1923-2012)*

ningioma. He, therefore, attributed the first removal of an acoustic neuroma to a Scot, Thomas Annandale (1838-1907), Regius professor of surgery in Edinburgh in 1895. The mortality and morbidity of the early cases were high due to late presentation, poor anesthesia and hemorrhage, usually related to the anterior inferior cerebellar artery, which resulted from the commonly used technique of finger enucleation.

Fedor Krause [6] (1857-1937) from Düsseldorf reported in 1903 that mortality during surgery using the unilateral suboccipital approach was 84%. This was reduced dramatically in Harvey Cushing's [7] first report in 1917 to 30% in his first thirty operations and later to 4 % in his 1932 report. Harvey Cushing had been taught surgery by the great general surgeon William Halsted in Baltimore. William Halsted was the first to introduce the use of rubber gloves in surgery in 1890. Harvey Cushing used bilateral suboccipital approach to the posterior fossa, which enabled not only a wide decompression but also provided the opportunity to explore both sides because it was not always possible to determine the exact location of the lesion preoperatively. Simple audiometry, using tuning forks, Francis Galton's whistle and voice tests, combined with Robert Bárány's caloric test, were the only available tests of the nerve VIII function. The discovery of x-rays by Wilhelm Röntgen in 1895 enabled Salomon Eberhard Henschen [8] (1847-1930) from Sweden to describe widening of the internal auditory meatus opening as a diagnostic sign. In 1911, Harvey Cushing invented silver clips to arrest hemorrhage. A year later, he left Baltimore to accept the position of chair of surgery at Harvard Medical School. He left behind a brilliant pupil Walter Dandy who, only 32 years old at that time, introduced ventriculography in 1918 and pneumoencephalography a year later. These diagnostic procedures enabled the accurate preoperative localization of intracranial masses. Walter Dandy favored the total removal of acoustic tumors via the unilateral suboccipital approach and performed his first surgery of this kind in 1917. By 1925 he had done the total removal in 17 patients.

In 1904, only a year after Fedor Krause's description of the suboccipital approach, Rudolf Panse [9] (1863-1942) from Dresden suggested that an approach through the labyrinth might allow removal of an acoustic neuroma as large as a hen's egg. He defined the anatomical limits of that exposure as the lateral sinus, the jugular bulb, the carotid artery and the temporal lobe. He thought that the facial nerve should be sacrificed but he did concede that with certain tumors it might be possible to re-route the nerve by mobilizing it from the geniculate ganglion to the stylomastoid foramen, thus anticipating the brilliant work of Ugo Fisch by three-quarters of a century. Franciscus Quix [10] (1874-1946) is usually credited with the first removal of an acoustic neuroma by the translabyrinthine approach in 1912. He used a mallet and gouge and removed the entire labyrinth by radical mastoidectomy. He was then stopped by bleeding from the superior petrosal sinus. After that he was able to return, remove the walls of the internal auditory canal and

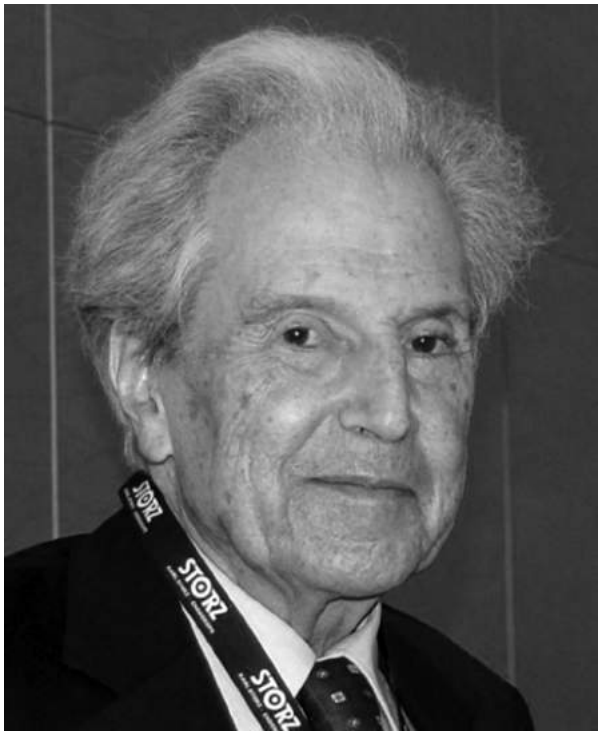

Figure 4. Ugo Fisch (b. 1931)
Slika 4. *Ugo Fiš (r. 1931)*

Figure 5. Charles S. Hallpike (1890-1979)
Slika 5. *Čarls S. Halpajk (1890-1979)*

expose the carotid artery and the tumor. Franciscus Quix predicted that the translabyrinthine approach could bring a small acoustic neuroma within the province of the otologist.

One of the principal causes of mortality in the suboccipital approach was the disturbance of the anterior inferior cerebellar artery. W. J. Atkinson [11] from London published a paper on the significance of this artery in 1949 and pointed out that if it was sacrificed, necrosis of the pons and cerebellar peduncles would ensue. Most neurosurgeons were nevertheless reluctant to recommend surgery unless the tumor was so large as to be causing pressure on the brainstem, or raised intracranial pressure. It was in this climate in 1956 that William House was persuaded to operate on acoustic neuromas. He referred a young fireman, who had been diagnosed to have an acoustic neuroma, to a neurosurgeon. The young man died three days postoperatively. The following year, two further cases were recommended for neurosurgery and although both survived, they suffered facial palsies. After the preliminary study, William House and the neurosurgeon John Doyle [12] performed the first middle cranial fossa approach to the internal auditory meatus using an operating microscope in 1961. The first few tumors were only partially removed. William House worked on the translabyrinthine approach using temporal bones and, since he disagreed with John Doyle, he performed the first operation alone. In 1963, William Hitselberger replaced John Doyle and the first otologist/neurosurgeon team was formed. This was the model which has spread around the world. William House [13] published his first 47 consecutive translabyrinthine cases in 1964.

There were no fatalities and the majority of patients had their facial nerve function preserved. The success of these cases was largely due to the policy of early diagnosis and surgery which depended also on advances in diagnostic techniques in the fields of audiology and radiology, as well as on the microsurgical skills of the otologist and neurosurgeon. Robert Scanlan [14], a radiologist in Los Angeles, developed the technique of meatocisternography in 1964, using contrast medium and polytomography to define the contents of the internal auditory meatus. Robert W. Rand [15] and Theodore L. Kurze, both from Los Angeles, were among the first neurosurgeons who applied microsurgical techniques to remove acoustic neuroma via the suboccipital transmeatal route. They performed it in 1965. This route regained popularity with otologists in the last part of the 20th century because it is possible to remove the tumor and preserve hearing in certain cases.

Los Angeles became Mecca for those wishing to study otoneurosurgery. William House, who deserved to take credit for founding modern otoneurosurgery, trained otologists from all over the world and did not only change the outlook for those patients suffering from cerebellopontine angle tumors, but also opened the whole field of microsurgical skull base surgery which has been in turn developed and popularized by Ugo Fisch [16] (born 1931) from Zurich and others.

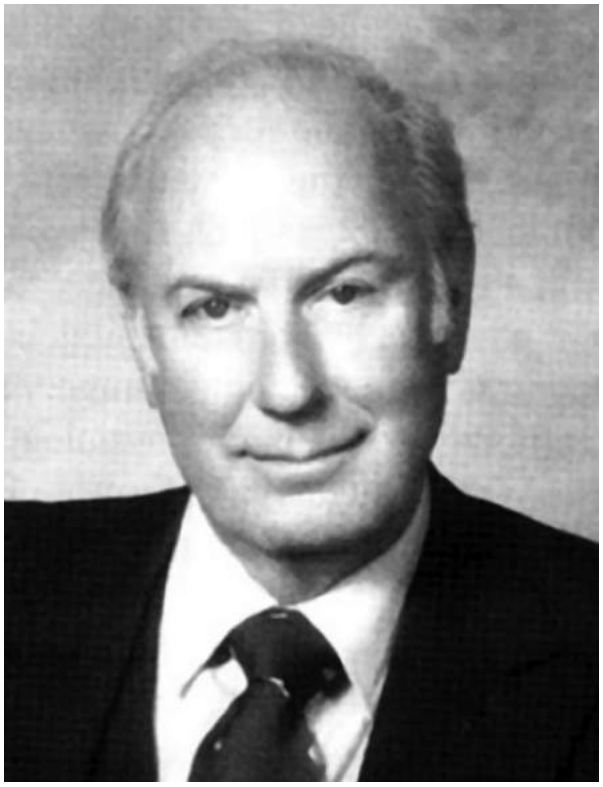

Figure 6. Harold F. Schuknecht (1917-1996)
Slika 6. *Harold F. Šukneht (1917-1996)*

Vestibular schwannomas are relatively rare tumors whose symptoms are based on their location and as the tumor grows, the symptoms usually advance according to Komazec Z et al. [17].

Surgical Treatment of Menière's Disease

After the description by Prosper Menière in 1861, Menière's disease or endolymphatic hydrops has produced the highest number of different forms of treatment because the etiology of the condition of endolymphatic hydrops is still unknown although the pathological process was described by Charles Skinner Hallpike [18] (1890-1979) and Sir Hugh Cairns (1896-1952) in their classic report in 1938.

Treatment has ranged from medical to surgical, the latter being further divided into destructive or conservative procedures.

The French neurologist Jean Martin Charcot [19] (1825-1893) put forward the idea in 1874 that a section of the eighth cranial nerve might arrest the symptom of vertigo. Robert Henry Parry [20] (1858-1943) from Glasgow reported the first successful intracranial section of the eighth nerve in 1904 and in the same year, Sir William Milligan [21] from Manchester and Richard Lake [22] (1861-1948) from London opened the horizontal semicircular canal and vestibule. The great pioneer neurosurgeon Walther Edward Dandy [23, 24] (1886-1946), from Baltimore, described the section of the vestibular nerve in 1928 and by 1941 he had operated on 401 cases with only one fatal outcome. In 1902 Colin Campbell [25], an English surgeon, used the seton knife in the nape of the neck. A few years later, Robert Parry [26] used the same instrument and confirmed its efficacy. Georges Portmann [27] from Bordeaux believed that Menière's disease was due to hypertension of the endolymph and reasoned in 1926, 12 years before the work of Charles Hallpike and Hugh Cairns, that the pressure could be relieved by decompression and drainage of the endolymphatic sac.

The next wave of surgical treatment came in the antibiotic and microscope era. Terence Cawthorne's [28] favorite procedure of all destructive ones was horizontal canal labyrinthotomy. Harold Frederick Schuknecht [29] (1917-1996), from Boston, introduced oval window labyrinthotomy with instillation of streptomycin into the vestibule in 1957. These procedures have been largely replaced by translabyrinthine or total labyrinthectomy, which forms a stage of the translabyrinthine approach to the internal auditory canal first used by Franciscus Hubertus Quix [10] from Utrecht in 1912 and reintroduced by William House from Los Angeles in the early 1960s. The same approach was used by Jack L. Pulec [30] (1932-2003) from Rochester, Minnesota and others to enable section of the vestibular nerves, and the cochlear nerve in case of troublesome tinnitus in the internal auditory canal.

Cervical sympathectomy, one of the conservative procedures, was first proposed by Richard Mogan and C. J. Baumgartner [31] from Los Angeles in 1934 but has not been widely used. Sacculotomy was described by Izak A. Van N. Fick [32] from Pretoria in 1964. His idea was extended in 1967 by D. Thane R. Cody [33] from Rochester, Minnesota who designed a stainless steel tacit that was placed permanently through the footplate of the stapes, ready to rupture a distended saccule which nudged against it, thereby equalizing the pressure between the endolymphatic and perilymphatic systems. Both these procedures carried an unacceptable risk of profound sensorineural deafness. Ultrasound applied to a "blue lined" horizontal semicircular canal was introduced by F. Krejci [34] from Vienna in 1951 and was applied to the round window membrane by Michele Arslan [35] from Padua in 1953. It was refined by John Angell-James [36] (1901-2002) in Bristol in the 1960s; however, poor calibration of the early generators, the risk to the facial nerve and the return of vertigo made the technique less attractive. Cryosurgical treatment of the promontory or the horizontal semicircular canal suggested by William House [37] in 1966 and Robert J. Wolfson [38] from Philadelphia in 1968, respectively, met the similar fate. A few years later, intratympanic gentamicin was recommended to destroy the balance mechanism selectively.

Endolymphatic sac surgery has enjoyed a renaissance and remains a popular conservative treatment. It is generally agreed that some form or drainage of

the sac is desirable, whether into the subarachnoid space using a shunt or into the mastoid cavity using Teflon® or Silastic® film or a capillary tube inserted into Silastic® sponge as recommended by Andrew W. Morrison [39] (1925-2006) from London.

The middle fossa approach to the ear, was first mooted by Pierre Clerc [40] (1910-1966) and Raymond Batisse from Paris in 1954 as a means of access to the first part of the facial nerve. It was popularized by William House [41]) in 1961 and further developed by Ugo Fisch [42] in 1970 as an access to the internal auditory canal for section of the vestibular nerve. The technique is now perhaps less commonly used and attention has been turned again to the posterior fossa approach for vestibular nerve section. With all the thought and ingenuity that has been expended on this one condition would it be too much to hope that in the not too distant future a biochemical cause of Menière's disease will be found and all these exacting surgical procedures will no longer be needed? In the meantime, although the results of endolymphatic surgery and vestibular nerve section seem to be encouraging, particularly in the relief of vertigo, they have not proved to be so effective.

Vestibular evoked myogenic potentials are a neurophysiological method for examining saccular function, the bottom of the vestibular nerve that innervates the sacculus and central vestibular pathways (Lemajić Komazec S, et al) [43].

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RADICAL HYSTERECTOMY IN SURGICAL TREATMENT OF INVASIVE CERVICAL CANCER AT THE DEPARTMENT OF GYNECOLOGY AND OBSTETRICS IN NOVI SAD IN THE PERIOD 1993-2013.

RADIKALNA HISTEREKTOMIJA U HIRURŠKOM LEČENJU INVAZIVNOG KARCINOMA GRLIĆA MATERICE NA NOVOSADSKOJ GINEKOLOŠKO-AKUŠERSKOJ KLINICI U PERIODU 1993–2013. GODINE

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Summary

Introduction. During the period from 1993 - 2013, 175 women with invasive cervical cancer underwent radical hysterectomy sec. Wertheim-Meigs at the Department of Gynecology and Obstetrics, Clinical Center of Vojvodina in Novi Sad. Indications for radical hysterectomy comprise histopathologically confirmed invasive cervical cancer in stages I B 1 – II B according to the International Federation of Gynecology and Obstetrics. **Material and Methods.** Stage of the disease or extent of the disease spread to the adjacent structures was assessed in accordance with the International Federation of Gynecology and Obstetrics staging system from 2009. Exclusion criteria were all other stages of this disease: I A and stages higher than II B, as well as the absence of definite histological confirmation of the cervical cancer (primary endometrial or vaginal cancer which infiltrates the uterine cervix). Prior the operation, the following had to be done: the imaging of pelvis and abdomen, chest X-ray in two directions, electrocardiography, internist and anesthesiological examination. **Results.** The patients' age ranged from 24-79 years (x : 46 years), and the operation duration was 120-300 minutes (x : 210 min.). Stage I B 1 was found in 64.6% of operated patients, 14.8% of the patients were in stage I B 2, 9.1% were in stage II A and 11.4 % were in stage II B. Blood loss during the operation ranged from 50-800 ml (on average 300 ml), and the number of removed lymph nodes per operation was 14-75 (x : 32). Intraoperative and postoperative complications developed in 6.8% of and 17.7% of patients, respectively. Recurrence was reported in 22 (12.5%) patients, most often in paraaortic lymph nodes (3.4%) and parametria (2.8%), while the overall 5-year survival rate was 87% until 2008. **Concluision.** Wertheim-Meigs radical hysterectomy is a basic surgical technique for the treatment of initial stages of invasive cervical cancer.

Key words: Hysterectomy; Uterine Cervical Neoplasms; Endometrial Neoplasms; Neoplasm Invasiveness; Obstetrics and Gynecology Department, Hospital; Gynecologic Surgical Procedures; Neoplasm Staging; Carcinoma + pathology; Diagnosis; Postoperative Complications; Blood Loss, Surgical; Lymph Node Excision; Recurrence; Survival Rate

Sažetak.

Uvod. U toku 20-godišnjeg perioda (1993–2013.), kod 175 žena sa invazivnim karcinomom grlića materice urađena je radikalna histerektomija po metodi Verthajm-Megz na Klinici za ginekologiju i akušerstvo Kliničkog centra Vojvodine u Novom Sadu. Indikaciju za radikalnu histerektomiju predstavljala je histopatološka potvrda invazivnog karcinoma grlića materice u stadijumu IB 1–IIB prema *International Federation of Gynecology and Obstetrics.* **Materijal i metode.** Procena stadijuma i proširenosti bolesti na okolne strukture vršena je primenom sistema stadiranja *International Federation of Gynecology and Obstetrics* iz 2009. godine. Kriterijumi za isključivanje iz istraživanja obuhvatili su sve druge stadijume bolesti: IA i stadijume preko IIB kao i odsustvo definitivne histopatološke potvrde karcinoma grlića materice na definitivnom preparatu (primarni karcinom endometrijuma ili vagine koji je zahvatio grlić materice). Pre operacije insistirali smo na sprovođenju imidžing metoda dijagnostike karlice i abdomena, rendgenskom snimku pluća u dva pravca, elektrokardiogramu, internističkom i anesteziološkom pregledu. **Rezultati.** Uzrast pacijentkinja kretao se 24-79 godina (x : 46 god.), vreme trajanja operacije iznosilo je 120-300 minuta (x : 210 min.). U stadijumu IB 1 bilo je 64,6% operisanih, 14,8% u stadijumu IB 2, 9,1% u stadijumu IIA i 11,4% u stadijumu IIB. Gubitak krvi u toku operacije kretao se 50-800 ml (u proseku 300 ml), broj uklonjenih limfnih čvorova bio je 14-75 (x : 32). Zabeležili smo 6,8% intraoperativnih i 17,7% postoperativnih komplikacija. Recidiv bolesti evidentiran je kod 22 (12,5%) pacijentkinje, najčešće u paraaortalnoj grupi limfnih čvorova 3,4% i u predelu parametrijuma 2,8%, dok je ukupno petogodišnje preživljavanje iznosilo 87% do 2008. godine. **Zaključak.** Radikalna histerektomija po metodi Verthajm-Megz predstavlja osnovnu hirurško tehniku u lečenju početnih stadijuma invazivnog karcinoma grlića materice.

Ključne reči: Histerektomija; Karcinom grlića materice; Karcinom endometrijuma; Invazivnost karcinoma; Ginekološko-akušerska klinika; Ginekološke hirurške tehnike; Stadijumi neoplazmi; Karcinom + patologija; Dijagnoza; Postoperativne komplikacije; Gubitak krvi, hirurški; Ekscizija limfnih čvorova; Rekurentnost; Stopa preživljavanja

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Abbreviations

FIGO – the International Federation of Gynecology and Obstetrics
WHO – the World Health Organization
MR – magnetic resonance
CT – computed tomography
US – ultrasound

Introduction

The basic principles of invasive cervical cancer treatment are precisely defined and depend on the stage, which is determined in accordance with the contemporary International Federation of Gynecology and Obstetrics (FIGO) classification [1, 2]. The choice of surgical procedure is planned depending on the performed diagnostic procedures, which include histopathological cancer diagnosis, rectovaginal gynecological examination, magnetic resonance (MR) examination of pelvic organs and parametria, cystoscopy, rectosigmoidoscopy etc. [3]. The degree and extent of radicality has to be adjusted to the tumor size and volume, presence of lymphovascular invasion, risk of local and lymphogenic dissemination and expected adjuvant therapy [4]. While performing radical surgical procedures, autonomous urinary bladder innervation and vascularization of ureters should be preserved, and parametrial lymph nodes should be removed. The choice of therapeutic procedure is planned individually for each patient depending on the presence of different factors, including the age and general health of the patient, factors regarding malignant tumor, institution where the therapy is administered, as well as the selection of patients [5]. Prognosis of further course and the treatment outcome is based on the detailed histopathological report, which should consist of precise information on the histological type, degree of cellular differentiation, tumor dimensions, depth of stromal invasion, lymphovascular space, tumor propagation beyond the cervix and presence of metastases in other organs, number and infiltration of lymph nodes by groups, length and condition of parametria, length of vaginal cuff, condition of resection margins of the vagina and parametria, the shortest distance between tumor and resection margins [6, 7]. The aim of the study was to present the results of the Wertheim-Meigs surgical treatment of invasive cervical cancer at the Department of Gynecology and Obstetrics, Clinical Center of Vojvodina in Novi Sad in the period from 1993 to 2013.

Material and Methods

Indications for radical hysterectomy include histopathologically confirmed invasive cervical cancer in FIGO stages I B 1 – II B. The stage of the disease or the extent of the involvement of the adjacent structures was assessed in accordance with the FIGO staging system from 2009, whereas the histopathological analysis was performed by a pathologist based on the World Health Organization (WHO) histopathological classification of malignant cervical tumors. Proper indications for radical hysterectomy are the FIGO stages I B1 - I II A, although this operation can also be performed in stages I A 2 and initial II B. Chemotherapy is nowadays administered first in stage I B 2, and if a reduction and decrease of tumor size occurs, surgery is performed [8, 9]. Criteria for data analysis in our study included patients who underwent Wertheim-Meigs radical surgery with histopathologically confirmed cervical cancer in the FIGO stages I B 1, I B 2, II A and II B. The exclusion criteria were all other stages of this disease: I A and stages higher than II B, as well as the absence of definite histological confirmation of the cervical cancer (primary endometrial or vaginal cancer which infiltrates uterine cervix). Our study included 175 patients with invasive cervical cancer in the FIGO stages I B1 – II B, who had been operated at the Department of Gynecology and Obstetrics, Clinical Center of Vojvodina in the period 1993-2013. Radical hysterectomy was always preceded by detailed preoperative preparation and conversation with the patient regarding the nature of the disease, technical aspects of the surgery, risks and possible complications. The patients had to sign the informed consent form thus confirming to accept the risks of operative treatment. Prior to the operation, the following procedures had to be done: the imaging of pelvis and abdomen, chest X-ray in two directions, electrocardiography (ECG), internist and anesthesiology examination. MR examination of pelvis was used because it is the best diagnostic tool for evaluating parametria. This examination was combined with computed tomography (CT) or abdominal ultrasound (US) examination for precise evaluation of kidneys, liver and paraaortic lymph nodes. If a higher grade of the disease (FIGO st. II B – IV) was suspected, an additional diagnostic test was performed, including cystoscopy, rectosygmoidoscopy or CT urography. During the preoperative preparation, the patients' laboratory blood (urea, creatinine, hepatic parameters) and urine tests had to be normal, together with sterile urinoculture and normal vaginal smear. Immediately before the operation, the patients were administered antibiotics (Cephalosporin of II or III generation, dose of 1-2 gr. IV), anticoagulant protection by subcutaneous administration of heparin or fraxiparine and "bandaging" of lower extremities by elastic bandages or compressive stockings up to the level of thighs [10]. Following the completion of surgical treatment and definite histopathological report, all patients were presented to the consilium of gynecologic oncologists at the Department of Gynecology and Obstetrics or Institute for Oncology in Sremska Kamenica. Depending on the presence of negative prognostic factors, the patients were administered adjuvant therapy in accordance with the standard protocols: conventional external beam radiation therapy or internal radiation therapy (brachytherapy), chemotherapy or their different combinations.

Surgical Technique - Wetheim-Meigs Radical Hysterectomy

In general, the applied surgical approach was lower midline laparotomy with correct hemostasis,

which enabled opening of all layers of the anterior abdominal wall. If needed, in obese patients, or when it was necessary to expand radical hysterectomy with additional paraaortic lymphadenectomy, incision was expanded by umbilicus upwards towards xiphoid process. After accessing the pelvic organs, placing automatic anterior abdominal wall retractor (retractor sec. *Balfour*) and isolating bowels from the operative field, the uterus was held by the sawtooth forceps in the region of uterine body. The peritoneum was then cut using electrocauter in the region of round ligament and inserted towards the urinary bladder, thus the avascular layer was reached and the urinary bladder was displaced downwards, with careful hemostasis. Peritoneal incision was then extended bilaterally from the round ligament upwards to the projection of iliac blood vessels, on the right to the insertion to the cecum, and on the left to the sigmoid colon. Retroperitoneal space was reached by forceps and the iliac blood vessels (external iliac artery and vein) were bluntly separated from the ureter, located medially and adjacent to peritoneum. The origin of the uterine artery crossing the ureter on its way to the lateral uterine wall was localized. Below and under the uterine artery there were superficial and deep uterine veins, which opened into internal iliac vein, and together with uterine artery passed through the lateral part of parametrium, dividing the paravesical and pararectal space. Further on, bilateral lymphadenectomy i.e. bilateral removal of the iliac and obturator lymph nodes was performed. The upper borderline of lymphadenectomy was 3-4 cm above the bifurcation of the common iliac artery and vein, whereas the lower borderline was the opening of the deep circumflex iliac vein. What had to be done after the completely performed lymphadenectomy was to isolate and separate the following elements: external iliac artery and vein, obturator nerve, iliopsoas muscle, as shown in **Figure 1**. After lymphadenectomy, the uterine artery was ligatured at the level of junction with the internal iliac artery, and the ureters were extricated from the tunnel through the lateral portion of parametrium. This was done by pulling the cut and ligated uterine end of uterine artery aside, the ureter was separated from the junction with the peritoneum, and the tip of closed scissors was inserted into the tunnel above the ureters. The scissors were placed towards the urinary bladder, while the ureters were gently and bluntly pushed downwards. Next, the finger was inserted into the tunnel in order to expand it, and the ureter was pushed downwards. The right angle clamp was inserted into the tunnel and directed to the surface, and two identical moves were enough to extricate the ureter from its tunnel up to the level of ureterovesical junction, with clamping, cutting and ligating parts of parametrium. The next move was to cut the peritoneum in the region of posterior vaginal wall, and extricate the rectum. Depending on whether the adnexa should be preserved or not, bilateral adnexectomy was performed by double ligation and cutting of the suspensory ligament of the ovary. The lateral and posterior portions of the parametrium with sacrouterine ligaments and paravaginal tissue were caught with Wertheim clamps, cut and ligated. The vagina was opened several millimeters above the bladder junction and ureter orifice, cut around the whole circumference, and the specimen (uterine body and cervix with part of the vagina and parametrium) was removed and sent to histopathological analysis. The vagina was then sutured by a single or continuous suture using slowly absorbable synthetic material of "0" thickness, and the drains were placed [11].

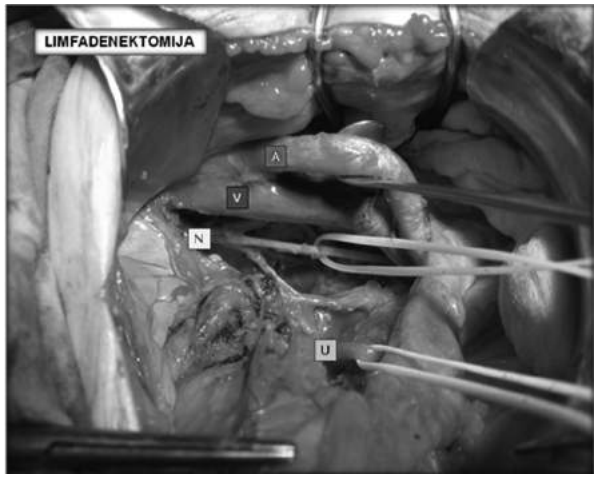
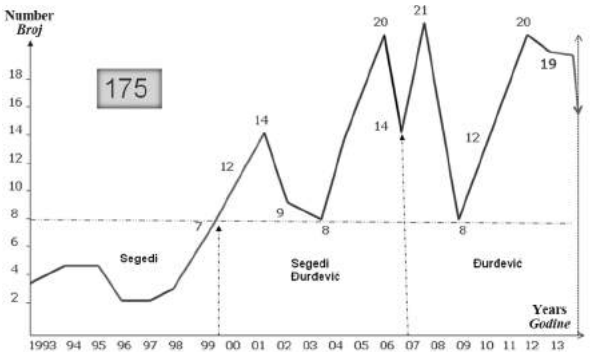


Figure 1. Precisely separated elements after lymphadenectomy: external iliac artery and vein, obturator nerve
Slika 1. *Precizno razdvojeni elementi nakon limfadenektomije*: *arterija i vena ilijaka eksterna, opturatorni nerv*

Results

During the period from 1993 to 2013, 175 women with invasive cervical cancer underwent Wertheim-Meigs surgery at the Department of Gynecology and Obstetrics, Clinical Center of Vojvodina in Novi Sad. **Graph 1** shows the trend analysis of radical hysterectomy. The patients' age ranged from



Graph 1. Trend analysis of radical hysterectomy at the Department of Gynecology and Obstetrics in Novi Sad in the period 1993-2013
Grafikon 1. *Trend primene radikalne histerektomije na Klinici za ginekologiju i akušerstvo u Novom Sadu, period 1993–2013. godine*

Table 1. Stage of the disease (FIGO), degree of cell differentiation (Gr), lymphovascular invasion (LVI) and histopathological classification
Tabela 1. *Stadijum bolesti (FIGO), stepen ćelijske diferencijacije (Gr), limfovaskularna invazija (LVI) i histopatološka klasifikacija*

Characteristics *Karakteristike*	Period: 1991-2013./*Vremenski period: 1991-2013. god.*	
	Number/*Broj*	%
FIGO stage of the disease *FIGO/Stadijum bolesti*		
I B 1	113	64.6
I B 2	26	14.8
II A	16	9.1
II B	20	11.4
Degree of cell differentiation/*Stepen diferencijacije ćelija*		
Gr 1	96	54.8
Gr 2	59	33.7
Gr 3	20	11.4
Lymphovascular invasion/*Limfovaskularna invazija*		
Positive/*Pozitivna*	110	62.8
Negative/*Negativna*	65	37.2
Histopathology/*Histopatologija*		
Planocellular carcinoma/*Planocelularni karcinom*	134	76.6
Adenocarcinoma/*Adenokarcinom*	29	16.6
Other types/*Ostali tipovi*	12	6.9
Total/*Ukupno*	175	100%

24 to 79 years (x : 46 years), and the length of operation was from 120 to 300 minutes (x : 210 min.). The basic characteristics of the patients (FIGO stage of the disease, degree of cell differentiation and histopathological type of tumor) are shown in **Table 1**. Lymphovascular invasion was present in 110 (62.8%) operated patients, and absent in 65 (37.2%). Blood loss during the operation was 50-800 ml (300 ml on average), and the number of lymph nodes removed per operation was 14-75 (x : 32). Positive lymph nodes with the presence of metastases were confirmed in 35 (20%) operated patients, which led to administration of adjuvant radiotherapy. In 12 (6.8%) patients in the FIGO stage I B 1, complete paraaortic lymphadenectomy was performed during the operation, and positive lymph nodes were detected in 5 patients. Three (1.7%) patients with cervical cancer in the FIGO stage I B 1 (2) and II B (1) were pregnant. Radical hysterectomy with "fetus in utero" was performed in 14th and 22nd gestational week in 2 (1.1%) patients, and 1 (0.6%) patient underwent Cesarean section in 35th gestational week, followed

Table 2. Intraoperative and postoperative complications of Wertheim-Meigs radical hysterectomy
Tabela 2. *Intraoperativne i postoperativne komplikacije radikalne histerektomije po metodi Verthajm−Megz*

Complications/*Komplikacije*	Period/*Vremenski period* 1991–2013.	
Intraoperative/*Intraoperativne*	Number/*Broj*	%
Injury of ureter/*Povreda uretera*	1	0.5
Injury of urinary bladder/*Povreda mokraćne bešike*	2	1.1
Injury of intestines/*Povreda creva*	1	0.5
Injury of blood vessels/*Povreda krvnih sudova*	6	3.4
Injury of n.obturatorius/*Povreda n.obturatoriusa*	2	1.1
Total/*Ukupno*	12	6.8%
Postoperative/*Postoperativne*	Number/*Broj*	%
Infection of abdominal wound/*Infekcija trbušne rane*	5	2.8
Dehiscence of abdominal wound/*Dehiscencija trbušne rane*	4	2.2
Necrosis of vaginal fornix/*Nekroza forniksa vagine*	4	2.2
Uroinfection sepsis/*Uroinfekcija/sepsa*	6	3.4
Pneumonia/*Pneumonija*	1	0.5
Pulmonary thromboembolism/*Tromboembolija pluća*	1	0.5
Vesicovaginal fistula/*Vezikovaginalna fistula*	2	1.1
Lymphocysts/*Limfociste*	7	4
Ileus/*Ileus*	1	0.5
Total/*Ukupno*	31	17.7%

Table 3. Localization of recurrence and lethal outcome
Tabela 3. *Lokalizacija recidiva i letalni ishod*

Recurrence and lethal outcome/*Pojava recidiva i letalni ishod*	Period/*Vremenski period* 1991–2013.	
Recurrence/*Recidivi*	Number/*Broj*	%
Lymph nodes iliaci communis/*Limfni čvorovi iliaci comunis*	1	0.5
Lymph nodes glutealis sup./*Limfni čvorovi glutealis sup.*	1	0.5
Paraaortic lymph nodes/*Paraaortalni limfni čvorovi*	6	3.4
Parametria/*Parametrijumi*	5	2.8
Obturator fossa/*Obturatorna jama*	2	1.1
Liver metastases/*Metastaze u jetri*	3	1.7
Lung metastases/*Plućne metastaze*	2	1.1
Diffuse metastases/*Difuzne metastaze*	2	1.1
Total/*Ukupno*	22	12.5%
Lethal outcome/*Letalni ishod*	24	13.7%

by radical hysterectomy in the same act. The distribution of intra and postoperative complications is shown in **Table 2**, and the incidence of recurrence and lethal outcome are given in **Table 3**. One (0.6%) patient in the FIGO stage I B 2 was administered a single dose of internal radiation therapy (brachytherapy) preoperatively, while 6 (3.4%) patients in stages I B 2-II B, were administered 3 series of neoadjuvant chemotherapy preoperatively. The overall 5-year survival in the period from 1993 to 2008 (103 patients) was recorded in 90 (87%) patients.

Discussion

Ernst Wertheim performed the first radical hysterectomy in Vienna in 1898. Having isolated the whole length of ureters, he removed broad portions of parametria and enlarged lymph nodes [12]. In the 1930s, Joe V. Meigs, an American surgeon from Boston, applied the original concept of Wertheim's operation, adding the complete and selective removal of pelvic lymph nodes [9]. Since then, different surgical schools (German, American, English and Japanese) have developed this surgical technique, numerous and different modifications of basic operation have been made, and there have been several attempts to make an anatomical classification of the surgical technique. Although there are different classifications, the Piver-Rurlidge one from 1974 is the most widely used [13]. A famous Japanese surgeon, Shingo Fuji said "there is still no consensus about radical hysterectomy-it has not been clearly defined what this term refers to" [14]. However, references suggest that radical hysterectomy has to be individually adjusted, and it always has to include adequate resection of parametria i.e. surrounding connective tissue and lymph nodes removal. Contemporary surgical trends imply sentinel lymph nodes technique, application of laparoscopic and robotic surgery in order to minimize surgical trauma and morbidity, as well as to improve patients' recovery, and it is most often used in small tumor, up to 2 cm in the largest diameter (FIGO stage I B 1) [15, 16]. Large tumors over 4 cm confined to the cervix (FIGO stage I B 2), as well as infiltration and propagation to surrounding structures, which classifies the disease into a higher stage (FIGO II A-II B), still pose a surgical problem [17].

This study shows the results of Wertheim-Meigs radical hysterectomy (or Piver class II/III) performed at the Department of Gynecology in Novi Sad by 2 surgeons, Segedi and Đurđević, who operated 175 patients during the last 20 years. The average patients' age was 46 years, the average duration of operation was 3.5 hours, while the average blood loss was 300 ml. The majority of operated patients (64.6%) had initial FIGO stage I B 1 of the disease, and planocellular type of cancer (76.6%) and well differentiated Gr 1 tumors (54.8%) were the most common. On average, 32 lymph nodes were removed per operation. Intraoperative complications developed in 6.8% of the patients. All injuries were immediately recognized and successfully treated without any sequelae. The surgical suture Vicryl 3/0 and 2/0 was used for urinary bladder and small intestine, while Prolen 5/0 with round needle was used for blood vessels and nerves. In the case of ureter injury, a urologist was called to perform reimplantation of ureter into the urinary bladder without a sequela. The most common postoperative complications (total of 17.7%) were infections of abdominal wound, vaginal fornix, uroinfections and pneumonia. Until 2007, peritonization of operative field was performed after operation, and vacuum drains were placed bilaterally into obturator fossa. They were removed after the drainage was below 25 ml/24 h. In this period, the incidence of lymphocysts increased. Peritonization of operative field has not been performed since 2007, and a single drain of diameter 26–28 mm was placed into Douglas recessus. In the period of 3 months following the surgery, 3 patients underwent redo surgery and drainage of chronic lymphocysts. One cyst was accompanied with infection and high temperature, and 4 were treated by an interventional radiologist, who placed a drainage catheter. In postoperative period, 2 (1.1%) patients developed a vesicovaginal fistula on the 7th postoperative day after the urinary

Foley catheter had been removed. Spontaneous closure of the fistula occurred in 1 patient six weeks after the catheter had been placed, while another patient underwent surgical treatment after 3 months. Recurrence was reported in 22 or 12.5% of patients, most commonly in the region of paraaortic lymph nodes (3.4%) and parametrium (2.8%), while distant metastases in lungs and liver were detected in 3.9% of cases. In this study, 62 (35.4%) patients were in the FIGO stages I B 2 - II B, where the risk of lymphogenic dissemination is high, and despite the administration of adjuvant therapy (chemo and radiotherapy), recurrence can be expected. In this group of patients, 5 (2.8%) were in the FIGO stage I B 1, 4 (2.3%) were in the stage I B2, 3 (1.7%) were in the stage II A and the remaining 10 (5.7%) were in the stage II B. With complete documentation and imaging reports (CT, MR), all patients were presented to the consilium of gynecologic oncologists who were to make decision about adjuvant therapy. Of 24 (13.7%) operated patients with lethal outcome, 2 patients had had recurrent disease and 2 patients passed away due to urosepsis in the postoperative period.

Metastases in lymph nodes are the most important prognostic factor in patients with cervical cancer [18]. Lymph node metastases in the pelvic and/or paraaortic region have negative impact on the survival rate of patients with invasive cervical cancer [19]. Numerous retrospective studies state that the 5-year survival rate in the patients in the FIGO stages I B-IIB of cervical cancer, without confirmed lymph node metastases is 80-100% compared to 47–78% in patients with positive pelvic lymph nodes [20, 21]. In our study sample, positive lymph nodes with metastases were detected in 35 (20%) operated patients, which led to administration of adjuvant radiotherapy. Recurrence in pelvic lymph nodes occurred in 2 (1%) cases, in the common iliac and superior gluteal groups, which had not been removed during the operation. The analysis of some studies has shown that the average 5-year survival rate of patients with positive paraaortic lymph nodes, who received radiotherapy with extended field is 42% [23, 24] that being shorter by 15% compared to the patients with positive pelvic metastases, and less by 47% compared to the patients with negative pelvic lymph nodes. In our study, there were 6 (3.4%) cases of recurrence in paraaortic lymph nodes confirmed by MR examination, which led to lethal outcome in all patients. Paraaortic lymphadenectomy, which is not a standard procedure within radical hysterectomy, was performed in 12 (6.8%) patients in the FIGO stage I B 1, and positive lymph nodes were found in 5 patients [22, 25].

Compared to the results of radical hysterectomy in 230 operated patients at the Department of Gynecology in Novi Sad, performed from 1969 to 1975, published by Petar Drača, a significant decrease in early complications and complications of urinary system is observed [24]. According to Drača's results, early postoperative infections of urinary system (cystitis, pyelonephritis) developed in 43.9 %, which is significantly higher compared to our results (3.4% of uroinfections). Drača reported 7 (3%) cases of ureterovaginal, 1 (0.4%) case of vesicovaginal and 2 (0.8%) cases of rectovaginal fistulas. In our study, there were also 2 (1.1%) vesicovaginal fistulas. The 5-year survival rate in 103 patients operated before 2008 was 87% in our study sample, regardless of the stage of the disease, whereas it was 85.1% in the FIGO stage I and 62.4% in stage II in the Drača's study sample. This difference in results can be explained by improved surgical technique and sharp preparation of blood vessels and ureter in our study, as well as by the absence of preoperative irradiation therapy [25, 26].

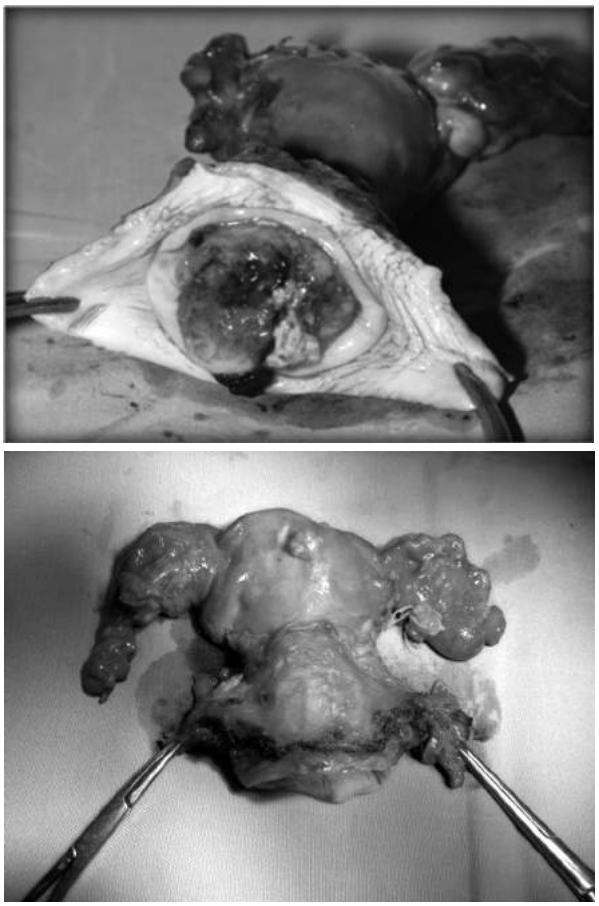


Figure 2. Uterus with ovaries and Fallopian tubes, part of parametria and vaginal cuff after Wertheim-Meigs radical hysterectomy
Slika 2. *Materica sa jajnicima i jajovodima, delovima parametrijuma i manžetnom vagine posle radikalne histerektomije po metodi Verthajm–Megz*

Conclusion

Wertheim-Meigs radical hysterectomy or Piver class II/III is a basic surgical technique for the treatment of initial stages of invasive cervical cancer.

Resection of the surrounding connective tissue-parametrium is obligatory besides the removal of uterus, upper third of vagina, lymph nodes of iliac and obturator region. Depending on the extent of parametrial dissection, Piver-Rutlidge classification places radical hysterectomy in II or III class of radicality, with about 90% of all operations performed in Europe being classified between classes II and III. Contemporary references strongly suggest that the extent of surgical dissection should be individually adjusted to each case, depending on the size and volume of the tumor, presence of lymphovascular invasion risk of local and lymphogenic dissemination and expected adjuvant therapy (radio and/or chemotherapy). In our study, we showed results of treatment after radical hysterectomy in 175 patients with cervical cancer in the International Federation of Gynecology and Obstetrics stage I B1-II B. Intraoperative and postoperative complications developed in 6.8% and 17.7% of operated patients, respectively, and recurrence occurred in 12.5% of cases, while the overall 5-year survival rate in the period until 2008 was 87%.

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DEPRESSIVE DISORDERS IN STUDENT POPULATION – COMPARATIVE STUDY CONDUCTED IN 2007 AND 2014

DEPRESIVNI POREMEĆAJ U STUDENTSKOJ POPULACIJI - KOMPARATIVNA STUDIJA 2007/2014

Ivana JOKSIMOVIĆ KNJISA[1], Lada MARINKOVIĆ[2] and Nataša ČOBRDA[1]

Summary

Introduction. The aim of this study was to determine the frequency of depressive symptomatology and its distinctive manifestations in student population in the interval of 7 years. **Material and Methods.** A sample of 790 students from the University of Novi Sad was asked questions about depression by means of the Patient Health Questionnaire 9 in 2007 and 2014. **Results.** The results show that the frequency of depression in student population ranges from 12.4% to 16.5%. Comparing the samples, in 2014 there were more mildly and severely depressed students, while the number of moderately depressed students was significantly lower. Suicidal thoughts were present in about 32% to 45% of depressive students and in about 7% of the total sample. The higher presence of depression was confirmed among female students in both study samples. **Conclusion.** The percentage of depressed students is stable over time. Symptomatology is very specific and suicidal thoughts are present in a great number of depressed students. Therefore, early diagnosis is essential.

Key words: Depressive Disorder; Students; Suicidal Ideation; Mental Health; Young Adults; Questionnaires; Signs and Symptoms; Risk Factors; Sex Factors

Sažetak

Uvod. Cilj ove komparativne studije je utvrđivanje učestalosti depresivne simptomatologije i njenih karakterističnih manifestacija u studentskoj populaciji u razmaku od sedam godina. **Materijal i metode.** Ispitivanje depresije sprovedeno je instrumentom *Patient Health Questionnaire 9* na uzorku studenata 2007. godine i na uzorku studenata 2014. godine. Ukupan uzorak činilo je 790 studenata Univerziteta u Novom Sadu. **Rezultati.** Utvrđena je učestalost depresije kod 12,4% do 16,5% studenata. Komparacija dve grupe studenata pokazuje da je u uzorku iz 2014. godine više blago i teško depresivnih, dok je umereno depresivnih statistički značajno manje. Suicidne misli prisutne su kod oko 32% do 45% depresivnih studenata i kod oko 7% ukupnog uzorka. U oba istraživačka uzorka potvrđena je veća prisutnost depresije kod studentkinja. **Zaključak.** Procenat depresivnih studenata stabilan je u vremenu. Simptomatologija je specifična a suicidne misli prisutne su kod velikog broja depresivnih studenata. Rana dijagnostika je neophodna.

Ključne reči: Depresivni poremećaj; Studenti; Suicidne misli; Mentalno zdravlje; Mladi ljudi; Upitnici; Znaci i simptomi; Faktori rizika; Polne karakteristike

Introduction

Studying usually lasts from 18 to 26 years of age, that being the period of late adolescence and the beginning of early adulthood from the aspect of development. The particularity of students' psychopathology is conditioned by the dynamics of developmental factors that are related to the age, as well as by specific social demands related to the very process of studying. In addition to familiar etiological factors, a number of specific factors resulting from the demands of academic life (change of the life style and the rhythm of life, personal planning of study time, inadequate communication with the faculty, moving to a new environment, separation from the family, high personal and family expectations related to success). Therefore, studying can become a burden for a vulnerable adolescent ego and consequently has a negative effect on the quality of life, general working abilities of a student and the development of depression. Studies have also shown that even the slightest degree of depressive symptoms can be significant for the occurrence of problems in the domain of academic achievements [1]. Unrecognized, undiagnosed, and untreated depression extends to further developmental phases and derange the complete further psychosocial functioning. With regard to the serious consequences to which the inadequate treatment of a student with symptoms of depression leads, the aim of this research was to determine the frequency of depressive symptoms in the student population at the University of Novi Sad, to recognize the specific symptoms of depression in students, to assess the frequency of suicidal thoughts and typical characteristics of depression in this population in relation with the gender.

Depression in Student Population

According to the data of the World Health Organization, the probability of experiencing episodes of

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Abbreviations

PHQ9 – The Patient Health Questionnaire 9
BDI – Beck Depression Inventory
ICD-10 – International Statistical Classification of Disease and Related Health Problems
DSM-IV – Diagnostic and Statistical Manual of Mental Disorders

depression in the course of life ranges from 8% to 20% in the total population. The data of the studies on the frequency of depression in the population of adults state the percentage span to be from 6% to 35% [2]. The presence of depression in the adolescence period goes from 5% to 9%, and as for the gender, it occurs twice more often in young women than in young men [3]. The frequency of depression in student population has been studied in numerous studies, and the results have shown that it goes up to even 50% [4].

Concerning the degree of severity of clinical picture, a depressive disorder can be mild, moderate and severe. According to the polarity of depression, it can be classified as unipolar and bipolar. Because of its heterogenic nature and layered structure, varieties of the depressive disorder forms (according to the *International Classification of Diseases* (ICD-10) and the *Diagnostic and Statistical Manual* (DSM-IV) and comorbidity of other mental disorders, it is crucial to identify the severity and the type of depression in time in order to administer adequate treatment [5]. Risk factors crucial for the prevalence, discovery and treatment of depressive disorders in adolescents are: 1. Biological factors (family history of depression and bipolar affective disorder (BAP), gender, the history of depression and chronic body diseases); 2. Psychological factors (comorbidity of psychiatric disorders, neurotic personal structure, negative cognitive style, low self esteem, and a traumatic event); 3. Familial factors (parents` mental illnesses, abuse of alcohol and psychoactive substances (PAS) by the parents, conflicting relationships in the family); 4. Social factors (bullying among peers, growing up in institutions, in exile, etc) [5]. In addition, academic achievements, social stressors, finance and separation from the family are specific for student population [6].

The comparison of studies performed since 1970s until today shows an increase in the number of depressed students when compared with other age groups. The frequency ranged between 12% and 53% in the 1990s [7–11]. Studies from the beginning of the twenty first century showed similar results, yet differences can be ascribed to the *type of studies* and *the chosen sample* (medical student population is described as particularly vulnerable, and the existence of depressive symptoms is three times more frequent than in other study groups) [12], to the country in which the research was done, or to the applied measuring instrument (Beck's Depression Inventory - BDI, Zung's Self Rating Depression Scale, Hospital Anxiety and Depressive Scale - HADS, Major Depression Inventory - MDI, Center for Epidemiology Studies Depression Scale - CES-D, Patient Health Questionnaire 9 - PHQ9 and others). In Slovenia, depression is present in 9.7% of students (according to Zung's Self Rating Depression Scale), in 10.4% of students (according to BDI scale) in Macedonia and in 20% of students (BDI) in Serbia [12]. In the ten-year study in which the frequency of depression was followed among students in our country [13] by the application of BDI scale, it was shown that around 22.7% of students manifested symptoms of depression, and that higher values in all measuring dimensions of the applied scale were observed among young women. One of the relevant studies which used the PHQ9 showed that the prevalence of depression and anxiety disorders in undergraduate students was 15.6%, and in recently graduated students it was somewhat lower, being around 13% [14].

In the National Study of Health in the United States of America [15], it was stated that 1 of 3 students had at least one depressive episode with difficulty in functioning, and that one out of 10 was seriously thinking about committing suicide. The frequency of suicidal ideation, the number of attempted suicides and the number of suicides among young people, especially among students, have been rarely studied in our country. It has been stated that the suicide rate among young people from 15 to 24 years of age is 6.9 in absolute figures in Serbia, that being 66 deaths per year [16]. According to some data, suicidal thoughts are present in 14.9% of non-clinical adolescent population (in 10.5% of boys and 17.5% of girls) [17]. Recent studies have found that between 20% and 43% of students had suicidal thoughts at some point [18], while there are some data on 60% of depressed young people who have thought of suicide, and about 30% of them have even attempted suicide [5].

Material and Methods

The applied PHQ9 makes it possible to get data on the existence of depression symptoms and their severity (mild, moderate and severe episode). This instrument matches the criteria for major depression in Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and International Statistical Cla-

Table 1. Descriptive statistical indicators for the total sample regarding the presence of depression
Tabela 1. *Deskriptivni statistički pokazatelji za celokupan uzorak u odnosu na prisustvo depresivne simptomatologije*

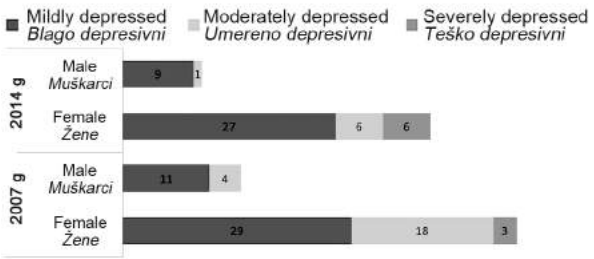
Year / *Godina*	No symptoms/*Bez simptoma*		Subsyndromal/*Supsindromalni*		Depressed/*Depresivni*		Total/*Ukupno*	
	N	%	N	%	N	%	N	%
2007	219	55,4	111	28,1	65	16,5	395	100
2014	227	57,5	119	30,1	49	12,4	395	100

Table 2. Severity of the episode of depression in the subsample of depressed students
Tabela 2. *Težina depresivne epizode u poduzorku depresivnih*

Severity of depression/*Težina depresivne epizode*	2007 (N)	valid/*ispravna %*	2014 (N)	valid/*ispravna %*
Mild/*Blaga*	40	61,5	36	73,5
Moderate/*Umerena*	22	33,8	7	14,3
Severe/*Teška*	3	4,6	6	12,2
Total/*Ukupno*	65	16,5	49	12,4

ssification of Diseeas and Related Health Problems (ICD-10). The instrument is highly sensitive (88%) and has a high specificity (88.2%) [2]. The respondents themselves estimate the occurrence of the mentioned problems in the last two weeks (without problem/sometimes, in more than seven days, almost every day). The total score is provided by adding the answers, and it indicates the category to which the respondent belongs. The scores of 10 and 14 refer to a mild episode of depression, from 15 to 19 to a moderate episode, and from 20 and upwards to a severe depressive episode. The scores from 5 to 9 indicate the subsyndromal form of depression. It takes only several minutes to fill in the questionnaire, and as much to process the results. Due to these characteristics, the instrument is very useful to the doctors in primary health care and therefore it is recommended to be used in the National guides for good practice for diagnosis and treatment of depression [19].

This study sample included 790 students from the University of Novi Sad, 267 male students (33.8%) and 523 female students (66.2%). All respondents were examined during their visit to the Institute for the Health Care of Students in Novi Sad. The anonymous questionnaire was filled in by the patients who visited the general practitioner for various reasons. The same number (395) of respondents was examined in 2007 and in 2014. Approximately the same number of male and female students were included in both samples (122 male students (30.9%) in 2007 and 145 (36.7%) in 2014 and 273 (69.1%) female students in 2007, and 250 (63.3%) in 2014. The sample included students from all years of study, as well as final year students. The students attending the first four years of study were evenly represented in the study sample (over 80% of respondents), and the rest were students attending



Graph 1. Gender and severity of depressive symptomatology
Grafikon 1. *Pol i težina depresivne simptomatologije*

the fifth and sixth year of study, final year students and post-graduate students or residents. The respondents were from 19 and 26 years of age, their average being 21.5 years and they attended 19 faculties or high schools of the University of Novi Sad.

The obtained data were processed with the statistical package SPSS Statistics 20.0. Descriptive statistical measures (frequencies and percentages) were calculated and the chi square (χ^2) test was used to check the statistical significance of the differences among subsamples regarding the severity of the episode of depression and gender.

Results

The descriptive statistical indicators obtained within the study performed in 2007 and in 2014 will be shown in order to assess the frequency of depression in student population. The respondents were categorized according to the criteria for assessing the severity of depression that was provided by the application of the PHQ9 questionnaire.

It can be concluded that over half of the respondents in both study years did not show any symptoms of depression (55.4% in 2007 and 57.5% in 2014).

The respondents with subsyndromal score (5 to 9) according to the applied instrument PHQ9 followed in number those without symptoms of depression. Such symptomatology, which does not meet the criteria for depression according to ICD 10 and DSM-IV criteria, seems to be wide spread among student population, and needs to be analyzed separately, therefore, it has not been the subject of this study.

The group of depressed students having the score over 10 in 2007 included 65 students, that being 16.5% of the total sample. There were 49 students in the group of depressed students in 2014, that being 12.4% of the total sample.

There was no statistically significant difference concerning the presence of depression obtained in the study performed in 2007 and 2014. The value of Pearson`s chi-square coefficient was 9,391, df (4), $p>0.05$ and the value of the coefficient of contingency was 0.108.

Table 2 shows the distribution of respondents only from the group of depressed students with regard to the severity of depressive symptomatology.

With regard to the severity of clinical picture, the mild form of depression was observed in the highest number of respondents in both study years, it was followed by the moderate form of depression

and the number of severely depressed students was the lowest.

By checking the statistical significance of differences between the number of depressed respondents in the 2007 and 2014 study sample with regard to the severity of manifested symptoms of depression according to Pearson`s chi-square test, the obtained value was 4.684, df(1), $p<0.05$. The value of the coefficient of contingency was 0.207. The difference was statistically significant at the level of 0.05.

By observing the number of respondents with different severity of depressive symptomatlogy in percentages, it is clear that the obtained difference resulted from the significantly lower percentage of moderately depressed and a slightly higher percentage of mildly and severely depressed students in 2014.

The presence of depressive clinical symptomatology in female and male respondents is given in the following graph:

It can be seen that 50 young women were depressed in 2007: mild form of depression was observed in 29 of them, moderate in 18 and severe in 3 female respondents. In the same year, out of 122 (30.9%) male respondents, 11 were mildly and 4 were moderately depressed. In 2014, out of 250 female students in the total sample (63.3%), 39 were depressed: 27 mildly, 6 moderately and 6 severely. In the same year, out of 145 (26.7%) male respondents, 9 met the criteria for the group of mildly depressed, while only one respondent was moderately depressed. None of the young men met the criteria for the category of severely depressed in either study year. All respondents in the group of severely depressed were females. Gender differences between the group of depressed and the group of those who were not depressed in both study years were statistically significant. The value of Pearson`s chi-square was 6.398, df (1), $p<0.05$. Depression was much more frequent in female students than in males, with the statistical significance of the difference at the level of 0.05.

In order to describe the characteristic symptoms of manifested episode of depression, the answers of the respondents given to the individual items of the applied questionnaire were analyzed.

In the group of depressed respondents from the 2007 sample, 38.5% claimed to have problems with sleeping *almost every day in the last two weeks*, 33.8% had negative self-perception, and 22.7% had trouble with appetite. The option *more than 7 days in the last two weeks* was chosen by 33.8% of depressed students who complained to have the feeling of emptiness, bad mood and hopelessness; 32% complained of fatigue, weakness and lack of energy, while 24% suffered from poor appetite. *Several days in the last two weeks* was chosen by 52.3% of the depressed students who complained of being less interested and satisfied when performing daily activities; 46.2% complained to have the feeling of emptiness and 44.6% had difficulties with concentration.

Data obtained in the 2014 study showed that 32% of respondents from the group of the depressed got tired very fast, felt tiredness and lack of energy *almost every day in the last two weeks*, 36% suffered from poor appetite and 26.5% were less interested or satisfied when performing daily routine activities. The option *more than seven days* was chosen by 42.9% who had the feeling of emptiness, 40.8% who felt fatigued, got tired quickly and 38.8% who had problems with sleeping, whereas 59.2% complained of being less interested and satisfied *several days in the last two weeks,* 44.9% were too slow and uneasy, and 42.9% had negative self-perception. Difficulties with concentration *during several days* were reported by 40.8% of depressed students.

A great number of depressed students from both study samples denied having suicidal thoughts (55.4% of the 2007 sample and 59.2% of the 2014 said *never in the last two weeks).* However, about 40% of the depressed students had suicidal thoughts with different frequency (8-9% of the 2007 sample and 9% of the 2014 sample said they thought of suicide every day, 7-12% of the 2007 sample and 12% of the 2014 sample thought of committing suicide more than seven days and 20% of the 2007 sample and 27% of the 2014 sample said to have thought of suicide *sometimes in the last two weeks*). Thinking of committing suicide should be additionally studied because it can suggest a depressive clinical picture, but not thinking does not exclude it completely.

Discussion

Student population manifests some specific characteristics in the type and frequency of psychopatological problems. Difficulties in learning, concentration, fear of exam, lack of motivation and similar difficulties which can be described as academic difficulties are among the most frequent students` problems according to some studies [20]. In some students, these problems might go much deeper to the level of mental disorder, which demands early detection and treatment. Consequently, the complete life quality of students is seriously endangered due to the presence of either chronic somatic diseases and pains or mental disorders [21]. The study aimed at detecting emotional disorders in their early stage in the students of the first and third year at the University of Novi Sad showed that out of 3500 students of both genders, 16% were at risk of developing some emotional disorders [22]. Depressive symptomatology and anxiety were the reasons for asking the professional help in 13% and 20% of cases, respectively [20]. A study performed in the United States of America (American College Health Association, 2005) [23] showed that from 12% to 18% of students had undergone treatment because of some mental disorder during their studies. These data are identical with the findings that the prevalence of psychiatric disorders in adolescent population goes between 10% and 20% depending on diagnostic criteria, age group and the choice of population [24]. Studies on the frequency of depression and other

mental disorders in student population are scarce in our country. The result of this research stating that depression occurs with frequency of about 12% to 17% confirms the results of similar studies [12, 13]. The finding that a lower percentage of students had depression in 2014 than in 2007 was unexpected to a certain degree. However, we cannot make conclusions with certainty about the reasons of this mild decrease due to the lack of information about numerous factors that could have caused these results. We can only conclude that the obtained difference in the results is not statistically significant. In that sense we can say that the frequency of depression among students is relatively stable in the observed interval of 7 years. More detailed studies should be done, which would include correlation with other variables such as the type of study course, place of residence, former history of mental disorder problems, comorbidity, current stressors, academic achievements and other elements that can be related to the occurrence of depressive symptomatology. What we consider encouraging for further monitoring the frequency of depression among students is the practice of introducing the compulsory screening on depression for people over 19 years of age. It has been introduced within the measures regulated by the law regarding the content and scope of the measures for prevention in the domain of health protection [25]. In this way those who are interested are enabled to widen their knowledge in this area and, what is more important, to protect mental health of the young people preventively.

This study was aimed at finding the answer to the question of the frequency of individual symptoms in the group of depressed students having different forms of depression and the frequency of thinking of suicide. First, we will discuss the results related to the frequency of symptoms with regard to the severity of clinical picture of depression.

The most striking difference between depressed students in two study years is very low number of mildly depressed in 2014. In addition, there were more mildly depressed (73% of all depressed students) as well as severely depressed students in the 2014 sample (their total number, although very low being only 6, was twice higher than in the 2007 sample). It might be concluded that students are either mildly depressed or severely depressed, without the moderate form of depression. As for the profile of depressive symptamotology between the sample from 2007 and 2014, there is a noticeable difference in the presence of somatic symptoms and disturbed voluntary instinctive dynamism. Namely, the most common symptoms in depressed students from the 2014 sample are fatigue, tiredness, lack of energy, problems with appetite and generally lesser interest and satisfaction in doing everyday activities. In depressed students from the 2007 sample, these symptoms were most common in the group of mildly depressed, while the symptoms suggestive of disturbed voluntary instinctive dynamisms (dream, sleep) as well as the existence of somatic symptoms occurred in more severe forms of depression as it could be expected. It seems that the depressed students from the 2014 sample were prone to one general anhedonia, that is apathy, they did not have adequate mechanisms to fight stress. Their tolerance to stress was very low and they were more vulnerable to depressive symptoms. Cognitive affective symptoms were dominant, while the loss of voluntary instinctive dynamisms was not so strongly manifested. Thus, the obtained profile of depressive symptomatology in the students from the 2014 sample shows same particularities and differences in comparison with the 2007 sample. In their book, the authors Howe and Strauss [26] say that today`s generations are not concerned about global problems but are occupied with their own achievements. Experts working with students agree with the claim that the pressure of parents often contributes to stress, anxiety and depression in students. It is believed that the pressure on a child to fulfill certain expectations is even stronger in small, nuclear families, thus adding to the tension. The authors conclude that new generations grow up under higher pressure of expected success, without being taught how to cope with failure as the integral part of growing up. Because of such undeveloped mechanisms for fighting stress the young can have more depressive symptoms that do not encroach voluntary instinctive mechanisms but can reduce the quality of life in the long run, particularly by impoverishing social contacts. These assumptions should be checked in future studies of student population in our country.

The issue of depressive contemplation must by all means be an integral part of every protocol when treating adolescents. However, the presence of suicidal thoughts should be analyzed and it is necessary to assess to which extent they are related to the clinical picture. Each suicidal thought must be seriously discussed with the young person. Data obtained in this research show that 31.8% and 45.6% of depressed students from the 2014 and 2007 sample, respectively, had suicidal thoughts with different frequency in the last two weeks. At the same time, only 7.6% of all respondents said in 2014 that they had had suicidal thoughts.

Conclusion

According to this study, which used the Patient Health Questionnaire 9 on the sample of students attending 19 faculties of the University of Novi Sad, the frequency of depression is between 12.4% and 16.5%. A lower number of depressed students was recorded in 2014, yet this decrease is not statistically significant. We can, therefore, conclude that the percentage of occurrence of depression in student population is relatively stable and ranges within the obtained results. Regarding the severity of clinical picture of depression there is a statistically significant difference in the presence of moderately depressed students, who are less numerous in 2014, while there is a recorded increase in the number of mildly and

severely depressed ones. As for the quality of symptoms which characterize the general clinical picture of depression in students, voluntary instinctive dynamisms were found to be slightly decreased (which was present in respondents in 2007) with the dominant lack of interest and satisfaction, feeling of emptiness and hopelessness, negative self-perception, difficulties with concentration. Suicidal thoughts occurred in 32-45% of the depressed students and in 7.6% of the total study sample. There was a difference between the genders regarding depressive symptoms. Female students with depression were found to outnumber male students regardless of the severity of clinical picture.

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ARTICULATION OF SPEECH SOUNDS OF SERBIAN LANGUAGE IN CHILDREN AGED SIX TO EIGHT

ARTIKULACIJA GLASOVA SRPSKOG JEZIKA DECE UZRASTA ŠEST DO OSAM GODINA

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Summary

Introduction. Phonetic and phonological system of the healthy members of one linguistic community is fully formed around 8 years of age. The auditory and articulatory habits are established with age and tend to be more difficult to be upgraded and completed later. **Material and Methods.** The research was done as a cross-sectional study, conducted at the preschool institution *"Radosno detinjstvo"* and primary school *"Branko Radičević"* in Novi Sad. It included 66 children of both genders, aged 6 to 8. The quality of articulation was determined according to the Global Articulation Test by working with each child individually. **Results.** In each individual vowel, plosive, nasal, lateral and fricative, the quality of articulation was statistically significantly better in the first graders compared to the preschool children ($p<0.01$). In each affricate, except for the sound /ć/, the quality of articulation was statistically significantly better in the first graders than in the preschool children ($p<0.01$). The quality of articulation of all speech sounds was statistically significantly better in the first graders than in the preschool children ($p<0.01$). **Discussion and Conclusion.** The most common disorder of articulation is distortion, while only substitution and substitution associated with distortion are less common. Omission does not occur in children from 6 to 8 years of age. Girls have slightly better quality of articulation. The articulatory disorders are more common in preschool children than in children who are in the first grade of primary school. The most commonly mispronounced sounds belong to the group of affricates and fricatives.

Key words: Voice; Child; Speech Articulation Tests; Articulation Disorders; Phonetics; Age Factors; Sex Factors

Sažetak

Uvod. Fonetsko-fonološki sistem pripradnika jedne jezičke zajednice u potpunosti je formiran oko osme godine života. Sa godinama se slušne i izgovorne navike ustaljuju i sve teže mogu da se nadograđuju i upotpunjuju. **Materijal i metode.** Istraživanje je sprovedeno kao studija preseka u Predškolskoj ustanovi „Radosno detinjstvo" i Osnovnoj školi „Branko Radičević" u Novom Sadu. U istraživanju je učestvovalo šezdeset šestoro dece, uzrasta od 6 do 8 godina, oba pola. Kvalitet artikulacije je procenjen na osnovu Globalnog artikulacionog testa, individualno kod svakog deteta. **Rezultati.** Kod svih pojedinačnih vokala, ploziva, nazala, laterala i frikativa kvalitet artikulacije statistički je značajno bolji kod dece u prvom razredu, u odnosu na decu predškolskog uzrasta ($p < 0,01$). Kod svih pojedinačnih afrikata, osim kod glasa /ć/, kvalitet artikulacije je statistički značajno bolji kod dece u prvom razredu, u odnosu na decu predškolskog uzrasta ($p < 0,01$). Kvalitet artikulacije za sve glasove zajedno je statistički značajno bolji kod dece u prvom razredu, nego kod dece predškolskog uzrasta ($p < 0,01$). **Diskusija i zaključak.** Najčešći poremećaj artikulacije je distorzija, dok se supstitucija izolovano i udruženo sa distorzijom, ređe javljaju. Omisija se ne pojavljuje kod dece uzrasta od šest do osam godina. Blagu prednost u kvalitetu artikulacije imaju devojčice. Artikulacioni poremećaji su učestaliji su kod dece predškolskog uzrasta nego kod dece koja pohađaju prvi razred osnovne škole. Najčešće je poremećen izgovor glasova iz grupa afrikata i frikativa.

Ključne reči: Glas; Dete; Artikulacioni testovi; Artikulacioni poremećaji; Fonetika; Uzrast; Pol

Introduction

Speech production is a complex, multi-staged process transforming conceptual ideas into an acoustic signal to be comprehensible to other people. These stages include conceptualization of the intended messages, adopting words, selection of appropriate morphological forms, sequencing of phonemes, word syllables, and phonetic encoding, as well as initiation and coordination of the sequences of tongue movement, lips and laryngeal muscles that cause vibration of the vocal folds and respiratory control for phonation and prosodic characteristic of speech [1].

From the acoustic point of view, different speakers pronounce each sound differently. From the range of possible sounds, every language "chooses" its specific speech sounds [2]. Speech production is a continuous order of speech sounds in an apparently discontinuous sequence of phonemes, whose connection forms semantic units (words and sentences) [3]. Pho-

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neme is the smallest distinctive unit, without a meaning but it sets the meaning of higher units. Different phonemes have different acoustic characteristics and different phonological features [2].

According to Golubović [4], the articulatory base is especially important for the proper articulation of speech sounds, which is a system of speakers' automated habits of pronunciation. This set of articulatory habits of a language, now tentatively called articulatory base, cannot be linked to an individual or even to a group of people. It represents the collective heritage of all members of a particular linguistic expression and it tends to change both in time and space [5].

The auditory and articulatory habits are established with age and tend to be more difficult to be upgraded and completed later. Therefore, if erroneous auditory and articulatory habits occur, they will become a part of the automatic activities in the domain of everyday life [5]. Preschool period is especially important due to the possibility of adapting erroneous habits, which can lead to significant morphological changes in the face region and thus jeopardize the proper acquisition of speech habits and the adoption of clean and clear pronunciation of sounds [6].

If speech and language disorders develop, they may hinder the child's functioning in their social environment [7]. According to Vladisavljević (quote Lazarević) [8], speech and language disorders can affect all modes of speech, sound articulation, language structure, reading, writing and they are caused or influenced by either environment or pathological changes in the speech system, and often by both of them. The study objective was to investigate the articulation in children before they start primary school and children in the first grade and to determine the most common type of disorder of the voice pronunciation. The hypothesis was that the articulatory abilities are less improved in preschool children than in children who are in the first grade of primary school, that the quality of articulation is better in girls than in boys, and specific for some sounds.

Material and Methods

The research was a cross-sectional study, conducted at the preschool institution *"Radosno detinjstvo"* and primary school *"Branko Radičević"* in Novi Sad. It included 66 children of both genders, from 6 to 8 years of age. The children were divided into two groups: one group had 33 preschool children and the other included 33 first graders. The native language of all children was Serbian, and the children were tested by two researchers, one of them being a speech therapist.

The quality of articulation was determined according to The Global Articulation Test [9] in each child individually. The test consisted of 30 words with the examined sounds in the inter-consonant position (vocals) or in the initial position (consonants). The protocol consisted of a table divided by vocal groups and a summary table for the results of The Global Articulation Test. There were 30 words in the test and each word corresponded to a single sound from Serbian language. A certain sound was observed in each word and the quality of its pronunciation was evaluated and scored with marks from 1 to 7.

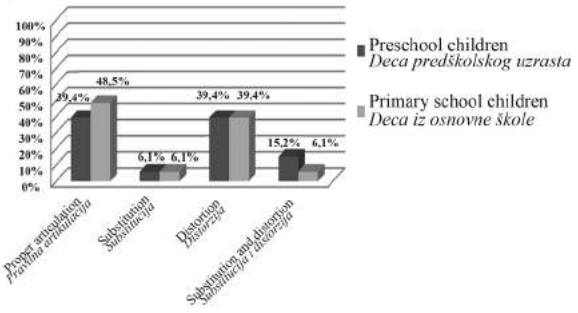
Marks 1, 2 and 3 indicated well-articulated speech sounds, marginal sounds got 4. There were sounds graded 5, but they were distorted. Mark 6 was for the sounds that were so badly damaged that they could not be identified out of context. The pronunciation of these sounds was distorted. Mark 7 was for the sounds that had been omitted (discharged) or substituted (replaced with a different sound). Finally, the marks by which the sounds were evaluated were summed up. The results were compared with the Mann-Whitney U Test, which is a non parametric test of the null hypothesis and has a high efficiency. The results were processed with SPSS 21 statistical software.

Results

The study sample consisted of 36 boys (55%) and 30 girls (45%). As for the age distribution, the number of children 7.5 to 8 years of age (30.3%) was slightly higher. The length of stay of children at the preschool institution was from less than 12 months (25.8%) to 4 years (66.7%).

Most of primary school first graders had proper articulation (49%), whereas substitution and substitution associated with distortion was recorded in only 6% of the study sample. Proper articulation was observed to a lesser degree (40%) in the preschool children than in the first graders. Substitutions were as rare in the preschool children (6%) as in the first graders and it was the least common speech disorder. Omission of speech sounds was found neither in the preschool children, nor in the first graders **(Graph 1)**.

The results of the Global Articulation Test showed that the quality of articulation for all individual vowels was significantly better in the first graders than in the preschool children, $p<0.1$. Statistically, the quality of articulation of all vowels



Graph 1. The structure of the sample according to the type of articulation disorders in preschool and primary school children

Grafikon 1. *Struktura uzorka prema vrsti poremećaja artikulacije kod dece predškolskog i školskog uzrasta*

Table 1. The quality of articulation of individually shown affricates in both groups of children
Tabela 1. *Kvalitet artikulacije pojedinačno prikazanih afrikata u obe grupe dece*

		Σ	$\bar{X}$	SD	Minimum *Minimalno*	Maximum *Maksimalno*	Mann-Whitney *U test*	p
C	1st group/*1. grupa*	84	2,55	0,711	2	4		
	2nd group/*2. grupa*	41	1,24	0,614	1	3	91,000	<0,01
	Total/*Ukupno*	125	1,89	0,930	1	4		
Ć	1st group/*1. grupa*	93	2,82	1,261	2	7		
	2nd group/*2. grupa*	83	2,52	1,906	1	7	412,500	>0,05
	Total/*Ukupno*	176	2,67	1,611	1	7		
Đ	1st group/*1. grupa*	80	2,42	0,561	2	4		
	2nd group/*2. grupa*	69	2,09	1,400	1	7	351,500	<0,01
	Total/*Ukupno*	149	2,26	1,071	1	7		
Č	1st group/*1. grupa*	98	2,97	1,447	2	7		
	2nd group/*2. grupa*	47	1,42	0,792	1	4	136,000	<0,01
	Total/*Ukupno*	145	2,20	1,395	1	7		
DŽ	1st group/*1. grupa*	100	3,03	1,425	2	7		
	2nd group/*2. grupa*	63	1,91	1,422	1	6	222,500	<0,01
	Total/*Ukupno*	163	2,47	1,521	1	7		

was significantly better in the first graders than in the preschool children, p<0.01. As for the group of plosives, the quality of articulation of each individual plosive was statistically much better in the first graders than in the preschool children, p<0.01. The quality of articulation of all plosives was statistically much better in the first graders than in the pre-school children, p<001.

An interesting discovery was recorded in the group of affricates. The quality of articulation of all individual affricates, except for the sound /ć/, was statistically much better in the first graders than in the preschool children (p<0.01). There was no statistically significant difference in the quality of articulation of the sound /ć/ between the preschool and primary school children, p>0.05. The quality of articulation of all affricates combined was statistically better in the primary school children than in the preschool children, p<0.01 **(Table 1)**.

In the group of fricatives, the biggest difference in the quality of articulation between the preschool children and the first graders was in the sound /ž/ and /r/. In all other individual fricatives, the quality of articulation was also significantly better in the first graders than in the preschool children, p<0.01. The quality of articulation was statistically much better in the first graders than in the preschool children, p<0.01.

As for the group of nasals, the worst was the sound /nj/. The quality of articulation of all individual nasals was statistically much better in the first graders than in the preschool children, p<0.01. The quality of articulation of all nasals was statistically much better in the primary school children than in the preschool children, p<0.01.

The speech sounds from the group of laterals were rated with good marks, 1 and 2 in both groups. However, the quality of articulation of all laterals was statistically much better in the first graders than in the preschool children, p<0.01.

In the first grade, 16 pupils (48.5%) had the proper articulation of all sounds of Serbian language (marks 1, 2, 3), while 9 pupils (27.3%) articulated 29 sounds properly. The sounds were properly articulated by 14 children (42.4%) of preschool age, while 6 children (18.2%) articulated 29 sounds properly. More preschool children had a low sum of properly articulated sounds; namely, 22, 23 and 24 of properly articulated speech sounds. Most of the first graders (60.8%) did not have a marginal sound marked with 4, while that percentage was slightly lower among the preschool children (57.6%). In the group of first graders who scored 4 at the test, 24.2% had one sound scored 4; whereas in the group of preschool children, even five children (15.2%) had three sounds scored 4. Most of the first graders (72.8%) did not have an erroneous sound (marked 5, 6, 7), while that percentage was slightly lower among the preschool children, being (60.7%). In the group of primary school children who were scored 5, 6 or 7 at the test, 21.2% had one erroneous sound; whereas in the group of preschool children, two or three sounds were scored 5, 6 or 7 in four children (12.1%). Although there were more boys than girls in the study sample, the girls had better quality of articulation of all groups of examined sounds of Serbian language (vowels, plosives, nasals, laterals, affricates and fricatives) although the difference between the boys and girls was not statistically significant (p>0.05).

Discussion

Veselinović et al. [10] have also found the sound distortion to be the most common disorder in tested

children. In their research, the sound distortion was observed in every child of 23.29% of those who had an articulation disorder.

According to this study, distortions are much more common than substitutions and omissions in speech. Distortions were equally observed in both groups of children (39.4%). Golubović et al. [4] reported that substitution was in 3.2% of the subjects, while Veselinović et al. [10] observed sound substitution in one case only (6.25%). This study yielded similar results: substitution was present in 6.1% of children from both groups. When the primary school children were compared in the terms of the frequency of substitution associated with distortion, they showed better articulation; associated substitution and distortion was found in 6.1% of them, whereas that frequency was 15.2% in the children of preschool age. Therefore, it can be concluded that the first graders had better quality of articulation regarding the type of dyslalia (isolated or associated).

According to Veselinović et al. [9], omission did not occur in children 6 to 10 years old, which is in agreement with Golubović and Čolić [11], who state that the omission of speech sounds almost never occurs at this age. In this study, omission of speech sound was not reported in any of the children from both groups, which is in agreement with the findings of the authors above. This suggests that omission as an articulation disorder is not present in the study sample of preschool and primary school children.

The results obtained by Golubović and Čolić [11] show that all tested children from 5.5 and 7 years of age have the proper pronunciation of all sounds, plosives and nasals, which is, according to the authors, expected given that these sounds are the first to be adopted in the speech sound system of Serbian language. Veselinović et al. [10] reported the articulation disorder of affricates in the majority of children (75%), while Vuletić and Ljubešić [12] claim that there is a high frequency of articulation disorders of fricatives in addition to affricates. This study shows too that vowels and plosives are more properly articulated. The frequency of articulation disorders in laterals was 18.18% in the primary school children, while this percentage was less than 3.03% in the preschool children. The worst quality of articulation was when pronouncing affricates and fricatives. The frequency of articulation disorders when pronouncing affricates was 36.36% in the primary school children, whereas it was 33.33% in the preschool children. The frequency of articulation disorders in case of fricatives was 24.24%, in the primary school children and 39.39% in the preschool children. The results are in agreement with the results of Vuletić and Ljubešić.

The frequency of articulation disorders is usually observed according to the age, gender and individual sounds or groups of sounds. According to Vuletić and Ljubešić [12] the significant difference in the development of articulation between boys and girls is in the period between 3 and 5.5 years of age, in favor of girls; furthermore, girls of all ages have a tendency toward better pronunciation. The number of problems with articulation decreases significantly with age in both genders. Veselinović et al. [10] studied the frequency of articulation disorders in 69 children 6 to 10 years old and have concluded that articulation disorders are more common in boys (25.36%) than in girls (18.51%). According to the research of articulation disorders in children from 5 to 11 years of age, Goulart and Chiari [13] claim that articulation disorders occur with the same frequency in both genders. In this study, it has been proved that there is no statistically significant difference in the quality of the sound articulation between boys and girls, but that girls have slightly better quality of articulation than boys, which is in agreement with most authors.

Vuković and Ilić [14] have found that articulation disorders are in correlation with age: the highest percent of disorders has been recorded in the second and the third grade, being 50% and 20.53%, respectively. Nešić et al. [7] have proved the hypothesis that speech and language disorders, which include the articulation disorders, are more common in children who are just starting school (92.85%) than during education (7.15%). This information is very important because it shows that education has an important role in elimination of speech and language disorders.

Majdevac et al. [15] published the results of research on 992 children from the province of Vojvodina. The children were 7 and 8 years old. Pathological speech conditions were found in 34.97% of the children and they were more common in urban than in rural areas.

In this research, the frequency of articulation disorders in the preschool children was 60.61%, while in the children attending the first grade it was 51.51%. There was a statistically significant difference in the quality of articulation of all sounds of Serbian language, except for the voice /ć/ between the preschool and primary school children, $p<0.01$. This shows that children in the first grade of primary school have statistically much better quality of articulation than preschool children, which may be the result of early affective attachment, different way of working in primary schools which implies more hours of activity, higher concentration and attention to work, the conditions and the atmosphere in the classroom, recognizing speech errors and correcting them on time, as well as repetition and the adoption of grapheme of Serbian language and encouragement to memorize, learning to read and write.

Conclusion

The most common articulation disorder is distortion, while the isolated substitution and substitution associated with distortion are less common. Omission does not occur in children from 6 to 8 years of age. Girls have slightly better quality of speech sound articulation. The articulatory disor-

ders are more common in preschool children than in children who attend the first grade of primary school. The most common mispronunciations come from the group of affricates and fricatives.

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SEXUAL BEHAVIOR OF STREET CHILDREN

SEKSUALNO PONAŠANJE "DECE ULICE"

Aleksandra STOJADINOVIĆ[1,2], Daliborka BATRNEK ANTONIĆ[3], Marija PERINOVIĆ[3] and Nevenka RONČEVIĆ[1]

Summary

Introduction. Street children and youth are at risk of getting engaged in different behaviors including risky sexual behavior, which adversely affects their development and health. The aim of this study was to examine sexual behavior of street children and youth, and the risks and consequences associated with sexual behavior. **Material and Methods.** A pilot study was conducted on a sample of 50 users of the Drop-in Centre for Street Children in Novi Sad, from 10 to 19 years of age. The study was conducted by a psychologist through structured interviews, with prior consent of the adolescent and parent. **Results.** Among the respondents who were sexually active, 41.2% had had the first sexual intercourse by the age of 12, their median age at that time being 14 years, while the age at the time of the first sexual intercourse is 16 years in the general population of Serbia. The majority of sexually active adolescents had several partners, one male adolescent had sex with a person of the same sex, and one was paid for sex. Very few respondents used a condom. Among 15 male sexually active respondents, three (ages 11, 12 and 14) were forced to have unwanted sexual intercourse, and a quarter of adolescents (three boys and one girl) were forced to do something unwanted during sex. **Conclusion.** Despite a small and unrepresentative sample, the results of this study indicate serious problems and significant risks associated with sexual behavior of children and young people who live and work in streets. This pilot study suggests that it is necessary to conduct new research on sexual behavior of street children and youth on a representative sample and with appropriate methodology. The results of a new study should be used to plan and carry out appropriate preventive measures regarding sexual behavior of street children.

Key words: Sexual Behavior; Risk-Taking; Child; Adolescent; Young Adult; Homeless Youth; Child Behavior Disorders; Coitus; Sexual Partners; Unsafe Sex; Condoms + utilization; Sex Offenses

Sažetak

Uvod. „Deca ulice" izložena su brojnim rizicima i angažuju se u različitim ponašanjima, među kojima su i rizični seksualni odnosi, koja štetno utiču na njihov razvoj i zdravlje. Cilj ovog istraživanja bio je da se ispita seksualno ponašanje dece koja su uključena u život i/ili rad na ulici, rizici i posledice u vezi sa seksualnim ponašanjem. **Materijal i metode.** Pilot-studija je sprovedena na uzorku od 50 korisnika usluga Svratišta za decu u Novom Sadu, uzrasta 10−19 godina. Ispitivanje je sproveo psiholog, uz prethodno dobijenu saglasnost adolescenta i roditelja. **Rezultati**. Među ispitanicima koji su seksualno aktivni 41,2% je imalo prvi seksualni odnos do uzrasta od 12 godina. Medijana stupanja u seksualni odnos je 14 godina, dok je za opštu populaciju u Srbiji 16 godina. Većina seksualno aktivnih adolescenta je imala više partnera, jedan adolescent je imao seksualne odnose sa osobom istog pola, jedan je bio plaćen za seks. Mali broj ispitanika je koristio kondom. Od 15 mladića, trojica su bila prisiljena na seksualni odnos, a četvrtina na neke postupke u seksu koje nisu želeli. **Zaključak**. Uprkos malom i nereprezentativnom uzorku, dobijeni rezultati ukazuju na ozbiljne probleme i značajne rizike u vezi sa seksualnim ponašanjem, kojima su izložena deca i mladi koji žive i rade na ulici. Ovo pilot-istraživanje zahteva da se što hitnije sprovede i istraživanje kojim će se uz odgovarajuću metodologiju na reprezentativnom uzorku ispititati seksualno ponašanje dece koja su uključena u život i/ili rad na ulici, kako bi se na osnovu dobijenih rezultata planirale i sprovele odgovarajuće preventivne mere.

Ključne reči: Sexualno ponašanje; Rizično ponašanje; Dete; Adolescent; Mladi ljudi; Deca beskućnici; Poremećaji ponašanja kod dece; Koitus; Seksualni partneri; Rizični seks; Kondomi + korišćenje; Seksualne devijacije

Introduction

Street children are girls and boys up to 18 years of age who have turned to streets as a place of living or earning a living, and who are not adequately protected and/or supervised by responsible adults. The children are temporarily, partially or completely separated from their families. These children earn their living by begging, collecting recycling materials, selling sexual services, indicating free parking spaces at car parks, washing windshields and other similar activities. The expression "children working and/or living on the streets" has recently been suggested as a more appropriate term for street children.

It is believed that there are street children throughout the world, both in the developed countries and

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Abbreviations
USA – United States of America

the developing ones. The number of children/youth on the streets is difficult to estimate because different epidemiology studies use different definitions. In addition, this population is frequently on the move - street children often go from one location to another, from one town to another. It is estimated that there are 100 to 150 million street children in the world but there are no reliable data [1, 2]. There are no official records on the number of children working and/or living on the streets of Serbia. According to the unofficial data published by the media, it is estimated that the number of children working and/or living on the streets of Serbia is from 2,000 to as many as 10,000.

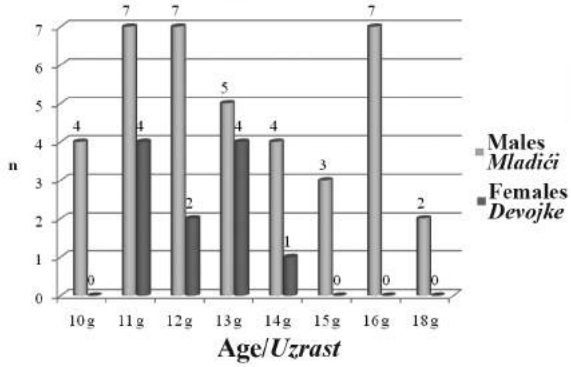
According to the internal data of Ecumenical Humanitarian Organization in Novi Sad covering the period from the 23rd February 2010 to the 31st December 2013, 651 children used the services of Drop-in Centre for Street Children. Outreach workers contacted and offered services to additional 360 children who did not attend the Drop-in Centre, the total number of registered street children in Novi Sad being 1.011.

Street children face numerous health and life hazards, while neither health and social care services nor education are easily available. Living and working on the streets have profound developmental and health consequences for children and youth. By living and working on the streets they are confronted with the highest risks and they get engaged in various harmful activities which have a damaging effect on their development and health. In comparison with children and adolescents who do not live and/or work on the streets, street children more often have acute illnesses, injuries, infections especially of digestive and respiratory tract, sexually transmitted diseases, inadequate diet, stunting and developmental delay, neurological disorders, problems with teeth and mouth, mental disorders, chronic illnesses, emotional problems, learning disorders. They use psychoactive substances more often and become victims of abuse, sexual exploitation and human trafficking and have higher mortality rate. Street children become sexually active at an early age, and they often have unplanned and unprotected sexual intercourse. Sexually transmitted diseases, unwanted and unplanned pregnancies are common with street children [3–9].

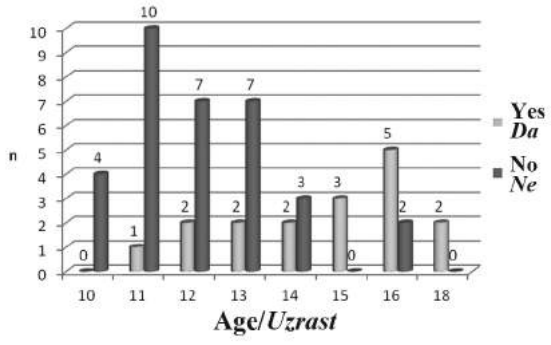
Data on the specific features of the children and youth who live and work on the streets and on their families had not been available in our country until 2011, when the way and conditions of living of street children and their families were studied as a part of the European Union (EU) project *Strengthening of Social Cohesion Through the Development of Non-Discrimination Public Policy for the Children who Live and/or Work on the Streets* [10]. The results of the research have shown that street children are most frequently from Roma families. The families live in extreme poverty, in unhygienic settlements with poor housing conditions. Most parents have either dropped out of primary school or have never enrolled. Four fifths of fathers and 97% of mothers are unemployed. Most parents work illegally, families usually live on collecting and selling recycling materials. Almost entire income is spent on food; normally they buy old food, and they are frequently forced to take food out of the waste containers. Children frequently work on the streets to contribute to their family budget. The parents in the examined families had children at a very early age: the youngest mother had her first child when she was 13 years old, and 65% of mothers gave birth to at least one child by the age of 17. These families have a large number of children, up to eleven. Children from these families have various health problems, among which the most frequent are: lice and mange infestations, teeth problems, learning disorders, injuries, malnutrition, asthma, bronchitis, infections of the digestive tract, burns, and behavioral disorders. More than 90% of children working and/or living on the streets have been exposed to violence or discrimination. Most of these children live on the margins of society and are unable to participate in the same activities as their peers (more than two thirds of the children have never been on a school trip, to a zoo, the cinema, a birthday party nor have they visited a non-Roma peer). As a part of the research, sexual behavior of street children has also been examined. Since it was not possible to provide privacy during the conversation between the interviewers and interviewees in this research, some contradictory or socially desirable answers were obtained. Some street children did not want to answer the questions. Since the obtained data were not reliable enough, it was necessary to conduct further research on sexual behavior of street children and the risks involved [10]. The aim of this research was to examine sexual behavior of street children, the risks and consequences related to the sexual behavior of children and youth living and working on the streets.

Material and Methods

The research was conducted on a sample of 50 users of the Drop-in Centre for street children, from 10 and 19 years of age in Novi Sad in 2012. A questionnaire containing 44 questions was used to gather data. Even though many users of the Drop-in Centre had attended or were attending school, most of them could not complete the questionnaires on their own, so a psychologist interviewed them and completed the questionnaires. During the interview the respondent and the psychologist were alone, therefore the interviewees felt freer and more honest than during the previously conducted research. For each of the respondents a written consent to participate in the research was obtained either from a



Graph 1. Age and gender of adolescents
Grafikon 1. *Struktura ispitanika po uzrastu i polu*



Graph 2. Sexual acitivity and age
Grafikon 2. *Seksualna aktivnost prema uzrastu*

parent or the child/adolescent him/herself. Prior to the interview, they were informed about the purpose and significance of the research. The interview lasted about 45 minutes, but many candidates found it difficult to focus on questions given in the questionnaire.

Results and Discussion

The research included 50 children living and/or working on the streets, 39 (78%) boys and 11 (22%) girls from 11 to 19 years of age. The sample included only those adolescents who wanted to participate; therefore it was not formed by the method of random sampling. There were no girls over 14 years of age, and that was a shortcoming of this study sample. The question may be asked why the girls do not use the Drop-in Centre and if the reason is staying at home to do household chores, marriage or something else. According to the available data, none of the interviewed girls was married or living in unmarried partnership at the time of the research (**Graph 1)**.

Even though 96% of the respondents attended school at some point, only 17 (34%) stated they could read well, and 24 (48%) stated they could read a bit. Out of the total number of respondents, 9 (18%) stated they could not read at all. Almost half of the respondents completed 4 years of primary education, but were still unable to complete the questionnaire on their own.

Seventeen (34%) respondents, 16 boys and one girl, confirmed having had sexual intercourse at some point in their lives. **Graph 2** shows sexual activity according to age.

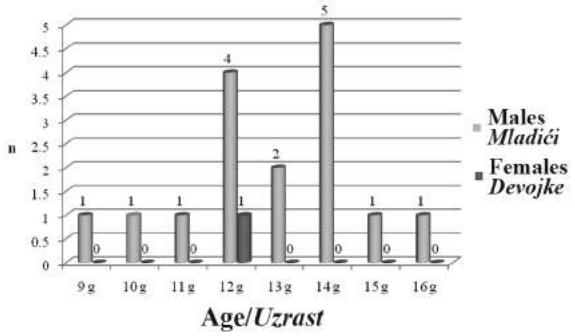
Graph 3 shows the age of the respondents at the time of their first sexual intercourse. It can be seen that among the respondents who had sexual intercourse at some point in their lives, 41.2% had their first sexual intercourse before 12 years of age. Most sexually active respondents had their first intercourse by the age of 14, which is at the same time the median age of starting sexual relations. According to the data from the research conducted by the Ministry of Health in 2006, the median age in Serbia for starting sexual relations was 16 [11]. According to the results of the research by Kapamadžija et al., 84.3% of young high school male students had their first full sexual intercourse at the age of 18, while the average age when they had their first experience was 15.55 [12]. According to the results of Mijatović-Jovanović et al., the average age of starting sexual relations in Novi Sad was 15.6 for boys and 16.5 for girls [13]. Results of the research by Van de Bongart et al. have suggested that sexual activity is closely connected to sexual behavior of the peers, which can be an explanation for early start of sexual activity of street children [14].

Graph 4 shows the reasons why the respondents had their first sexual relations. All of the sexually active respondents claimed they had not been under the influence of alcohol or drugs at the time of their first sexual intercourse.

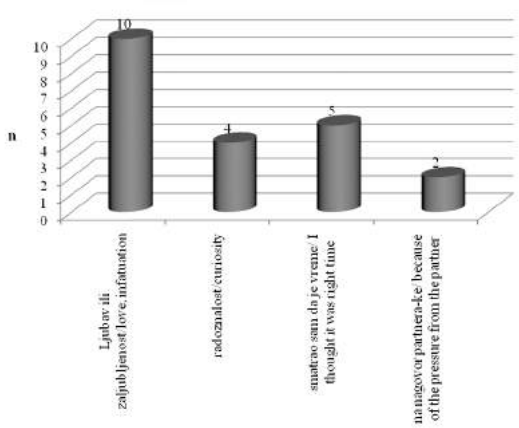
Fifty-eight percent of the respondents said they had started sexual relations out of love and infatuation; however, they mentioned other reasons as well (they believed it was time - a 12-year-old girl,

Table 1. Number of sexual partners and gender of adolescents
Tabela 1. *Broj partnera sa kojima su ispitanici imali seksualne odnose tokom života prema polu ispitanika*

Gender *Pol*	Number of sexual partners/*Broj seksualnih partnera do sada*					Total *Ukupno*
	1 person *jedna osoba*	2 persons *2 osobe*	3 persons *3 osobe*	4 persons *4 osobe*	6 or more persons *6 ili više osoba*	
Male/*Muški*	2	4	3	4	3	16
Female/*Ženski*	1	0	0	0	0	1
Total/*Ukupno*	3	4	3	4	3	17



Graph 3. Age of adolescent at the time of their first intercourse
Grafikon 3. *Uzrast ispitanika prilikom prvog seksualnog odnosa*



Graph 4. Reasons for the first intercourse
Grafikon 4. *Razlozi zbog koji su ispitanici prvi put stupili u seksualne odnose*

out of curiosity and because they were persuaded by their partner). The majority of sexually active adolescents said that they had had sexual relations with more than one partner, and two 18-year old males said they had had six or more sexual partners, which greatly increases the risk of sexually transmitted diseases and pregnancies **(Table 1).** One of them stated he became sexually active at the age of 11, and another at the age of 12. According to research conducted in Egypt, 54% of young people on the streets, between 15 and 17 years of age had more than one sexual partner [15].

Forty five respondents (90%) said they had heard of a condom and 5 (10%) denied having heard about it. Five respondents (29.4%) said they had used a condom during each sexual intercourse in the previous 12 months, 2 (11.8%) said they had used it most of the time, one respondent (5.9%) had used it occasionally, 3 respondents (17.6%) had used it rarely, and 6 (35.3%) had never used a condom. The most common reason for not using a condom, according to the respondents, was its high price, difficulty in obtaining or their embarrassment to ask for it. It is unclear why the respondents replied in this way, having in mind that there are frequent workshops in the Drop-in Centre about sexuality, protection against unwanted pregnancy or sexually transmitted diseases, and that the condoms are given to the users of the Drop-in Centre free of charge. We believe that all respondents must have attended those workshops in the Drop-in Centre because they have been organized many times. It is possible that they used the condoms to play or to sell them - information about that could not be obtained.

Out of 15 sexually active young males, three were forced by their sexual partners to have a sexual intercourse when they did not want it. They were 11, 12 and 14 years old at that time. When sexual violence is concerned, it is usually girls who are discussed. However, little is known about the sexual violence against boys and it is rarely taken into consideration. Since this research included only one girl who had had sexual relations, the extent to which the girls living and working on the streets are exposed to sexual violence is not known, that being another drawback of this research. According to data from the United States of America (USA), 7.3% of high school students (10.5% of girls and 4.2% of boys) were forced to have sexual intercourse when they did not want [16]. According to the results of research on street children conducted in Egypt, 93% of these children experienced some form of harassment or abuse, and out of 53 girls living and working on the streets, 90% were the victims of sexual abuse [15].

Table 2 shows how many times in the previous 12 months the respondents were forced to do something in sex they did not want.

Four respondents stated they had been forced to perform certain things in sex they did not want, which suggests that these young people cannot or often do not know how to define what is acceptable

Table 2. How many times during the previous year were you forced to do something in sex you did not want?
Tabela 2. *Koliko puta si tokom prethodnih 12 meseci bio primoran da uradiš u seksu nešto što nisi želeo/želela?*

	n	%	Cumulative %/*Kumulativni %*
Never/*Nijednom*	13	76.4	76.4
2 ili 3 times/*2 ili 3 puta*	2	11.8	88.2
4 to 5 times/*4 do 5 puta*	1	5.9	94.1
6 or more times/*6 ili više puta*	1	5.9	100.0
Total/*Ukupno*	17	100.0	

for them or not. This status and behavior in sexual relations additionally increases risks of sexual behavior of street children (exposure to violence, unprotected sexual intercourse). Consequences of risky sexual intercourse in these children and youth can be physical and psychological trauma, sexually transmitted diseases, unwanted pregnancy.

It is believed that sexual orientation is defined before adolescence, but its expression can be delayed until the early adulthood or later, making it difficult to define the prevalence of homosexuality in adolescence. One respondent said he was attracted to members of both sexes, but later continued to have sexual intercourse exclusively with members of the same sex. He stated he was insulted for being attracted by the same-sex people, but he was not physically abused.

One male adolescent said he had been paid for sex by a member of opposite sex.

Three respondents said their girlfriends were pregnant, and a sexually active girl did not state she had ever been pregnant. One 11-year-old boy said his girlfriend was pregnant, one 14-year-old and 18-year-old boy said the same. The pregnancy of the 11-year-old boy's partner was unwanted, and the other two were wanted. An 18-year-old boy said he had a child, his partner had given birth at the age of 15, and the child lived with him.

Two boys and a girl said they had sexually transmitted disease (11-year-old boy, 14-year-old boy and the only sexually active girl who was 13 years old). A boy and a girl had visited a doctor because of the sexually transmitted disease. Sexually transmitted diseases affect people of all ages, but they are especially common in young people. The Center for Disease Control - CDC in the USA estimates that the persons from 15 to 24 years of age account for one quarter of sexually active population, and that half of the newly discovered sexually transmitted diseases in the USA occur among them [17]. It is also estimated that one out of four sexually active adolescents has a sexually transmitted disease, such as Chlamydia or human papillomavirus [18]. Due to their early start of sexual activity, children and young people living and working on the streets are at a substantially higher risk of getting sexually transmitted disease. Each of these infections can harm health and well-being of a young person, both in the present and future. Even though sexually transmitted diseases increase the risk of human immunodeficiency virus (HIV) infection, and hepatitis B and C, they can also be complicated in adolescents and cause permanent damage to the reproductive system and infertility [19].

The drawbacks of this research are that the data were not obtained from a representative sample, the respondents were not selected by the method of random sampling, they did not complete the questionnaire themselves, and a small number of female adolescents were included. In spite of the disadvantages of this research, the results indicate very serious problems and substantial risks to which children and youth living and working on the streets are exposed.

Conclusion

Based on the results of this pilot study, it can be concluded that children/youth living and working on the streets start having sexual intercourse early, they have a large number of partners, they do not use sufficient protection against sexually transmitted diseases and unwanted pregnancy, they are exposed to sexual violence and some of them trade sexual favors for money.

In order to obtain valid data on sexual behavior of street children based on which comprehensive programs could be planned and conducted to protect reproductive health of this population, it is necessary to carry out a survey which would include a representative sample of children and youth living and working on the streets with appropriate methodology.

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PARAMETERS OF HEMODIALYSIS ADEQUACY AND PATIENTS' SURVIVAL DEPENDING ON TREATMENT MODALITIES

PARAMETRI ADEKVATNOSTI HEMODIJALIZE I PREŽIVLJAVANJE BOLESNIKA U ZAVISNOSTI OD MODALITETA LEČENJA

Petar S. ĐURIĆ[1], Jovan POPOVIĆ[1], Aleksandar JANKOVIĆ[1], Jelena TOŠIĆ[1] and Nada DIMKOVIĆ[2]

Summary

Introduction. Retrospective studies showed that hemodiafiltration was associated with a reduced risk of mortality compared with standard hemodialysis in the patients with end-stage renal disease. Recently, a few prospective randomized clinical trials found no advantage in survival with hemodiafiltration as compared with high-flux hemodialysis and low-flux hemodialysis. The aim of this study was to compare the parameters of hemodialysis adequacy and two-year survival of patients depending on the modality of hemodialysis. **Material and Methods.** A total of 159 hemodialysis patients were divided into 3 groups according to the type of hemodialysis treatment: group A – low-flux hemodialysis, group B – high-flux hemodialysis, and group C – hemodiafiltration. All patients had the same duration of hemodialysis sessions. The analysis included average one-year biochemical parameters, and two-year survival of patients. **Results.** The patients on hemodiafiltration were significantly younger, they had longer dialysis vintage and higher index of dialysis adequancy as compared with the patients on low-flux hemodialysis and high-flux hemodialysis, but without a difference between the two latter groups. Compared to the patients on low-flux hemodialysis, the patients on hemodiafiltration and high-flux hemodialysis had significantly higher hemoglobin value with less frequent erythropoietin stimulating agent use. According to Kaplan-Meier survival analysis, the patients on hemodiafiltration and high-flux hemodialysis had significantly better two-year survival than the patients on low-flux hemodialysis. Cox proportional hazards model confirmed that high-flux hemodialysis caused a significantly lower relative risk of mortality (56% reduction) compared to low-flux hemodialysis (hazard ratio 0.44; P=0.026), and hemodiafiltration caused a 58% reduction in the relative risk of mortality compared to low-flux dialysis (hazard ratio 0.42; P=0.105), but without a statistical significance. **Conclusion.** This study has demonstrated two-year survival benefit with high-flux hemodialysis and hemodiafiltration compared with low-flux hemodialysis. There was no difference in survival between high-flux hemodialysis and hemodiafiltration groups.

Key words: Renal Dialysis; Hemodiafiltration; Survival Rate; Anemia; Mortality; Treatment Outcome; Kidney Failure, Chronic + therapy

Sažetak

Uvod. Brojne retrospektivne studije su pokazale da je hemodijafiltracija u vezi sa smanjenjem rizika od mortaliteta nad standardnom hemodijalizom kod bolesnika sa terminalnim stadijumom bubrežne slabosti. Međutim, u nekoliko skorašnjih prospektivnih randomizovanih studija nisu pronađene prednosti u preživljavanju bolesnika lečenih hemodijafiltracijom naspram standardne bikarbonatne hemodijalize sa visokopropusnim i niskopropusnim membranama. Cilj ove studije bio je poređenje parametara adekvatnosti hemodijalize i dvogodišnjeg preživljavanja bolesnika u zavisnosti od modaliteta lečenja. **Materijal i metode.** Ukupno 159 bolesnika na hemodijalizi, sa jednakim vremenom dijaliziranja, podeljeno je u tri grupe prema vrsti modaliteta hemodijalize: grupa A – bolesnici lečeni niskopropusnim membranama, grupa B – visokopropusnim membranama i grupa C – hemodijafiltracijom. Analizirali smo jednogodišnje prosečne biohemijske parametre i dvogodišnje preživljavanje bolesnika. **Rezultati.** Bolesnici lečeni hemodijafiltracijom bili su značajno mlađi, imali su duži dijalizni staž i značajno više vrednosti indeksa adekvatnosti dijalize u odnosu na druge dve grupe, a bez razlike između grupe bolesnika lečenih visokopropusnim membranama i bolesnika lečenih nisokopropusnim membranama. U odnosu na bolesnike lečene nisokopropusnim membranama, bolesnici lečeni hemodijafiltracijom i visokopropusnim membranama imali su značajno više vrednosti hemoglobina, uprkos ređoj primeni agenasa stimulacije eritropoeze. Prema Kaplan-Majerovoj analizi preživljavanja, bolesnici lečeni hemodijafiltracijom i visokopropusnim membranama imali su značajno bolje dvogodišnje preživljavanje u odnosu na bolesnike lečene nisokopropusnim membranama. Lečenje visokopropusnim membranama je uzrokovao 56% manji relativni rizik od mortaliteta u poređenju sa bolesnicima lečenim nisokopropusnim membranama (*hazard ratio* 0,44; P = 0,026), dok je hemodijafiltracija uzrokovala 58% manji relativni rizik od mortaliteta u poređenju sa grupom bolesnika lečenih nisokopropusnim membranama (*hazard ratio* 0,42; P = 0,105), ali bez statističke značajnosti. **Zaključak.** Studija je pokazala prednost u dvogodišnjem preživljavanju kod bolesnika lečenih visokopropusnim membranama i hemodijafiltracijom u poređenju sa bolesnicima lečenim nisokopropusnim membranama. Nije bilo razlike u preživljavanju bolesnika lečenih visokopropusnim membranama i hemodijafiltracijom.

Ključne reči: Hemodijaliza; Hemodijafiltracija; Preživljavanje; Anemija; Mortalitet; Ishod lečenja; Terminalna bubrežna insuficijencija + terapija

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Abbreviations

Kt/V – index of hemodialysis adequancy
HD – hemodialysis
NCDS – National Cooperative Dialysis Study
HEMO – Hemodialysis Study Group
HDF – hemodiafiltration
ESA – erythropoietin stimulating agents
CRP – C-reactive protein
HDL – high-density lipoprotein
BMI – body mass index
ERI – erythropoietin resistance index
iPTH – intact parathyroid hormone
RR – relative risk

Introduction

Traditional hemodialisis (HD) prescription consists of three sessions per week in duration of 4 hours and it is regarded as sufficient in most cases to reach adequate HD [1]. HD adequacy implies not only the clearance of uremic toxins, but also optimal rehabilitation and control of uremic complications [2]. Adequate dialysis includes the optimal correction of anemia, immune competence, mineral-bone metabolism, nutritional disorders, general quality of life and improved morbidity and mortality [2]. On the basis of data from the NCDS (*National Cooperative Dialysis Study*) [3], the concept of 'dialysis dose' was introduced in the form of the Kt/V urea formula, based on urea as a marker of uremia, and for more than two decades, the clearance of low-molecular weight uremic toxins remained the measure of dialysis adequacy [4]. Several guidelines recommend minimum target values of Kt/V urea, with the goal of delivering an adequate dialysis dose [5].

The randomized HEMO study (*Hemodialysis Study Group*) found no advantage in survival of the patients treated with higher dialysis dose (expressed by Kt/V) or using high-flux dialysis membrane compared to the patients treated with low-flux membrane [6]. Although the results of the study indicated that high dialysis dose did not give benefit to the patients on HD, the overall reduction in mortality in the group of patients treated with high-flux membrane in the HEMO study was 8% which was not statistically significant [7].

Hypothetically, high-flux dialysis as well as hemodiafiltration (HDF) increases the removal of uremic toxins of small and middle molecular mass compared to low-flux dialysis. During HDF, the clearance of uremic toxins of small and middle molecular mass is additionally increased with convective transport compared to high-flux HD [8]. Whether the increased clearance of middle molecules brings benefit in terms of higher survival of patients has not been proved with strong evidence even though some epidemiology studies as well as meta analyses suggest such benefit in patients treated with high-flux dialysis and HDF [9–11]. Numerous studies, mainly observational ones, have suggested that dialysis with high-flux membranes and HDF may lead to better correction of anemia parameters and to a reduction in frequency and dose of erythropoietin stimulating agents (ESA) compared to the patients treated with low-flux membranes. At the same time, these patients have a better control of hyperphosphatemia and secondary hyperparathyroidism, along with a reduced intake of phosphate binders and metabolite of vitamin D [12–15]. Furthermore, there are many reports about the positive effects of high-flux dialysis and HDF on nutritional parameters [16] and survival rate compared to the patients treated with low-flux dialysis [11, 12, 17]. The aim of this study was to compare dialysis adequacy and two-year patient survival depending on the modality of treatment.

Material and Methods

This observational retrospective-prospective study included a total of 159 patients (93 men and 66 women, mean age 62.7±11.8 years) treated with chronic HD for more than 6 months at the Department of Nephrology and Disorders of Metabolism with Dialysis "Prof. Dr Vasilije Jovanović" Clinical Center „Zvezdara" – Belgrade. The patients were classified and analyzed according to the HD modality into group A – the patients treated with bicarbonate HD with low-flux membranes; group B – the patients treated with bicarbonate HD with high-flux membranes and group C – the patients treated with HDF. All 159 patients were treated with HD three times a week, and each session lasted for 4 hours.

Laboratory parameters were analyzed retrospectively for the period of one year while the survival of patients was followed up prospectively for the period of two years.

The samples for laboratory analyses were taken at the beginning of dialysis procedure after a weekend pause once in three months and the following laboratory parameters were analyzed: total proteins, serum albumins, serum bicarbonates, C-reactive protein (CRP), hemoglobin (Hb), ferritin, calcium (Ca), phosphorus (P), total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides which were measured by standard laboratory techniques. The average of analysis was calculated for the period of one year except the values for parathyroid hormone, which was checked at least twice a year using chemiluminescent assay (*DPC, Diagnostic Product Corporation, USA*).

The patients' data were taken from medical records: age, sex, duration of dialysis vintage (expressed in months), presence of diabetes and hypertension, cardiovascular diseases until the beginning of the study; intake of vitamin D metabolites and phosphate binders, cumulative dose of calcium carbonate and vitamin D metabolites during the last year, the use of statins and weekly dose of ESA. Body mass index (BMI) was calculated according to the patients' weight and height [18]. Erythropoietin resistance index (ERI) was expressed as a quotient of average weekly ESA dose and body mass of patient

Table 1. Characteristics of patients regarding hemodialysis modality
Tabela 1. *Karakteristike bolesnika u odnosu na hemodijalizni modalitet*

	Group A/*Grupa A* (LFHD) N=69	Group B/*Grupa B* (HFHD) N=64	Group C/*Grupa C* (HDF) N=26	P
Gender-male/*Pol-muški* %	50,7	68,8	53,8	>0,05
Age, years/*Godine starosti*	67,2±10,8	59,9±11,8	57,4±10,3	<0,001*
Dialysis vintage, months/*Dužina hemodijalize*, *meseci*	44,6±36,5	96,1±67,2	117,9±39,1	<0,001**
DM/*DM*, %	18,8	14,1	23,1	>0,05
HTN/*HTA* %	91,3	87,5	98,5	>0,05
Statin use/*Upotreba statina*%	14,5	12,5	23,1	>0,05
HCO_3^-/HCO_3^- (mmol/L)	17,9±2,2	17,2±2,0	17,2±3,8	>0,05
Kt/V/*Kt/V*	1,32±0,2	1,25±0,31	1,50±0,3	**<0,001**†

LFHD - low-flux hemodialysis/*niskopropusna hemodijaliza*; HFHD - high-flux hemodialysis/*visokopropusna hemodijaliza*; HDF - hemodiafiltration/*hemodijafiltracija*; DM - diabetes melitus/*dijabetes melitus*; HTN/*HTA* - arterial hypertension/*arterijska hipertenzija*; Kt/V - index of dialysis adequacy/*indeks adekvatnosti dijalize*; group A vs. group B/**grupa A vs. grupa B*, p<0,001, group A vs. group C/*grupa A vs. grupa C*, p<0,001**group A vs. group B/*grupa A vs. grupa B*, p<0,001, group B vs. group C/*grupa B vs. grupa C*, p=0,012; group A vs. group C/*grupa A vs. grupa C*, p<0,001; † group A vs. group C/*grupa A vs. grupa C*, p=0,006, group B vs. group C/grupa B vs. grupa C, p<0,001

divided by average hemoglobin value. The adequacy of dialysis was expressed using Kt/V for urea in accordance with Daugirdas formula [19].

Cardiovascular morbidity score was calculated for each patient and on the basis of previous medical dialysis data file by giving one point for the following diagnosis: cardiomyopathy, ischemic heart disease, peripheral vascular disease and stroke.

Statistical calculations were performed using the SPSS (version 16.0) program. Data were expressed as percentage for discrete variables and mean values for continuous variables. Statistical analyses included exploratory analysis method (descriptive and analytic statistics). The analysis of variance (ANOVA) was used to compare the variables with normal distribution on different groups while Bonferroni test was used for setting the difference between the groups (post hoc analysis). In case where variables did not have normal distribution, Kruskal Walis test was used for comparing groups and the differences between groups were analyzed by Mann-Whitney test. Cox proportional hazard model was used to establish the impact of HD modality on the patients' mortality. Survival analysis was shown using Kaplan-Meier method while the statistical significance was tested using log-rank test.

The results were shown in tables and graphs. In all comparisons, p <0.05 was considered a statistically significant value.

Results

Characteristics of patients depending on HD modality are shown in **Table 1.** The patients from group A were significantly older compared to the patients in groups B and C, but there was no difference between group B and C. HD vintage was significantly different between the groups since the patients from group C and B were treated longer with HD compared to the patients from group A. Adequacy of dialysis expressed as Kt/V was statistically different among the groups – the highest values of Kt/V were seen in the patients in group C, which was significantly different when compared with the other

Table 2. Parameters of anemia in relation to hemodialysis modality
Tabela 2. *Parametri anemije u odnosu na hemodijalizni modalitet*

	Group A/*Grupa A* (LF HD) N=69	Group B/*Grupa B* (HF HD) N=64	Group C/*Grupa C* (HDF) N=26	P
Hemoglobin /*Hemoglobin*,g/dL	10,2±0,7	10,7±1,2	10,6±0,7	0,005*
Ferritin/*Feritin*, umol/L	366,3±160	347,9±173	412,0±237	>0,05
ESA use/*ASE upotreba*, %	97,1	76,6	80,8	<0,001†
ESA, IU/per week/*ASE, IJ/nedeljno*	5194±3190	5700±4940	7071±5800	>0,05
ERI/*ERI*	8,2±5,0	9,0±8,2	10,4±10	>0,05

LFHD - low-flux hemodialysis/*niskopropusna hemodijaliza*; HFHD - high-flux hemodialysis/*visokopropusna hemodijaliza*; HDF - hemodiafiltration/*hemodijafiltracija*; ESA - erythropoietin stimulating agents/*ASE - agensi stimulacije eritropoeze*; ERI - erythropoietin resistance index/*ERI - indeks rezistencije na ASE*; group A vs. group B/**grupa A vs. grupa B*, p=0,007;† Chi-square/*Hi kvadrat test* p<0,001

Table 3. Parameters of nutrition and inflammation in relation to hemodialysis modality
Tabela 3. *Parametri nutricije i inflamacije u odnosu na hemodijalizni modalitet*

	Group A/*Grupa A* (LFHD) N=69	Group B/*Grupa B* (HFHD) N=64	Group C/*Grupa C* (HDF) N=26	P
BMI/ *BMI*, kg/m²	24,1±4,6	24,4±4,0	23,6±4,8	>0,05
CRP/ *CRP*, mg/L	10,3±11,4	9,0±9,0	9,0±9,6	>0,05
Serum albumin/*Serumski albumin*, g/L	37,9±2,7	38,6±2,8	38,0±3,1	>0,05
Total cholesterol/*Ukupni holesterol*, mmol/L	4,5±0,9	4,53±0,9	4,74±1,0	>0,05
LDL cholesterol/*LDL holesterol*, mmol/L	2,6±0,7	2,6±0,7	2,7±0,7	>0,05
HDL cholesterol/*HDL holesterol*, mmol/L	1,2±1,1	1,0±0,3	1,1±0,3	>0,05
Triglycerides/*Trigliceridi*, mmol/L	1,9±0,8	1,8±1,1	2,2±2,4	>0,05

LFHD - low-flux hemodialysis/*niskopropusna hemodijaliza*; HFHD - high-flux hemodialysis/*visokopropusna hemodijaliza*; HDF-hemodiafiltration/*hemodijafiltracija; BMI - indeks telesne mase, CRP - C-reaktivni protein; LDL - lipoprotein male gustine holesterol; HDL - lipoprotein velike gustine holesterol*

Table 4. Parameters of mineral metabolism in relation to hemodialysis modality
Tabela 4. *Parametri metabolizma minerala u odnosu na hemodijalizni modalitet*

	Group A/*Grupa A* (LFHD) N=69	Group B/*Grupa B* (HFHD) N=64	Group C/*Grupa C* (HDF) N=26	p
iPTH/*iPTH*, pg/ml	345±356	554±637	451±402	0,054*
Calcium/*Kalcijum*, mmol/L	2,29±0,19	2,25±0,15	2,31±0,12	>0,05
Phosphorus/*Fosfor*, mmol/L	1,48±0,36	1,71±0,44	1,65±0,41	0,003**
Phosphate binders/*Vezivači fosfata*, %	84,1	82,8	92,3	>0,05
Yearly cumulative $CaCO_3$ dose *Kumulativna godišnja doza* $CaCO_3$	1016,5±517	1132,3±494	1238,3±664	>0,05
Vit D metabolites/*Vit D metaboliti*, %	47,8	51,6	59,8	>0,05
Yearly cumulative dose of vit D metabolites *Kumulativna godišnja doza metabolita vit D*	319,7±210	316,3±250	400,9±398	>0,05

LFHD - low-flux hemodialysis/*niskopropusna hemodijaliza*; HFHD - high-flux hemodialysis/*visokopropusna hemodijaliza*; HDF - hemodiafiltration/*hemodijafiltracija*; *group A vs. group B/*grupa A vs. grupa B*, p=0,048; **group A vs. group B/*grupa A vs. grupa B*, p=0,002

two groups; however, there was no difference between them.

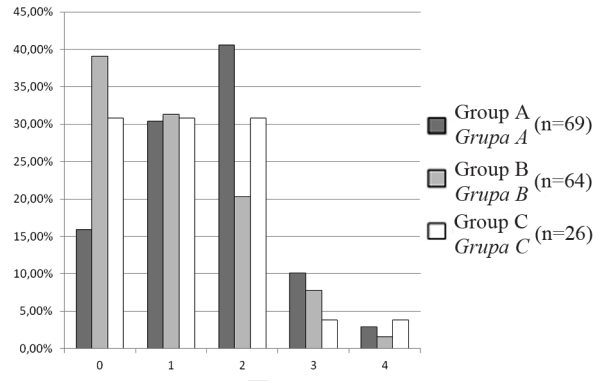
Parameters of anemic syndrome are presented in **Table 2.** The patients in group B had the highest values of hemoglobin which was statistically different from the patients in group A, while there was no significant difference between group B and C. The patients in group C had the highest values of ferritin while the lowest value was observed in the patients from group B but without a statistical significance among the groups. A significant difference was observed in ESA dosing: ESA were given most frequently to the patients in group A and least frequently to the patients in group B but without a difference between the average weekly doses of ASE among the groups in those patients who had it in therapy. There was no difference regarding ERI among the groups.

Parameters of nutrition and inflammation are shown in **Table 3.**

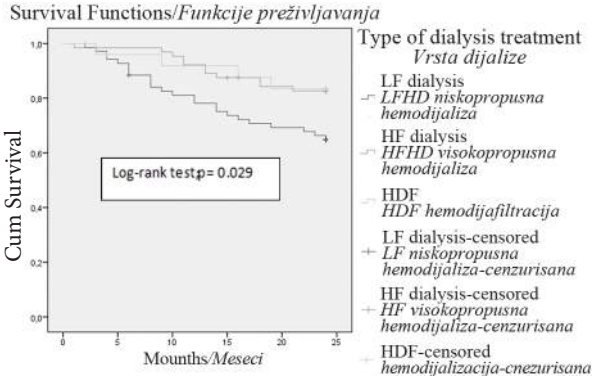
Parameters of mineral metabolism are shown in **Table 4**. It was revealed that the lowest values of intact parathyroid hormone (iPTH) were in the patients from group A while the highest values were found in the patients from group B and the difference was statistically significant. No significant difference was found in the values of serum calcium among the groups. The patients in group A had the lowest value of serum phosphorus while it was the highest in group B and the difference was statistically significant. There was no difference in the frequency of phosphate binder use among the groups. There was no difference in the cumulative yearly dose of calcium-carbonate and the metabolite of vitamin D in the patients receiving such therapy.

Score of cardiovascular morbidity is shown in **Graph 1.** The patients in group B and C had cardiovascular morbidity score zero more frequently than the patients in group A. Compared to the average value of cardiovascular morbidity score, there was a statistically significant difference between group B and A. The patients in group B had the lowest value of cardiovascular morbidity score (1.02) compared to the patients in group A (1.54) and group C (1.19).

According to Kaplan-Meier survival analysis, the patients in group C and B had a significantly better two-year survival compared to the patients in group A (**Graph 2**). In two-year period, the relative risk (RR)



Graph 1. Cardiovascular morbidity score in relation to hemodialysis modality
Grafikon 1. *Skor kardiovaskularnog morbiditeta u odnosu na hemodijalizni modalitet*



Graph 2. Kaplan-Meier survival curves of patients treated with different hemodialysis modalities
Grafikon 2. *Kaplan-Majerova kriva preživljavanja bolesnika lečenih različitim dijaliznim modalitetima*

of mortality was 56% lower in the patients in group B than in group A (HR 0.44; 95% CI 0.22 - 0,905; p=0.026); whereas the patients in group C had 58% lower RR of mortality for the same period than the patients in group A: however, no statistical significance was reached (HR 0.42; 95% CI 0.15 – 1.202; p=0.105)

Discussion

This study analyzed the parameters of HD efficiency depending on the type of dialysis membrane (low-flux and high-flux) and dialysis technique (standard bicarbonate HD vs. HDF). There was a statistically significant difference among the groups in dialysis adequacy measured by Kt/V index. Higher values of Kt/V index in the patients treated with HDF compared to the patients treated with standard bicarbonate HD were also seen in other studies and they were expected because of additional convective transport of small molecules [20]. The patients in group A had slightly higher Kt/V values than group B even though they were statistically irrelevant. Since such a difference cannot be explained by the type of membrane used, it is likely that other factors, which were not taken into consideration in this study, also affected Kt/V such as the type of vascular access and blood flow through the vascular access, the speed of blood pump and the number of hypotensive episodes during HD session and shortening of dialysis session. The above mentioned parameters were not the subject of this study but they can explain these subtle differences in Kt/V values which did not reach statistical significance. Better acid-base status was not seen in the patients treated with high-flux HD and HDF compared to the patients treated with low-flux HD, which has been seen in some other studies [16].

Regarding some parameters of anemia, a partially favorable effect of high-flux HD and HDF was found since the patients from these treatment groups had higher values of hemoglobin with less frequent use of ESA. However, no difference was seen in either the average dose of ESA or in the resistance to ESA in the patients who had used such therapy; what is more, the patients in group B and C received higher doses of ESA and they had higher values of ERI but there was no statistically significant difference between the groups. These data are in contradiction with some other studies regarding the effect of dialysis treatment on the correction of anemia and ESA dose [13, 21–24]; while smaller and observational studies suggested a positive effect of high-flux HD and HDF on anemia indices [13, 21], bigger and more recent randomized studies did not confirm these findings [22–24].

This study found no statistically significant difference among the groups regarding some nutrition parameters, such as BMI, serum albumins and lipids. These results do not suggest better nutritional status in the patients treated with high-flux HD and HDF. Regarding the values of CRP, there was no significant difference among the groups so better correction of anemia could not be explained by the absence of active inflammation. Neither did some recent prospective studies find a difference in the nutritional status between the patients treated with high-flux HD and HDF [16, 25] nor between the patients treated with high-flux HD and HDF compared to the patients treated with low-flux HD [22–26]. This suggests that the nutritional status hardly depends on the type of membrane and dialysis technique. It is known that the inflammatory status within MIA syndrome (syndrome of malnutrition, inflammation and aterosclerosis syndrome) has the highest impact on malnutrition [27].

Although unexpected, the lowest iPTH and serum phosphorus values were observed in group A but the mean values in all three groups were within the reference range. Some recent prospective studies showed significantly lower phosphorus values in the patients treated with HDF and high-flux HD compared to the patients treated with low-flux HD [15, 26]; however, that finding was not seen in our study. Such

results in our study may not be interpreted as better appetite in the patients treated with HDF and high-flux HD because there was no difference among the groups regarding nutritional parameters. We believe that these results may have resulted from better compliance with the recommended dietetic regime shown by the patients in group A, which is characteristic of older population. A possible reason for higher iPTH values in group B and C compared to group A could also be a result of different Calcium concentration in dialysate (lower values of Calcium in dialysate in group B and C), but that parameter was not tested in our study. Literature data suggest that lower values of iPTH are more frequent in older people and in those with diabetes, which can be an additional explanation for this finding [28]. In the CONTRAST study, a decrease in iPTH values was not seen after switching from low-flux HD to HDF [15], which can partially be compared with our findings suggesting that HDF treatment did not lead to a better iPTH control. In addition, the same study did not reveal a reduction in frequency and dose of phosphate binders after switching to HDF, which is in agreement with our results.

Due to a lower score of cardiovascular morbidity in group B and C, lower mortality was expected as a result in these two groups, which was also proved using Kaplan-Meier survival analysis in a two-year period. The patients in group C and B had better two-year survival compared to the patients in group A (without a statistical significance between group C and A probably due to the unequal number of patients). High-flux HD was related to the RR of mortality reduced by 56% compared to low-flux HD, while HDF had the RR of mortality reduced by 58% compared to low-flux HD. Lower mortality in group B and C compared to group A could be a consequence of the difference in age of the patients as well as of the difference in dialysis membrane and technique used. However, a statistical significance was reached only between group B and A and possible explanations is not only the unequal number of patients but also the longest dialysis vintage in group C and the highest number of high-risk patients with diabetes and hypertension in the same group. Some observational studies reported better survival of the patients treated with HDF compared to the patients treated with high-flux HD (which was not seen in our study) and better survival as compared to those treated with low-flux HD (which is similar to our results) [16, 27]. However, several randomized controlled studies as well as meta analyses which had compared survival of the patients treated with HDF and high-flux HD, HDF compared to the patients treated with low-flux HD and high-flux compared to low-flux HD, did not find a difference in patients' survival [11, 17, 29–33], except for the ESHOL study and *post hoc* analysis in ''Turkish study'' when high substitution volumes during HDF were used [29, 31]. The amount of convective volume during HDF was not followed in this study and it could be one of the reasons why there was no difference in survival of the patients treated with HDF and high-flux HD. By analyzing 33 randomized controlled studies which had compared high-flux and low-flux HD, Palmer et al. concluded that cardiovascular mortality was reduced by about 15% in the patients treated with high-flux HD [17].

Conclusion

Regarding parameters of adequacy, the study showed that the patients treated with hemodiafiltration had higher Kt/V index values compared to the patients treated with high-flux and low-flux hemodialysis. In addition, the patients treated with hemodiafiltration and high-flux hemodialysis had better correction of anemia parameters (higher hemoglobin values with less frequent administration of erythropoietin stimulating agents), whereas there was no difference among the groups regarding nutritional parameters. The study showed the advantage in two-year survival in the patients treated with high-flux hemodialysis and hemodiafiltration (statistical significance was not reached) compared to the patients treated with low-flux hemodialysis. There was no difference in survival between the patients treated with low-flux hemodialysis and hemodiafiltration.

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REVIEW ARTICLES
PREGLEDNI ČLANCI

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Review article
Pregledni članak
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PHARMACOGENOMIC DETERMINANTS OF RESPONSE TO CARDIOVASCULAR DRUGS

ULOGA FARMAKOGENOMSKIH FAKTORA U ODGOVORU NA KARDIOVASKULARNE LEKOVE

Karmen M. STANKOV[1,2], Bojan G. STANIMIROV[1,3] and Momir M. MIKOV[1,3]

Summary
Cardiovascular diseases are the leading cause of morbidity and mortality worldwide. Despite considerable advances in cardiovascular pharmacology, significant inter-individual variability in response to drugs affects both their efficacy and safety profile. Drug-gene associations have emerged as important factors determining a spectrum of response to therapy. Pharmacogenomic interactions in cardiovascular medicine are also involved in etiology of adverse effects that may be life-threatening, such as statin-induced myopathy or a hemorrhage/thrombosis event during anticoagulant therapy. Introduction of genetic tests prior to the initiation of therapy and implementation of genetically-guided therapy represent a step forward to achieving a goal of individualized medicine in cardiology, already present in recommendations for warfarin and clopidogrel. However, further investigations addressing genomic predictors of variability in response to drugs are still needed and translating these findings into routine clinical practice remains a substantial challenge.
Key words: Cardiovascular Agents; Pharmacogenetics; Individualized Medicine; Treatment Outcome; Drug-Related Side Effects and Adverse Reactions; Practice Guideline; Polymorphism, Genetic; Hydroxymethylglutaryl-CoA Reductase Inhibitors; Thienopyridines; Warfarin; Adrenergic beta-Antagonists; Angiotensin-Converting Enzyme Inhibitors; Anti-Arrhythmia Agents; Genetic Testing

Sažetak
Kardiovaskularna oboljenja predstavljaju vodeći uzrok morbiditeta i mortaliteta širom sveta. Uprkos značajnom napretku u razvoju kardiovaskularnih lekova, pojava interindividulane razlike u odgovoru na terapiju utiče i na efikasnost i na bezbednosni profil ovih lekova. Genetski polimorfizmi predstavljaju značajan faktor koji utiče na odgovor na primenu lekova. Farmakogenetske interakcije u kardiovaskularnoj medicini se često nalaze u osnovi neželjenih dejstava koja mogu biti potencijalno fatalna kao što je statinima indukovana miopatija, krvarenje ili tromboembolijski događaji tokom terapije antikoagulantnim ili antiagregacionim agensima. Izvođenje genetskih testova pre primene lekova i implementacija terapijskih smernica u skladu sa farmakogenetskim profilom predstavlja korak napred ka dostizanju personalizovane terapije u kardiologiji, a već je prisutno u smernicama za terapiju varfarinom i klopidogrelom. Međutim, neophodna su dalja istraživanja u definisanju genetskih prediktora koji utiču na terapijski odgovor, uz brojne faktore koji utiču na brzinu translacije ovih rezultata u svakodnevnu kliničku praksu.
Ključne reči: Kardiovaskularni lekovi; Farmakogenetika; Individualizovana medicina; Ishod lečenja; Komplikacije i neželjeni efekti izazvani lekovima; Vodiči u praksi; Genetski polimorfizam; Statin; Klopidogrel; Varfarin; Beta blokatori; ACE inhibitori; Antiaritmici; Genetsko testiranje

Introduction

As a leading cause of morbidity and mortality, cardiovascular diseases represent one of the most pervasive and expensive disorders worldwide [1]. Significant inter-individual variability in response to cardiovascular drugs affects both their efficacy and safety profile [2, 3]. This may occur as a result of either perturbations in drug pharmacokinetics or pharmacodynamics. Various factors underlie the inter-individual variability to therapy, including clinical (age, comorbidities, pregnancy, etc.), environmental (drug-drug and drug-food interactions) and genetic factors, including intestinal microbiota composition [4, 5]. Pharmacogenomics is a discipline that studies the genetic determinants of individual variation in response to a given drug, aiming to facilitate the personalization of ther-

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Abbreviations

ABCB1 – ATP binding cassette sub-family B member 1
ACE I/D – Angiotensin converting enzyme insertion/deletion
ACEI – Angiotensin converting enzyme inhibitors
ACS – Acute coronary syndrome
ADR – Adverse drug reaction
CPIC – Clinical Pharmacogenetics Implementation Consortium
GWAS – Genome-wide association studies
HMGCR – 3-hydoxy-3-methylglutaryl-coenzyme A reductase
INR – International normalized ratio
OATP1B1 – Organic Anion Transporting Polypeptide 1B1
PCI – Percutaneous coronary intervention
RAAS – Renin-angiotensin-aldosterone system
SLCO1B1 – Solute carrier organic anion transporter family, member 1B1
SNP – single nucleotide polymorphism
TdP – Torsade de Pointes
VKORC1 – Vitamin K-epoxide reductase subunit 1
DNA – deoxyribonucleic acid
LDLc – low-density lipoprotein cholesterol
CYP – cytochrome P 450

apy through genotype-informed selection of a drug and/or dose in order to predict and improve the responsiveness to therapy, as well as to minimize the risk of adverse drug reactions (ADRs) [2]. Following the success of the Human Genome Project, the HapMap Project and the 1000 Genomes projects have profoundly increased our knowledge of genetic architecture and polymorphisms in the human genome. The translation of genetic association to clinical practice has been generally slow and its impact is most profound in the field of oncology [6–8]. However, the substantial progress in cardiovascular pharmacogenomics during the past decade improved our understanding of genetic determinants influencing the response to certain cardiovascular medicines including statins, warfarin and clopidogrel, enabling the realization of the vision of genomics-based healthcare and personalized medicine.

A Brief Review of Commonly Used Terminology

The deoxyribonucleic acid (DNA) sequence represents the unique genotype of an individual, whereas a trait resulting from the protein product encoded by the gene is a phenotype. The genotype is formed from two alleles per autosomal gene, one maternal and one paternal. Homozygotes possess two of the same alleles, while heterozygotes possess two different alleles. A haplotype is a combination of alleles or polymorphisms at nearby locations on a chromosome that are inherited together. The most common allele in population is referred to as the wild-type one. Several types of genetic variations are relevant to pharmacogenomics. The most common form is single nucleotide polymorphism (SNP), a substitution of a single DNA base pair within a genome. SNPs may occur within introns, the regions that are not translated to messenger ribonucleic acids (RNA) and proteins. However, SNPs also occur within exons, the protein-coding regions of the gene, in which they do not cause an alteration of the amino-acid sequence in protein (synonymous polymorphisms), or SNPs lead to a change in amino-acid sequence (non-synonymous polymorphisms) [9]. The identification of genomic variation can be performed by focused studies of genes or genomic regions of interest or through genome-wide association studies (GWAS) that are performed with high-density SNP genotyping platforms in thousands of subjects with important potential to discover the novel genetic associations.

Statins

Cholesterol-lowering agents - statins, the most commonly prescribed class of medicines worldwide, are indicated for both primary and secondary prevention of cardiovascular disease. Their pharmacological action is based on a competitive inhibition of 3-hydoxy-3-methylglutaryl-coenzyme A reductase (HMGCR), a rate limiting enzyme in endogenous, hepatic cholesterol synthesis pathway [10]. Besides decreasing cholesterol synthesis, statins up-regulate the hepatic expression of low-density lipoprotein receptor (LDLr), which results in increased clearance of low-density lipoprotein cholesterol (LDLc). Inter-individual variability in the extent of LDLc lowering by statins, resulting in the increased risk of cardiovascular events for the patients with specific genotype despite the multiple dose adjustments, is influenced by genetic heterogeneity. Moreover, genetic variants have been associated with statin-induced myopathy as a serious side effect. Therefore, pharmacogenomics contributes to identification of genetic polymorphisms that may influence the pharmacokinetics and pharmacodynamics of statin therapy, being relevant to the efficacy of treatment, prevention of adverse drug reactions as well as for the patient's compliance [11].

Simvastatin, atorvastatin and lovastatin are inactivated by cytochrome P 450 (CYP3A4); therefore, polymorphisms in gene encoding this enzyme modify the pharmacokinetics of these statins and affect the dosing requirements. The carriers of loss-of-function allele variant, CYP3A4*22, require only 20–60% of the statin dose compared to the non-carriers taking stable doses of atorvastatin, simvastatin, or lovastatin for the optimal lipid control [12]. About 7% of Caucasian population possess at least one CYP3A4*22 allele [13]. Genetic variation of HMGCR can also result in significantly attenuated responses to statin pharmacotherapy. H7 haplotype of HMGCR, including three intronic SNPs: rs17244841, rs3846662, and rs17238540, is thought to be involved in production of HMGCR isoform through alternative splicing of transcript. The rs# code refers to the unique identification number for genetic polymorphism recorded in SNP Database, maintained by the National Centre for Biotechnology Information (NCBI) in collaboration with the Human Genome Research

Institute (NHGRI) [14]. Carriers of H7 haplotype have an attenuated reduction of LDLc following simvastatin and pravastatin therapy; however, this effect was not observed in studies with other statins [15]. Another HMGCR haplotype, H2 (rs3846662), as well as L5 haplotype of LDLr, diminish the sensitivity to statins, particularly in African population. Genetic variations in apolipoprotein-E (haplotypes ε2, ε3, and ε4 defined by two SNPs: rs7412 and rs429358) have been shown to attenuate the statin effectiveness [16, 17]. Adenozin-triphosphate (ATP)-binding cassette sub-family B member 1 gene (ABCB1) encodes p-glycoprotein which promotes the efflux of statins and their metabolites from hepatocytes, enterocytes and renal tubular cells, affecting the statins bioavailability. A sequence variation in ABCB1 gene, namely 2677 G>T(A) (indicating that the polymorphism has a thymine or adenine in place of guanine at the base position 2677 of the ABCB1 complementary DNA sequence), has been shown to be associated with improved lipid-lowering efficacy of statin treatment [18]. The associations between genetic variants in other candidate genes including cholesterol ester transferase protein, calmin, and kinesin-like protein 6 and statin efficacy should be investigated more thoroughly.

Solute carrier organic anion transporter family, member 1B1 (SLCO1B1) gene encodes the statins influx transporter, an organic anion-transporting polypeptide 1B1 (OATP1B1). Regarding the statin adverse effects, the pharmacogenomic association of greatest magnitude found so far is between SLCO1B1 non-synonymous SNP polymorphism rs4149056 and statin-induced muscle toxicity (521C>T, Val174Ala amino-acid change from valine to alanine, defining SLCO1B1*5 variant). The association between SLCO1B1*5 polymorphism and muscle toxicity exists for multiple statins (such as pravastatin and pitavastatin),]; however, the evidence is strongest for simvastatin, whereas the currently available data do not support the clinical translation of SLCO1B1*5 for the prediction of atorvastatin- or rosuvastatin-induced myopathy [19]. The rs4149056 polymorphism causes the perturbation of the OATP1B1 localization in the cell membrane of hepatocytes reducing its transport activity, which consequently results in increased plasma concentration and systemic exposure of simvastatin, thus leading to the increased risk of muscle toxicity [13]. Fifteen percents of the population are the carriers of rs4149056 and 60% of patients with myopathy have been shown to be the carriers of risk allele [20]. Since the OATP1B1 transports statins from the circulation into the hepatocytes, representing the primary cholesterol-lowering site of statins action, this polymorphism has been expected to result in lower statin efficacy. However, significant reductions in efficacy have not been reported yet. In addition, some statin-treated patients develop an immune-mediated necrotizing myopathy that continues even after discontinuation of statin. This myopathy is characterized by forming HMGCR auto-antibodies. This sub-phenotype of myopathy has been associated with HLA-DR1*11:01 polymorphism [21].

Based on the highly prevalent use of simvastatin, Clinical Pharmacogenetics Implementation Consortium (CPIC) generated the guidelines in October 2014 with clinical recommendations regarding the implementation of genetic information on SLCO1B1 genotype in order to reduce the potential risk of myotoxycity and to guide the therapeutic decisions in rs4149056 carriers. For patients with a modest risk, the recommendations include the use of lower doses of simvastatin and routine creatine kinase monitoring. If myotoxycity occurs or desirable LDLc level is not achieved, the use of an alternative statin is recommended [22].

Warfarin

Being the most frequently prescribed oral anticoagulant agent worldwide, warfarin is widely used in the treatment and prevention of thrombo-embolic events. Warfarin is administered as a coumarin-derived racemic mixture that antagonizes vitamin K-epoxide reductase subunit 1 (VKORC1) and inhibits the activation of vitamin K-dependent coagulation factors II, VI, IX and XI. The degree of anticoagulant action is monitored by measuring the international normalized ratio (INR); however, due to significant inter-individual dose-response variability and narrow therapeutic window, the INR is frequently outside the target therapeutic range, which increases the risk of thromboembolism and bleeding [23]. Clinical factors such as age, weight, diet and interacting drugs account for 26% of inter-individual therapeutic dose warfarin variability [24]. However, clinical factors associated with genetic factors are considered to be implicated in 60% of warfarin maintenance dose variability [25]. Genetic polymorphisms at three loci have been associated with variable response to warfarin dosing [26].

CYP2C9 enzyme catalyzes the predominant reaction of hydroxylation, which results in the transformation of more active enantiomer S-warfarin into an inactive metabolite. CYP29C genotype accounts for up to 10% of warfarin dosing variability [27]. More than 30 allelic variants of CYP2C9 gene are recognized. Two most common minor loss-of-function allele variants in Caucasian population are CYP2C9*2 (rs1799853) and CYP2C9*3 (rs1057910) with frequencies of 0.13 and 0.07, respectively [23]. CYP2C9*2 and CYP2C9*3 polymorphisms result in the production of proteins with enzymatic function reduced by 40 and 90%, respectively [28]. This results in the prolonged half-life of warfarin, elevated warfarin concentrations and increased susceptibility to hemorrhagic complications during treatment. A large meta-analysis confirmed that, compared to wild-type homozygotes (*1 allele), the heterozygous carriers of CYP2C9*2 and CYP2C9*3 need reduction in warfarin dosing by 19% and 33%, respectively, whereas in homozygous carriers even great-

er dose reductions are required, up to 36% and up to 78%, respectively, in order to achieve a steady state [29]. Since CYP2C9 is also responsible for the bioactivation of losartan and other angiotensin-receptor blocking agents, the presence of loss-of-function alleles could also result in reduced antihypertensive effects [30].

VKORC1 is a rate limiting enzyme of vitamin K cycle which converts the oxidized, inactive form of vitamin K into the active form, and represents a pharmacological target of warfarin. SNPs in the non-coding promoter region of VKORC1 gene, rs9923231 (-1639G>A) and rs9934438 (-1173C>T) result in reduced promoter activity, decreased enzyme expression and lower warfarin dose requirements [23]. On the other hand, several rare non-synonymous VKORC1 polymorphisms resulting in a changed amino-acid protein sequence confer warfarin resistance, thus resulting in higher dose requirements to achieve the stable anticoagulation.

CYP4F2 also metabolizes the reduced, epoxide form of vitamin K to an inactive form, hydroxy-vitamin K. GWAS have identified a non-synonymous polymorphism rs2108622 (1297G>A, Val433Met) as a predictor for higher warfarin dose requirement [31].

Despite six decade-long clinical experience, warfarin has been identified as the second leading cause of drug-related emergency room visits due to its ADRs: thrombo-embolism and hemorrhage. Numerous warfarin dosing algorithms that include genetic information (predominantly CYP2C9, VKORC1 with or without CYP4F2) have been designed and clinically evaluated in order to facilitate the clinical implementation of genetic information [32]. The International Warfarin Pharmacogenetics Consortium (IWPC) pharmacogenetic algorithm is one of the high-performing and validated algorithms, recommended by the CPIC guidelines, with the aim to predict warfarin dose based on available information on genomic variation [23]. Patients may benefit from incorporation of pharmacogenomic information into the warfarin dosing algorithms by reducing the time to achieve the initial therapeutic and stable INR values, optimizing time spent within therapeutic range and reducing ADRs. The ongoing clinical trials aimed at genotype-guided dosing will provide more clinically-relevant information.

Clopidogrel

Clopidogrel is a second generation thienopyridine. Its active metabolite binds to $P2Y_{12}$ receptors located on the platelet membrane and antagonizes the adenosine diphosphate-mediated platelet aggregation throughout their life time. As a pro-drug, clopidogrel undergoes multiple bioactivation processes mediated by CYP1A2, CYP3A4/5, CYP2B6, CYP2C9, and CYP2C19 enzymes to generate pharmacologically-active metabolite. Clopidogrel is indicated in the prevention of thrombo-embolic events including myocardial infarction and stent thrombosis. However, cardiovascular events occur in 12% of patients with acute coronary syndrome (ACS) on clopidogrel. Considerable inter-individual variability in its anti-platelet response has been shown to be associated with certain genotypes [33].

Polymorphisms in CYP2C19 are associated with decreased or increased function of this enzyme, which is mainly responsible for clopidogrel bioactivation. The most common loss-of function SNP defining CYP2C19*2 variant (rs4244285; 681G>A) is associated with the reduced enzymatic activity and subsequently impaired clopidogrel activity [34]. Carriers of this polymorphism have a significantly increased risk of adverse cardiac events, particularly the stent thrombosis following percutaneous coronary intervention (PCI), compared to non-carriers (*1/*1) [35]. The risk is high for heterozygous genotype variant carriers (*1/*2, "intermediate metabolyzers"), which is found in 25%, and even higher in homozygous allele carriers (*2/*2, "poor metabolyzers") which was found in 2% of Caucasian population [36]. Other loss-of-function alleles including CYP2C19*3 (rs4986893), CYP2C19*4 (rs28399504), and CYP2C19*5 (rs72552267) have minor allele frequency in Caucasians. On the other hand, CYP2C19*17 variant (rs12248560; -806C>T) is the most frequent polymorphism that results in enhanced transcription and increased enzymatic activity [36]. Carriers of this allele, the so called "ultra-rapid metabolizers", have an increased risk of hemorrhage [37].

Another significant polymorphism that affects a response to clopidogrel treatment represents a variant of ABCB1, gene encoding P-glycoprotein - an extensively distributed efflux transporter with broad substrate specificity. Common 3435 C>T polymorphism in ABCB1 gene (rs1045642) has been associated with reduced intestinal absorption and bioavailability of clopidogrel, and higher rates of adverse cardiovascular outcomes, particularly in homozygous TT carriers [38]. Moreover, a missense Gln192Arg variant of paraoxonase-1, an enzyme responsible for bioactivation of clopidogrel, is thought to be associated with a higher risk of stent thrombosis [39]. Carboxylesterase-1 is an enzyme responsible for inactivation of clopidogrel's active metabolite. Non-synonymous minor allele variant Gly143Glu (rs71647871) impairs the catalytic activity of this enzyme, resulting in a higher level of clopidogrel active metabolite [40].

Although a routine CYP2C19 genotyping in clinical practice for clopidogrel therapy was not recommended by the American Heart Association consensus guidelines due to insufficient amount of convincing data, CYP2C19 genotyping should be considered in the patients believed to be at high risk to have poor prognosis (e.g. patients undergoing PCI for extensive coronary ischemic disease) before introducing clopidogrel therapy [41]. According to CPIC guidelines, the patients with ACS managed with PCI and available CYP2C19 genotype status should be administered an alternative antiplatelet therapy (prasugrel or ticagrelor) if loss-of-function

CYP2C19 allele is present [36]. Investigators at Vanderbilt University have already described the program implementing the pre-emptive CYP2C19 genotyping in candidate patients for clopidogrel therapy [42].

Beta–Adrenergic Antagonists

Beta–adrenergic antagonists (β-blockers) are indicated for the management of numerous conditions including hypertension, angina pectoris, ACS, arrhythmias and heart failure. β-blockers act by antagonizing the endogenous catecholamine action at β-adrenergic receptors, β1 and β2 receptor subtypes being the most important for cardiovascular pharmacology. Inter-individual variability in response to β-blocker therapy has raised the question of genetic components associated with β-blocker response.

Two common non-synonymous polymorphisms in β-1-adrenergic receptor gene, ADRB1: rs1801252 (Ser49Gly), and rs1801253 (Arg389Gly) result in the modulation of β-blocker action. Arg389 variant common in Caucasian population is associated with enhanced agonist-mediated G-protein-coupled signaling and provides increased β-blocker responsiveness. In patients with heart failure, homozygous carriers of this polymorphism, therapy with β-blockers (carvedilol, metoprolol, and bucindolol) has been shown to result in a significantly greater improvement in the left ventricular ejection fraction compared to non-carriers [43]. Similarly, improved anti-hypertensive response to β-blockers has been reported among homozygous carriers of rs1801253 [25].

Two common polymorphisms in β-2-adrenergic receptor gene, ADRB2: rs1042713 (Arg16Gly), and rs1042714 (Gln27Glu) result in the resistance to agonist-mediated down-regulation; however, the majority of studies have not confirmed the associations between these polymorphisms and clinical outcomes so far [19].

Common deletion in α_{2C}-adrenergic receptor gene, ADRA2C (ADRA2C Del 322-325), results in the loss of four amino-acids. Patients with heart failure, carriers of this genotype have been found to have worse disease-related outcomes [44]. However, carriers of this genotype have a greater improvement of left ventricular function during treatment with metoprolol but not with bucindolol [45].

Several β-blockers, including propranolol, metoprolol, timolol, and carvedilol, are metabolized by CYP2D6, whose loss-of-function polymorphisms are common among Caucasian population. Polymorphisms underlying a poor metabolizing phenotype have been shown to result in significantly elevated plasma concentrations of metoprolol, potentiating its hypotensive effects and increased risk of bradyarrhythmias [46]. On the other hand, carvedilol is also CYP2D6 substrate; however, clinical effects have not been observed in poor metabolizers; therefore, it is not necessary to consider dose adjustments in these patients [25]. The United States Food and Drug Administration (FDA) recommendations suggest that caution should be exerted among heart failure patients treated with β-blockers who are the carriers of CYP2D6 loss-of-function polymorphism in order to avoid adverse drug reactions [47].

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors (ACEI) antagonize the renin-angiotensin-aldosterone system (RAAS) and are indicated in the therapy of hypertension, chronic heart failure, ACS and diabetic nephropathy. A common polymorphism in ACE gene, an insertion/deletion (ACE I/D) within intron 16 (rs4646994) correlates with plasma enzyme levels [48]. An observational study reported a significantly higher mortality risk among homozygous carriers of D allele (D/D) compared to those with I/I genotype [49]. However, neither of these findings were replicated in other prospective studies nor the pharmacogenomic interaction between ACE I/D polymorphism and ACEI therapy has not been confirmed so far. Other candidate genes in RAAS have been examined; however, only two polymorphisms in angiotensin-II receptor type I and one in the bradykinin type-1 receptor gene were associated with beneficial effects during therapy with perindopril [50]. A rare adverse drug reaction following therapy with ACEI is angioedema, which manifests in 0.1-0.7% of population, most commonly long after ACEI initiation. A recent GWAS found no significant SNP associations for ACEI-induced angioedema [51]. Furthermore, no association between ACE I/D genotype and ACE-induced cough has been found in recently performed meta-analysis [52]. Due to the insufficiency and inconsistency of the results, there is no clear candidate gene of RAAS for clinical implementation of routine pharmacogenomic testing.

Antiarrhythmics

Drug-induced ventricular arrhythmias are unpredictable and present the potentially fatal adverse drug reactions. Antiarrhythmic drugs act by perturbing the cardiomyocytes repolarization and causing prolongation of QT interval, which may be associated with an increased risk of developing the malignant arrhythmia Torsade de Pointes (TdP). TdP is a common cause of drug relabeling and withdrawal. Most drug induced-TdPs are related to antiarrhythmic drugs including amiodarone, flecainide, and sotalol, as well as to non-cardiovascular drugs such as erythromycin, domperidone, and chlorpromazine. In addition to clinical factors including electrolyte imbalances, co-medication or cardiac disease, multiple polymorphisms in at least 13 genes encoding ion channels or proteins that modulate channel function significantly contribute to inducing prolonged QT interval and TdPs [53]. Non-synonymous SNP in gene that encodes the potassium channel subunit, potassium voltage-gated channel subfamily E member 1 (rs1805128), leads to an amino acid substitution from aspartic acid to asparagine at position 85 of the translated protein (Asp85Asn; D85N). This polymor-

phism, relatively common in population (minor allele frequency 1-2%), has been associated with significantly increased risk of TdPs [54]. In addition, SNP polymorphism in nitric oxide synthase 1-adaptor protein, rs10919035, a protein which interacts with neuronal nitric oxide synthase and accelerates cardiac repolarization, increases the risk for amiodarone-induced TdPs [55].

Conclusion

Introduction of genetic tests prior to the initiation of therapy and implementation of genetically-guided therapy represents a step forward to achieving a goal of individualized medicine in cardiology, providing a potential to identify the patients who are likely to respond to therapy but who require lower or higher doses, as well as the patients who should be given an alternative therapy (those likely to be non-responders and those at an increased toxicity risk). This approach is already present in recommendations for warfarin and clopidogrel. Despite the increasing number of established drug-gene associations, further investigations addressing genomic predictors of variability in response to drugs are still needed and substantial challenge remains in translating these findings into routine clinical practice. Incorporation of pharmacogenomic research findings into clinical practice and development of evidence-based guidelines represent the fundamentals of personalized therapy concept, enabling clinicians to individualize cardiovascular drug therapy based on anticipated response of the patient.

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THINGS THAT CAN BE CHANGED IN EARLY INTERVENTION IN CHILDHOOD

STVARI KOJE SE MOGU IZMENITI U RANOJ INTERVENCIJI U DETINJSTVU

Špela GOLUBOVIĆ[1,2], Jasminka MARKOVIĆ[1,3] and Lidija PEROVIĆ[4]

Summary

Introduction. Early intervention implies a model of support focused on a child, family and a broader community from early childhood. The aim of this study was to analyze the elements of the successful early intervention in childhood, as well as to assess the role of a special educator and rehabilitator and level of their involvement in implementing the program on the territory of Novi Sad. **Material and Methods.** The study sample included 100 parents of children with disabilities (aged 3-7), who completed the questionnaire designed for the purposes of this research, based on a similar questionnaire design. **Results.** Speech delay is one of the most common reasons (over 50%) why parents seek professional help. By the end of the first year of life of their child, 43% of parents responded that they had noticed the first problems, that is, a problem was identified in 25% of children of this age group, and the same number was included in the treatment. About 55% of children were involved in organized treatment from 3 years of age onwards. Special educators and rehabilitators are usually involved in treatment when the team consists of three or more professionals. **Conclusions.** It is necessary to improve early intervention services, to educate staff, and provide conditions which would make it possible to overcome the existing disadvantages in treating children from an early age. In addition, the involvement of special education and rehabilitation professionals in treatment teams since children's early age is vital.

Key words: Early Intervention (Education); Early Diagnosis; Health Care Facilities, Manpower, and Services; Parents; Child; Child, Preschool; Disabled Children; Questionnaires; Language Development Disorders; Education, Special

Sažetak

Uvod. Rana intervencija podrazumeva širok opseg podsticanja usmeren prema detetu i njegovoj porodici i široj okolini, od najranijeg uzrasta. Cilj istraživanja bio je da se analiziraju navedeni elementi uspešne rane intervencije u detinjstvu, kao i da se ispita koja je uloga defektologa i koliko je uključen u samo sprovođenje programa na području grada Novog Sada. **Materijal i metode.** Uzorak je činilo 100 roditelja dece sa smetnjama u razvoju (uzrasta 3−7 godina) koji su popunili upitnik konstruisan za potrebe istraživanja po uzoru na slična istraživanja. **Rezultati.** Jedan od najčešćih razloga (više od 50%) zbog kog se roditelji obraćaju stručnjacima za pomoć jesu problemi u govoru. Do kraja prve godine, 43% roditelja navodi da su primetili prve probleme kod deteta, odnosno 25% dece je u tom uzrastu imalo identifikovan problem, a isto toliko je uključeno u tretman. Oko 55% dece je uključeno u organizovan rad od treće godine pa nadalje. Defektolog je najčešće uključen u rad kada se radi o timovima sa tri i više stručnjaka. **Zaključak.** Neophodno je razvijati servise rane intervencije, edukovati kadar i obezbediti uslove koji bi omogućili da se postojeće manjkavosti u radu sa decom od najranijeg uzrasta prevaziđu. Pored toga, neophodno je angažovanje defektologa za rad sa decom od najranijeg uzrasta u okviru timskog rada.

Ključne reči: Rana intervencija; Rana dijagnoza; Zdravstveni kapaciteti, ljudstvo i servisi; Roditelji; Dete; Predškolsko dete; Deca sa smetnjama u razvoju; Upitnici; Poremećaji razvoja govora; Specijalna edukacija

Introduction

Over the past forty years, there have been growing concerns and interest in implementation of early intervention programs designed for children with perinatal risk factors for adverse neurodevelopmental outcome, developmental disabilities, problems in socio-emotional development, children from disadvantaged backgrounds and their parents. In developed countries, the number of children with neurorisks ranges from 10 to 15% [1, 2]. The European network for early intervention proposes an early intervention as a model of support focused on children, families and broader communities from

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the earliest stage of a child's life, with the aim to improve the child's condition and development and assist the family in meeting their child's developmental needs [3]. The program has been designed to include children 0 to 5 years of age. This period is the time of rapid motor, cognitive, linguistic, and social-emotional development [4]. One of the benefits of interventions initiated at the earliest age is the ability to exploit plasticity of the childs brain at an early age, which provides the opportunity to implement a variety of intervention programs that help children acquire and improve a variety of skills at early ages [5–7]. The findings stated by Pinjatela [8] show that the programs introduced nine months after birth have the most positive effects on the subsequent development in children. Early intervention programs relate to children, families and social environment, and beneficial effects they produce can be seen through their implementation.

Based on the knowledge of child's mosaic development and inconsistency of children's response to the same programs, as well as the selection of the program in relation to the type and degree of disability, the effects are expected to be different for each child [9]. The impact evaluation of implemented child-focused programs confirmed their contribution to the social-cognitive development in children, development of their social competence, improved school achievements, reduced dropout and repetition rates, reduced need for special education, continued education, reduced behavioral problems in adolescence and lower abuse of psychoactive substance [5–14].

Parental inclusion, in particular, appears to be of crucial importance as a key factor for successful intervention. Parents are faced with the fact that their child has a problem which may have harmful effects on the later development and learning ability. This situation causes parenting stress related to a sense of social isolation, loss of self-confidence, many crisis situations, changes in the partner and family relationships, as well as health problems, which can all have a negative effect on the child's development [15–19]. Early intervention helps parents to cope with potential frustrations and challenges of parenting children with disabilities [20]. Parent-centered work aimed at strengthening their parenting potential, self-confidence, improving parental skills, stress reduction, enhancing sensitivity in relation to the child, and his/her abilities and needs has resulted in more effective treatment of children [21, 22]. Parents play a large and significant role in the early childhood period; however, professional related programs in treating the child directly give better results than those relating to indirect treatment and parent-implemented interventions.

In working with children and their families, a team of professionals specialized in a variety of fields carries out the planned therapeutic procedures. The program will be implemented in different types of settings, such as home, various specialized centers and institutions, as well as services that provide support to families. Some common features of the programs that have already been successfully implemented are highly qualified teams, small groups of children and a sufficient number of professionals who work with them, supportive environment, mutual trust and open communication between families and professionals and the child's active role in activities.

Thus, the essential elements involved in the delivery of successful early intervention are reflected in commencing interventions as soon as possible, adequate intensity of interventions, children's inclusion in their treatment conducted by the professionals, parenting support, service provision and various support networks, as well as monitoring and maintaining the results achieved [9]. In the absence of a common approach to an organization of early intervention programs in our setting, there are insufficient resources and a lack of epidemiological data about intervention programs in the childhood.

The aim of this research was to analyze all the presented elements of successful early childhood intervention, as well as to assess the role of a special educator and rehabilitator and the level of their involvement in implementing the program on the territory of Novi Sad.

Material and Methods

The sample consisted of 100 parents of children with disabilities (aged 3-7 years, 35 girls and 65 boys) who completed the questionnaire designed for the

Table 1. The most frequently reported reasons why the child is undergoing treatment
Tabela 1. *Najčešće navođeni razlozi zbog kojih je dete na tretmanu*

Reasons for treatment /examination/*Razlog tretmana*	N	%
Speech and language problems/*Problemi u govoru*	51	51.0
Psycho motor delayed development/*Kašnjenje u psihomotoričkom razvoju*	40	40.0
Problems in motor skills development/*Problemi u razvoju motorike*	35	35.0
Emotional problems/*Emocionalni problemi*	19	19.0
Risk factors at birth/*Faktori rizika na rođenju*	10	10.0
Intellectual disabilities/*Problemi u intelektualnom funkcionisanju*	8	8.0
Vision impairments/*Oštećenje vida*	6	6.0
Hearing impairments/*Oštećenje sluha*	2	2.0

Table 2. Comparative overview of the dynamics of child's inclusion in treatment
Tabela 2. *Uporedni prikaz dinamike uključivanja deteta u tretman*

Child's age (years) *Uzrast deteta*	When parents noticed problems *Kada su roditelji posumnjali da postoji problem*	Age when the problem was identified *Vreme identifikovanja problema*	Age when the child was included in treatment *Vreme uključivanja deteta u tretman*
1	43.2%	25.0%	25.0%
2	20.5%	20.4%	20.4%
3	11.4%	18.2%	11.4%
4	13.6%	25.0%	27.4%
5	9.1%	9.1%	11.3%
6	2.2%	2.3%	4.5%

purposes of this research based on the similar research in other counties. The questionnaire contained 10 questions related to the reasons for the child's treatment/examination, time when the parent noticed the problem, when the first signs of developmental disorders were identified, time when the child was included in treatment, where and how long treatment was provided and who provided it, the number of professionals working with a child, as well as the usefulness of information the parents received from the professionals. The questionnaire was completed by a parent/guardian, who accompanied the child to the institution where the child had undergone treatment or control examination (health centre, school centre). All children had already been diagnosed with developmental disorders. This study was approved by the Ethical Committee of Health Center in Novi Sad and school for children with special needs SOŠO "Milan Petrović" in Novi Sad. The parents were first informed on the purpose of research and having given their written consent to participate in the study they completed the questionnaire. The questionnaire was completed by the mother (91%), the father (8%), or the guardian (1%). All respondents were from the same town, which represents a limitation of this study because the data were obtained only for a reference sample.

Results

The reasons for seeking professional help are numerous and often multiple. By checking one or multiple choice questions, the parents gave reason/reasons why their children were treated at the institution at that time (**Table 1**). As shown in practice, one of the most common reasons for seeking help from professionals was speech delay. The total of the above mentioned problems exceeded 100% since parents could check more than one reason given in the questionnaire for including their child in treatment.

Table 2 gives a comparative overview of the points of time when the parents suspected their child had a problem, when the problem was identified and professionals were involved in the child's treatment. The parents reported that by the first year of life of their child they had recognized or suspected that their child had a problem (in 43%) when compared to their elder child or other children of their age. The number of children of this age group identified with a problem was halved (25%), but it is positive that there was the same number of children involved in treatment at this age. The largest number of children, over 50%, was treated by professionals from 3 years of age onwards.

Parents sought the doctors' help in the early stages, first of all they addressed the pediatricians, which is understandable because they were oriented towards them and they trusted them. After the child's developmental problem had been identified, the parents reported that they received most information about further services and rehabilitation program for the child by a psychologist. In fact, they very rarely mentioned other professionals, such as a speech language therapist and special educator and rehabilitator (**Table 3**). The parents said that the information given by the professionals had been the most helpful for them to understand their children and their needs and how to include them in everyday activities.

Moreover, we were interested in the number of professionals who were currently treating the child. There were usually one or two professionals (a psychologist and/or psychiatrist), whereas a special educator and rehabilitator and a speech therapist were most commonly included when the team consisted of three or more professionals. Knowing that the program is much more efficient when it is implemented directly between the therapist and the child than indirectly when the parent is playing the role of a therapist, we enquired about the place where the treatment was performed (**Table 4**). The total of the above mentioned settings exceeded 100% since the parents could check more than one place for treatment. The responses obtained indicate that in the greatest number of cases, interventions were delivered by parents who had received instructions on how they could assist their child at home.

Discussion

More and more parents are now "wandering" to get an accurate diagnosis, which is very often difficult to make. Sometimes, some developmental problems may manifest immediately after the child's birth, and one of the first symptoms of developmen-

Table 3. Source of information for possibilities of the child's further treatment
Tabela 3. *Izvor informacija o mogućnostima daljeg rada sa detetom*

Professionals/*Stručnjaci*	N	%
Psychologist/*Psiholog*	47	47.0
Pediatrician/*Pedijatar*	24	24.0
Speech and language pathologist/*Logoped*	15	15.0
Special educator and rehabilitator/*Defektolog*	13	13.0
Physiotherapist/*Fizioterapeut*	12	12.0
Ophthalmologist/*Oftalmolog*	4	4.0
Geneticist/*Genetičar*	3	3.0
Psychiatrist/*Psihijatar*	3	3.0
Physiatrist/*Fizijatar*	2	2.0
Neurologist/*Neurolog*	2	2.0
Other parents/*Drugi roditelji*	2	2.0

tal disabilities at the earliest age may be evident through disorders and delays in the motor skill development [23, 24]. In this study, these problems were reported in 35% of the children, while the leading problems were related to speech (51%). Problems in speech and language development were often combined with other disabilities, and thus they were most frequently stated by our respondents. Speech impairment often occurred in children born before full term with low birth weight, those with delayed intellectual development and with impaired hearing or motor impairment [25–28]. Blaži [29] reported that problems in speech were the reason why parents had sought professional help in 80% of the children.

Timely identification of problems provides an opportunity for an early initiation of interventions, taking advantage of brain plasticity at an early age to achieve the best possible results. Early start of the intervention is important because an intensive intervention of good quality results in reduced need for special education, and fewer support services are required later in life [30]. The results of early involvement yielded greater benefit for children who had undergone the intervention before the age of two and for longer time [5]. Age is therefore important when problems are suspected, and when professionals advise children and parents about further treatment. Kosičeк et al. [1] reported that parents usually noticed a problem within the first three months of their child's life (51%), it was diagnosed in 43% at that age and 32% of children were initially included in rehabilitation therapy. In our study, that percentage was 43% by the end of the first year of life; namely, the problem was identified in 25% of children who exhibited symptoms of developmental delay, and the same number was included in the treatment. While it is evident that the same number of children whose problem was identified received organized treatment, there were another 55% of children whose treatment was delayed since they were not included in organized treatment before the age of three. This leaves a high number of children without adequate intervention from an early age, which reduces the chances of achieving better results. The duration and frequency of intervention are directly related to its effects on the children's cognitive and social emotional development, as well as on their health status [31, 32]. In our study group, the duration and frequency of treatment was far below the time proved to be effective in the Perry preschool program, which included 5 hours a day, five days a week. The parents in our study sample reported that children usually had two hours of treatment per week, which was insufficient to yield any serious results. The reason for this is probably a small number of services available for this type of work. Knowing that the prevalence of children with neurodevelopmental risk factors is about 10%, it is necessary to provide adequate services with the professionals trained for the implementation of early intervention including special education and rehabilitation professionals among them. Furthermore, a possible reason why parents do not seek help and information on the possibilities of (re) habilitation, besides the insuf-

Table 4. Place where treatment was performed in the last 6 months
Tabela 4*. Mesto sprovođenja tretmana u poslednjih 6 meseci*

Place/*Mesto*	N	%
Home (alone with advice)/*Kod kuće (sami uz savete)*	41	41.0
Health centre/*U zdravstvenoj ustanovi*	24	24.0
Special service/*U specijalizovanoj ustanovi*	23	23.0
Private practice/*Privatna ordinacija*	21	21.0
Other combinations/*Kombinovano*	15	15.0

ficient number of special educators and rehabilitators, is insufficient information about their scope of work. In adition, more information should be given to other health professionals such as medical doctors, nurses, and physiotherapists about the scope of work and competencies of special educators and rehabilitators in order to ensure better team work. It is crucial that they are given educational opportunities to acquire new knowledge, which would help to solve this systemic problem.

Parental involvement in implementing interventions is vital and necessary. The parents in our study sample claimed that they mostly had to carry out this treatment themselves at home, receiving occasional advice from the professionals.

The results from an American research study suggest that interventions performed by parents themselves at home may have weaker effects than those performed in specialized centers [30], because the majority of home visiting programs are mainly focused on parents and less on a child. Studies show that home visiting programs were carried out by poorly trained associates, where families were not sufficiently involved, the programs were not intense and comprehensive, but were focused on a small number of domains, and thus showed little consistent effect on children's achievement. Programs carried out by paraprofessionals are generally ineffective because studies have shown that the professionals are required in order to achieve optimal results [5, 33, 34]. In our study, the results obtained show that treatment provided by early childhood professionals most commonly included one or two professionals, and rarely three or more. Although this number was insufficient and the teams consisted of a psychologist and a psychiatrist only, these programs had potential to provide more effective treatment since the parents did not mention involvement of paraprofessionals. Special educators and rehabilitators are usually involved in treatment when teams consist of three or more professionals. Considering the fact that children's disabilities are most often related to the problems in speech, motor skills and intellectual development, this information is troublesome because of the small number of specialists included in the treatment of children with developmental disabilities. Furthermore, knowing that both a special educator and rehabilitator have been specially trained to treat children with disabilities, it is surprising that their participation in those teams is so low. Since the domain of their work is directed towards the prevention of disabilities and their improvement, or at least maintaining the existing abilities, the absence of their interventions leads to failure to provide the necessary support for children's development. A multidisciplinary approach is required in order to provide better conditions for functioning of children with disabilities and improve their quality of life [35]. What is particularly worrying is the fact stated by the largest number of parents that the duration of treatment delivered by the professionals was two hours a week per a child. The parents further explained that their children received treatments as often as they were made available by official institutions.

In spite of the place and role of special educator and rehabilitator within the systems of health care, education and social welfare, they are still not available in all the necessary services. Our suggestion would be to follow the example set by developed countries and to establish Centers for childhood early intervention on the local level for children from 0 to 5 or possibly 6 years of age. Furthermore, because early intervention is also focused on the family, it would be most advantageous to form mobile teams, as a part of these Centers, which would visit families and provide interventions in less restrictive and more natural environments for the child and the parents. These teams should consist of professionals such as medical doctors, special educators and rehabilitators, psychologists, social workers, nurses, physiotherapists who would be included in the work with the children and their family when the need arises.

Conclusion

Early identification of developmental delays and neurorisk factors and early introduction of intervention program provide an opportunity to achieve the best possible effects on the child's later development. In optimal conditions, the quality and quantity of program implementation are related to the developmental outcomes for children. Moreover, more flexible programs that integrate various approaches outperform strict and rigid programs. The implementation of such programs should be carried out continuously through the professional teamwork, providing support to parents and children through a system of services. Only well-designed programs conducted by trained professionals can have positive results. It is necessary to develop early intervention services, educate staff and provide conditions that would make it possible to overcome the existing disadvantages in treatment of children from their earliest age. In addition, it is vital to involve special education and rehabilitation professionals to work within teams with children from the earliest age**.** On the local level in Novi Sad, there are inadequate resources as well as insufficient information about such an important issue as intervention in early developmental period.

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CASE REPORTS
PRIKAZI SLUČAJEVA

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Case report
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HUMAN SUBCUTANEOUS DIROFILARIASIS – CASE REPORT

HUMANA SUPKUTANA DIROFILARIJAZA − PRIKAZ SLUČAJA

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Summary

Introduction. Human dirofilariasis is a zoonotic disease caused by Dirofilaria repens and Dirofilaria immitis. It usually presents as a nodular lesion in the lung, subcutaneous tissues or eyes. In animals, dirofilariasis is a very common disease with serious cardiovascular and respiratory manifestations. If adequate therapy is not given at the beginning of the disease, dirofilariasis can lead to animal death. On the contrary, human dirofilariasis is frequently mild, sporadic and asymptomatic disease. Complications in humans are very rare. In Europe, human dirofilariasis is a very rare zoonotic disease even in endemic areas such as Italy, Spain and the Mediterranean. **Case report.** The authors reported the case of a 43-year-old male with a subcutaneous nodule caused by Dirofilaria repens. The patient who lives in Budva, Montenegro, had a nodule in the right-hand side of the anterior abdominal wall just below the sternum with maximum diameter of 3 cm. His health condition was good and all laboratory analyses were normal. The lesion was surgically removed and the histopathological examination confirmed the parasitic infection by Dirofilaria repens. After surgical excision, the patient was treated with dual antimicrobial therapy (100 mg doxycycline per os twice a day for 28 days and 200 mg albendazole per os twice a day for 10 days). **Conclusion**. It is very difficult to make the diagnosis of a subcutaneous nodule. The difficulties arise in the differential diagnosis because subcutaneous nodules are suspected to be malignant neoplasm or other pathologies such as tuberculosis, fungal infections, sebaceous cysts, hamartomas, abscesses, and so on. Although human dirofilariasis is a rare disease, the number of reported cases has recently been increasing worldwide.

Key words: Dirofilaria repens; Dirofilaria immitis; Dirofilariasis; Subcutaneous Tissue + parasitology; Subcutaneous Tissue + surgery; Skin Diseases, Parasitic; Diagnosis

Sažetak

Uvod. Humana dirofilarijaza je zoonoza koju izazivaju *Dirophilaria repens* i *Dirophilaria immitis*. Najčešće se prezentuje kao nodularna lezija pluća, supkutani nodus ili lezija oka. Kod životinja, dirofilarijaza je veoma česta bolest sa ozbiljnim kardiovaskularnim i respiratornim manifestacijama. Bez adekvatne terapije, date na početku bolesti, dirofilarijaza može dovesti do uginuća životinje. Suprotno, kod ljudi dirofilarijaza je retka, sporadična i asimptomatska bolest. Komplikacije su veoma retke. U Evropi, humana dirofilarijaza je veoma retka zoonoza čak i u endemskim krajevima kakvi su Italija, Španija, i Mediteran. **Prikaz slučaja.** U ovom radu prikazan je slučaj dirofilarijaze kod bolesnika starog 43 godine sa supkutanim nodusom koju je uzrokovala *Dirofilaria repens*. Pacijent koji živi u Budvi (Crna Gora), imao je nodus na desnoj strani prednjeg trbušnog zida, odmah ispod sternuma, maksimalnog dijametra 3 cm. On je bio dobrog opšteg stanja i rezultati svih laboratorijskih analiza bili su uredni. Ovaj nodus je hirurški odstranjen i patohistološkim pregledom je potvrđena infekcija čiji je uzročnik *Dirofilaria repens.* Posle hirurške ekscizije pacijent je lečen dvojnom antimikrobnom terapijom (100 mg doksiciklin dva puta na dan oralno 28 dana i 200 mg albendazol oralno dva puta na dan tokom 10 dana). **Zaključak**. Dijagnoza supkutanog nodusa je veoma teška. Poteškoće nastaju u diferencijalnoj dijagnozi jer supkutani nodus može da imitira maligne neoplazme ili druge patološke supstrate kao što su tuberkuloza, gljivične infekcije, ciste lojnih žlezda, hamartome, apscese,…Iako je humana dirofilarijaza retka bolest, broj prijavljenih slučajeva je u porastu poslednjih godina.

Ključne reči: Dirofilaria repens; Dirofilaria immitis; Dirofilarijaza; Potkožno tkivo + parazitologija; Potkožno tkivo + hirurgija; Parazitarne kožne bolesti; Dijagnoza

Introduction

Dirofilariasis is an infectious disease of warm-blooded carnivores, mostly dogs and cats, caused by parasites of the genus *Dirofilariae* (*Dirofilaria (D.) repens* and *D. immitis)*. Dirofilariasis has also been reported in foxes, wolves and bears (*D. ursi*) [1–3].

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Abbreviations
D – Dirofilaria
PCR – polymerase chain reaction
Ig – immunoglobulin

These animals are the definitive parasite hosts, in which the entire parasite life cycle is completed. Adult parasites release microfilariae into the host's bloodstream and these microfilariae can be ingested by blood-sucking mosquitoes (genera *Aedes, Anopheles, Culex*) which serve as intermediate hosts and disease transmitters. Some species of flies, lice, and ticks are also presumed to act as vectors [3].

Dirofilariae are mosquito-transmitted between animals and from animals to humans when infective larvae penetrate into the skin during the feeding of bloodsucking mosquitoes.

In dogs and cats, dirofilariasis is a very common disease with serious cardiovascular and respiratory manifestations. If adequate therapy is not given at the beginning of the disease, dirofilariasis can lead to animal death. On the contrary, human dirofilariasis is frequently mild, sporadic and asymptomatic disease. Complications in humans are very rare.

In human infections, a single larva usually develops and does not reach fertility [2, 3]. The larva wanders through the human body and finally forms a nodule without systemic manifestation of the disease [2, 3].

Human dirofilariasis is caused by *D. repens* and *D. immitis.*

D. repens infection is the most common and is responsible for the subcutaneous and the ocular form of the disease. *D. immitis* causes human pulmonary dirofilariasis.

In Europe, human dirofilariasis is a very rare zoonotic disease even in endemic areas such as Italy, Spain and the Mediterranean. In non-endemic areas, human dirofilariasis is a completely sporadic disease [2].

Some parts of Serbia and Montenegro are hyperendemic areas for dirofilariasis in dogs (about 60% of dogs are infected) caused by *D. repens* [4].

The autors reported the case of a patient residing in Budva, Montenegro with subcutaneous nodule caused by *D. repens.*

Case Report

A 43-year-old male, married, a caterer, who lives and works in Budva, Montenegro, was in North America in 2011 for about a month, and visited Bosnia and Herzegovina and Croatia in 2012. He was in good health and his history revealed no chronic disease. He has an 8-year-old dog. The dog is healthy and happy and has no cardiovascular or respiratory illness.

In March 2013, the patient noticed a nodule in the right armpit and sought medical attention. An inflammation of the sebaceous cyst was diagnosed on surgical examination. About two weeks later, the nodule ruptured, spontaneously drained and the wound healed leaving a small scar.

Two months later, in May 2013, the patient periodically had vision problems in the form of discomfort in the eyes as well as a pain in the right inguinal pit, which he felt at night as if something was squirming inside.

Laboratory analyses were conducted, including complete blood count, erythrocyte sedimentation rate, urinalysis, and liver and renal function tests, and all results were normal. The findings of chest X-ray, abdominal ultrasound, echocardiography, ophthalmological examination and colonoscopy were also normal. The ultrasound of axillary and inguinal regions revealed lymphadenopathy (axillary lymph nodes up to 20 mm, inguinal lymph nodes up to 11 mm).

In January 2014, the symptoms ceased and the patient was in excellent general health condition. However, he noticed a nodule in the right-hand side of the anterior abdominal wall just below sternum and a solitary firm and mobile subcutaneous nodule with the maximum diameter of 3 cm was identified on physical examination. The skin on the right side of the anterior abdominal region showed neither erythema nor ulcer and seemed absolutely intact. The surgical excision was performed one week later. The excised material was shown to be a firm fibrotic granuloma containing a filiar 10 cm long parasite. The subcutaneous dirofilariasis was suspected. The isolated parasite was sent to the Parasitology Department of the Clinical Center of Serbia, Belgrade, where the diagnosis of filariasis was definitely established and the parasite was identified as *D. repens* (**Figure 1**). The parasite sample was shipped in 5% formaldehyde and was in such a condition that the polymerase chain reaction (PCR) diagnostics was not possible.

After surgical excision at a hospital in Budva, in January 2014, the patient was hospitalized at the University Clinic for Infectious and Tropical Diseases of the Clinical Centre of Serbia, a reference

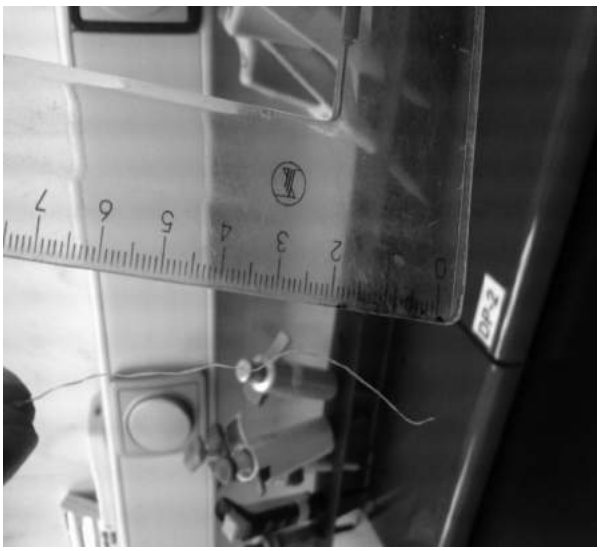

Figure 1. *Dirofilaria repens* which is removed from the subcutaneous nodule
Slika 1. *Dirofilaria repens izvađena iz supkutanog nodusa*

institution for this region. During hospitalization, laboratory investigations were conducted, including complete blood count with eosinophils, erythrocyte sedimentation rate, C reactive protein, fibrinogen, immunoglobulin (Ig) concentration (IgG, IgA, IgM and IgE), urinalysis, and liver and renal function tests, and all results came back normal. Infectious disease screening was performed and showed negative serology for *Echinococcus granulosus, Toxoplasma gondii, Toxocara canis, Trichinella spiralis, hepatitis B virus* (HBV), *hepatitis C virus* (HCV) and *human immunodeficiency virus* (HIV). Microfilariae were not found with the Knott's method in several samples of venous blood.

The follow-up chest X-ray and abdominal ultrasonography were normal, but the ultrasonography of the inguinal pits showed the right-side inguinal lymphadenopahty. The patient had pain and a tingling sensation in his right groin and surgical excision was performed. The right inguinal lymph node histopathology showed reactive lymphadenopathy.

The patient was treated with dual antimicrobial therapy consisting of 100 mg doxycycline per os twice a day for 28 days and 200 mg albendazole per os twice a day for 10 days. The patient complained of headaches during the treatment but the nuclear magnetic resonance (NMR) imaging of the head revealed no irregularities.

The disease had a positive outcome and the patient was cured and discharged in excellent health.

Discussion

Human dirofilariasis is a very rare disease. The incubation can be very long even up to several years. The disease usually presents as a subcutaneous nodule of variable size. The first case of human dirofilariasis was reported in the Socialist Federal Republic of Yugoslavia in 1971 [5].

Since then, a few cases from Serbia and Montenegro were reported in the literature until mid-2014. None of the cases had a complicated form of the disease [6].

In humans, different cases of dirofilariasis have been described. In most cases, a single parasitic lesion is found, and two lesions are found in less than 1% of cases [7–11]. Most frequently the parasitic lesion is located in the head region (64.6% of patients) and 39.3% of lesions involve the area around eyes [11]. Lesions are found in other locations less frequently - dirofilariasis of limbs in 9% of cases, in the torso in 11.8% of cases, the male genitalia (scrotum) in 4.1% of cases and the mammary glands in about 2.5% of cases [11].

The infection with *D. repens* can occur at any age, but it is most frequent between 21 and 40 years of age, being more common in females [11].

The human subcutaneous dirofilariasis caused by *D. repens* is a benign form of the human dirofilariasis because the disease remains localized without systemic manifestation.

The human dirofilariasis is usually underdiagnosed because doctors do not take this etiology into consideration. The diagnosis of a subcutaneous nodule is very difficult. The human subcutaneous dirofilariasis causes few or no symptoms and is frequently detected incidentally, as it was the case in our patient. The initial clinical diagnosis is often wrong because subcutaneous nodules are suspected to be malignant neoplasm or other pathologies such as tuberculosis, fungal infections, sebaceous cysts, hamartomas, abscesses, etc. [2, 12, 13]. The diagnosis of human subcutaneous dirofilariasis is based on the histopathological examination of the surgically excised nodule.

In the case of our patient, the illness lasted longer and had a favorable outcome. The difficulties existed in the preoperative diagnostics because the patient had had unspecific symptoms before the appearance of a subcutaneous nodule. As expected, microfilariae were not isolated from the patient's blood, although blood samples were examined in accordance with the protocol. There has only been one case of human dirofilariasis caused by *D. repens* reported in the literature where the blood was positive to microfilaria [14].

IgE and eosinophil levels were not determined before surgery, but were normal in all tests conducted afterwards. This is in accordance with observations reported by other authors. In our patient, serological analyses for other parasites (*Trichinella spiralis, Echinococcus, Toxocara canis)* were negative, while some authors [15] reported the positive serological findings for *Echinococcus.*

There is a disagreement regarding administration of therapy after surgical excision and identification of a parasite. Some authors deny the necessity of specific therapy [16], while other authors recommend it [15, 17]. The authors of this case report have accepted the latter recommendation, bearing in mind that their experience is limited, and that the patient had enlarged lymph nodes in the armpit and groin. The patient was treated with oral antimicrobial therapy and responded well to treatment. The extirpation of the lymph node in the groin was also performed and the histopathological findings were in agreement with reactive lymphadenopathy.

It is interesting that, contrary to the expectations, human dirofilariasis is rare in some areas hyper-endemic for canine dirofilariasis [4]. It could be expected that regions hyper-endemic for canine dirofilariasis would have a greater number of human dirofilariasis, but this is not the rule. This suggests that besides the presence of parasites in animals, vectors and climate have a very important if not the crucial impact [18].

This statement is supported by a higher incidence of disease in Italy, Spain and the Mediterranean than in some parts of Serbia and Montenegro (hyper-endemic areas of canine dirofilariasis – with over 60% of dogs infected) [4].

Finally, the global climate changes and a less frequent use of chemicals for destruction of vectors, contributes to the increased disease incidence [18].

The current travelling trends from non-endemic to endemic regions, where travelers are accompanied by their canine pets also contribute to an increase in human dirofilariasis incidence in non-endemic areas.

Conclusion

The incidence of human infections caused by *Dirofilariae* is on the increase in both endemic and non-endemic regions. These infections do not usually cause no severe clinical symptoms but can be mistaken for tumors. The difficulties arise in the differential diagnosis, especially if the parasite is located in the cavity of the orbit, the tissue of the breast, lung, genital organs or skin. It is certain that the number of cases of dirofilariasis will rise in the future, given the current climate changes and more frequent trips.

Therefore, *dirofilariasis* must be included in the differential diagnosis in patients with subcutaneous nodules.

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CHRONICLE OF THE «ANGLO -YUGOSLAV CHILDREN'S HOSPITAL» IN SREMSKA KAMENICA

ISTORIJAT ANGLO-JUGOSLOVENSKE DEČJE BOLNICE U SREMSKOJ KAMENICI

Dušanka DOBANOVAČKI[1], Želimir MIKIĆ[1] and Nada VUČKOVIĆ[1,2]

Summary
As a peacetime work of Katherine S. Macphail (Glasgow, 1887-St.Andrews, 1974) MB ChB (Bachelor of Medicine and Surgery), the Anglo-Serbian Children's Hospital in Belgrade was established after World War I, and the English-Yugoslav Children's Hospital for Treatment of Osteoarticular Tuberculosis was founded in Sremska Kamenica in 1934. Situated on the Fruška Gora slope, the hospital-sanatorium was a well-equipped medical institution with an operating theatre and x-ray machine providing very advanced therapy, comparable to those in Switzerland and England: aero and heliotherapy, good quality nourishment, etc. In addition, school lessons were organized as well as several types of handwork as the work-therapy. It was a privately owned hospital but almost all the children were treated free of cost. The age for admission was up to 14. During the period from 1934 to 1937, around 458 children underwent hospital treatment, most of them with successful results. During the war years the Sanatorium was closed but after the war it was reactivated. In 1948 by the act of final nationalization of all medical institutions in the communist Yugoslavia, the hospital was transformed into a ward of orthopedic surgery under the supervision of the referent departments in Belgrade and Novi Sad. Today, hospital is out of work and deprived of its humanitarian mission. The building is neglected and in ruins although it has been proclaimed the national treasure by the Regional Institute for Protection of Monuments of Culture.
Key words: History of Medicine; Hospitals, Pediatric; Famous Persons; Great Britain; Yugoslavia; History, 20th Century; Tuberculosis, Osteoarticular; Health Resorts; Female

Sažetak
Posle završetka Prvog svetskog rata misija dr Ketrin Makfejl (Glazgov, 1887. Sveti Andrej, 1974.), MB ChB (bečelor medicine i hirurgije), bila je osnivač Englesko-srpske dečje bolnice u Beogradu, a zatim 1934. godine Englesko-jugoslovenske dečje bolnice za lečenje osteoartikularne tuberkuloze u Sremskoj Kamenici. Bolnica-sanatorijum bila je izgrađena na padini Fruške gore i ispunjavala sve uslove za najsavremenije lečenje ove bolesti po ugledu na švajcarske i engleske sanatorijume: imala je operacionu salu, rendgensku dijagnostiku, aero i helioterapiju, koja se primenjivala uz odgovarajući higijensko-dijetetski režim. Školska nastava i drugi oblici radne terapije bili su značajni za svakog malog bolesnika. Iako je bolnica bila privatno vlasništvo, većina dece čiji je uzrast bio do 14 godina bila je lečena besplatno. Tokom vremenskog perioda 1934-1937. godine oko 458 dece bilo je podvrgnuto bolničkom lečenju, većina sa zadovoljavajućim rezultatom. Tokom Drugog svetskog rata bolnica nije radila, ali je počela odmah posle oslobođenja. Godine 1948., sa procesom nacionalizacije svih medicinskih ustanova u komunističkoj Jugoslaviji, bolnica postaje ortopedsko odeljenje uz stručni nadzor prvo beogradske a zatim novosadske ortopedije i rehabilitacije. Danas, u svojoj osamdesetoj godini bolnica je bez pacijenata i misije, oronula i zapuštena iako je od Pokrajinskog zavoda za zaštitu spomenika Vojvodine proglašena za spomenik od nacionalnog značaja.
Ključne reči: Istorija medicine; Pedijatrijska bolnica; Poznate ličnosti; Velika Britanija; Jugoslavija; Istorija 20. veka; Osteoartikularna tuberkuloza; Sanatorijumi; Žena

Introduction

During the war (1915-1918) and the post-war years in Serbia, Katherine Macphail, being an experienced medicine woman, noticed that a perennial poverty and hunger induced an increased number of chronic tuberculosis patients: "After many years of working with children in this country, I realized that there is a need for a special hospital for the children whom long-time treatment is necessary, especially for children suffering of the tuberculosis

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This article was written to commemorate the humane and selfless work of people who had been devoted to helping others.

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Abbreviations
UNRA – United Nations Relief and Rehabilitation Administration

of bones and joints, as well as for children with various other deformities. There would be provided adequate medical care, fresh air and good food for a longer period of time, possible treatment and rehabilitation, healing and correction, or at least stop further progression of their deformity".

In the early thirties of the XX century, Katherine Macphail started to look for a suitable place for the hospital building that would meet modern diagnostic and therapeutic conditions for its purpose. At the same time, it would be the memorial of British women's work in Serbia during and after World War I. Assisted by friends, she found such a place which was old orchards and vineyards stretching over Čardak, a hill in Sremska Kamenica. The selected field was located on a hill in an open country with a lot of fresh air and sunshine required for the tuberculosis treatment, and it was easily accessible **(Figure 1)**.

Figure 1. Katherine S. Macphail (1915)
Slika 1. *Katerin S. Makfejl (1915)*

Katherine S. Macphail, MD, MB ChB (Glasgow, 1887 - St.Andrews, 1974) was born into a wealthy medical family. She studied medicine and surgery at the University of Glasgow, Scotland and graduated in 1911. During the World War I, she joined the team of Scottish Women's Hospital for Foreign Service, and as a volunteer came to Serbia in January 1915 (Fig. 1.). After the war, she continued the humanitarian work and founded the "Anglo - Serbian Children's Hospital", the first school for nurses in Belgrade, and the children's sanatorium «Anglo -Yugoslav Children's Hospital» for bone and joint tuberculosis treatment in Sremska Kamenica in 1934. She represents an imposing figure among the many British women who were committed to supporting Serbia during the difficult wars and post-war days. Her resume reflects the timeless dimension of a heroin and humanist.

1933

The Land Registry Cadastre of the municipality of Sremska Kamenica has an entry under the number 1341 stating that the three plots on the hill Čardak became the property of Macphail Katherine, a doctor from Belgrade. According to the plan, the Katherine Macphail architect's draft consisted of three-wing building with a courtyard and a terrace along the wings so that children could be exposed to the sun. The project was approved by the Administration of the Danube Banovina in Novi Sad in September 1933 and building permits were obtained. Queen Maria Karadjordjević was the sponsor of the entire action. Late in the summer, the first works started and developed well.

1934

In the spring, construction work on the new hospital was over, the equipment was ordered, and the lists of patients for admission were created. The Royal Commission of Banovina government gave permission to the English-Yugoslav children's sanatorium to be opened and start working: "The hospital building is built on the slope that goes down to village Sremska Kamenica. Hospital is exposed to abundant and beneficial effects of the sun and air. The building consists of a main frontal part and two symmetrically placed wings. In the main part there are three hospital departments, out-patients department, operating theatre, imaging and radiotherapy department, pharmacy department, sterilizing instruments and room for isolation of the patients with childhood infectious diseases. There are also office for administration, storehouse for medicaments and instruments. In the wings of the building are kitchen with pantry and dining room for children. On the top floor are four bedroom-apartments for doctors and nurses. There are four hygienic bathrooms and lavatories that are arranged in the wings of the building. The hospital was built according to the plan for therapy and long stay patients. In front of the southern and western fronts terraces are built. The whole yard is fenced and looks like a park, there is an orchard and vineyard **(Figure 2)**."

The hospital - sanatorium was officially opened on September 23, 1934 under the auspices of Her Majesty Queen Maria Karadjordjevic.

The first patients were transferred from a Belgrade hospital on August 1. Treatment of patients was

Figure 2. Sanatorium in Sremska Kamenica (1936)
Slika 2. *Sanatorijum u Sremskoj Kamenici (1936)*

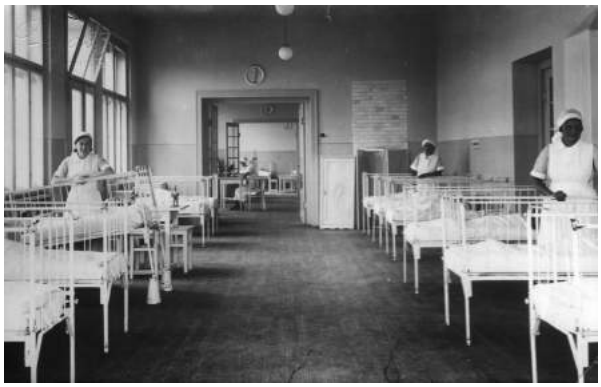

Figure 3. The hospital's interior (1934-35)
Slika 3. *Pogled u unutrašnjost bolnice (1934-35)*

focused on the children who suffered from tuberculosis of bones and joints, polio, rickets and so on. Treatment consisted of fresh air, exposure to the sun, good food, extensions, rest, massage, immobilization in a cast, and surgery if necessary. The hospital admitted children up to 14 years of age. There were 50 children during summer, and 32 in winter **(Figure 3)**. The Chief of hospital was Katherine Macphail, the surgeon Svetislav Stojanovic, primarius and a doctor in General State Hospital in Belgrade, the head nurse was Agnes Hardy, and Alice Murphy was a secretary. Two nurses, one teacher and support staff were also employed.

The main problem was the financing of hospital because children were predominantly treated free of charge. The costs were covered by many donors. The hospital received grants from the Ministry of Social Affairs and Public Health of the Royal Regional Administration of the Danube Banovina, and the Fund to rescue the children, as well as various other donations. All this was not enough to cover the expenses of the hospital and Katherine Macphail always had to lead fundraising campaign.

1936

At the end of the year, the report on the two-year work of the hospital was submitted stating that 115 patients had been hospitalized (hospitalization in some patients lasted up to 24 months) and 160 children were treated as outpatients, 25 surgical procedures, 194 punctures and 113 X-rays were performed and 84 plaster apparatus were put on. Fifty-two children were discharged from the hospital as successfully treated, 12 children had improved health status at discharge, and the rest were kept for further treatment. The conclusion was that the Yugoslav – English hospital fulfilled all the tasks in those two years despite limited funds and a small number of beds.

In the hospital, Katherine Macphail strictly enforced the verified method of treatment introduced by Dr. A. Rolijea, who had a famous resort in Liezen in the Swiss Alps, and she described it all later in the scientific article published in 1960. The principle of treatment of bone and joint tuberculosis in those days before the discovery of antibiotics and antituberculotics consisted in raising the general resistance of the patient hygienic-dietary regime, fresh air therapy, heliotherapy (natural sunshine during the day, artificial light during winter days) **(Figure 4)**, immobilization and a variety of surgical procedures. Special attention was paid to hygiene in the hospital. Kindergarten curriculum was taught to pre-school children. School-age children attended daily classes appropriate to their age and the curriculum, and they received certificate at the end of the school year. The hospital also organized occupational therapy including art lessons with handwork for the children. Once a week an orthodox priest from Kamenica village came to the hospital for religious instruction. The hospital had a library with lots of children's and educational book, as well as a large number of toys. Each day of those small patients was fulfilled with work, learning and fun.

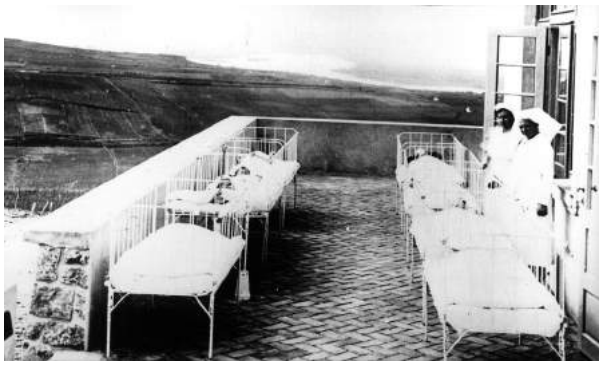

Figure 4. West terrace of the hospital where the children were exposed to the sun (1936–1937)
Slika 4. *Zapadna terasa bolnice gde su deca bila izložena suncu (1936–1937)*

1937

Svetislav Stojanovic presented the data on treatment during the first three years of the hospital work at the first Yugoslav Congress of Pediatrics in Belgrade: "During this period, 458 children of both sexes aged 1 to 13 years were treated in hospital. The average length of treatment was 2 years and 3 months. Many of them were discharged from the hospital healthy and with corrected spine and limbs. We believe that the results of treatment are satisfactory and encouraging, bearing in mind that most of the cases were severe and neglected forms of the disease with deformities and fistula collections."

1939

The sanatorium in Sremska Kamenica worked very well and gained the great reputation. Headed by Katherine Macphail, the staff worked diligently and efficiently. Despite financial troubles, there was always a surplus of food that was distributed to the homeless and day laborers from the village.

1940

The war clouds appeared over Europe. The situation became more serious in the region and staff in sanatorium started with military preparations against the enemy attack.

1941

In January, the traditional event usually held on the birthday of Prince Tomislav Karadjordjevic was organized in good atmosphere and gifts were given to all children. In February, Catherine had plan for timely evacuation of children. Three weeks before the outbreak of war, all the children were sent to their homes. The complete hospital equipment was packed and removed to the basement where it was protected from possible bombing. The social situation was getting very serious and the British embassy advised all British people to leave the country. So, Katherine Macphail and Alice Murphy handed the hospital keys over to some confidential people, and went. Soon afterwards, an anti-aircraft battery with 120 soldiers was settled in the building.

1941-44

A local hospital was soon organized in the building. The staff sympathized with the partisan movement in Fruska Gora and often gave them medication and food, which was the reason why the hospital was attacked and the building was abandoned and devastated. During the war years, the hospital was occasionally used by enemy forces for their soldiers.

1945

Katherine Macphail came to Belgrade with the UNRA mission (United Nations Relief and Rehabilitation Administration - Management of the United Nations Relief and Reconstruction) for Yugoslavia and units of the Children's Rescue Fund, and visited Sremska Kamenica. She found the hospital building, which was desolate and without doors and windows, electric, plumbing and medical equipment.

At this time the Children's Rescue Fund in London collected funds and Katherine began negotiations in July to re-open the hospital in Sremska Kamenica. The Minister of Public Health of the Democratic Federal Yugoslavia gave the permission to start work from the 15th of August. Katherine Macphail undertook with the trained staff, provide foreign medical supplies and other items necessary for surgery. From the UNRE and charities in Canada and the United Kingdom, beddings and blankets were purchased for the hospital.

The complete operating room equipment was found in a military hospital in Karlovac and returned. Katherine received 46 crates of clothing and bedding for children from a friend and supplied not only the hospital and staff employed, but also the poor children in the village. Complete repair of hospital was funded by the Government of Autonomous Province of Vojvodina and it started to work on December 19, 1945. The harsh winter weather conditions and snowdrifts made it almost impossible to provide daily supplies to the hospital.

1946

During the war, the number of children suffering from tuberculosis increased. The hospital worked now with the capacity of 75 beds and was constantly full. Working conditions were very difficult due to shortage of everything because it was difficult to supply the hospital with equipment and food. However, the orchards and vineyards surrounding the hospital yielded a good crop which contributed to the small hospital economy. Weather conditions were excellent: the air was fresh and the sun was strong for healing. Soon, life and work in the hospital continued.

However, the new government gradually grew distrust of Katherine and her associates. The work in the hospital was normal but uncertainty, mistrust and fear prevailed in the atmosphere of insecurity. She suggested to the Ministry of Health to turn the hospital into a rehabilitation centre for disabled children, as well as for the children handicapped due to tuberculosis or other diseases where they would be eligible for various useful work. She also planned to establish workshops and recruit disabled adults to make orthopedic appliances.

1947

The new regime nationalized all hospitals, and the English-Yugoslav children's hospital was handed to the Yugoslav authorities in autumn. Realizing that nothing could stop the implementation of the communist program, Katherine went to Scotland.

Having been nationalized, the hospital continued to exist as the State sanatorium for tuberculosis of bones. During the following winter 82 children were treated.

1948

The hospital in Sremska Kamenica was registered as a national property and became a part of Orthopedic Surgery Department of the Faculty of Medicine in Belgrade headed by Professor Svetislav Stojanovic MD, PhD. The number of patients in hospital increased, the number of beds was 100, and the patients were under 14 years of age. In addition to climatic, dietetic, hygienic measures, and immobilization in an appropriate position, new medications were used. The pharmacological achievements of the century in treatment of tuberculosis were streptomycin and other antituberculotic drugs. In some cases, surgery was necessary and it was performed at the Clinic for Orthopedic Surgery and Traumatology in Belgrade. Postoperative recovery and rehabilitation were organized in Sremska Kamenica. Particular attention was paid to different types of work therapy, as well as the education of children. The hospital was working efficiently in these difficult post-war years despite poverty and other afflictions.

1949

Katherine Macphail and Alice Murphy visited the hospital and were welcomed warmly and friendly: "The hospital looked nice, fresh painted, exposed to the sun and surrounded by fertile vineyard. Everything seemed as before: the children were in school classes, in the outpatient department regular work was conducted, the staff was in daily tasks in the kitchen preparing meals, freshly washed laundry flapping in the wind. "It seemed like it used to be but the hospital was overcrowded with more than a hundred children who were placed in the auxiliary building, beds crammed, there was not enough medical supplies or trained staff. The patients were very pale because heliotherapy was not properly implemented. The quality of life and work decreased since there was no support from abroad.

1954

The 22nd of September was celebrated to mark the twenty years of hospital and in the entrance hall of the hospital a memorial plaque was placed with the inscription that Katherine Macphail was the founder of the hospital which is a great monument to the friendship of Great Britain and Yugoslavia. The ceremony was also attended by Katherine Macphail, and her associates Alice Murphy and Flora Sands. She was very pleased to see that the hospital continued with work. She went to St Andrews and continued her life of retirement.

1955

In June the sanatorium became the Department for bone and joint tuberculosis treatment under the supervision of General hospital in Novi Sad. The profile of work was not changed because the influx of children with tuberculosis was great. However, years of intensive work with a high number of patients without a regular renewal and modernization of hospitals caused considerable deterioration of the hospital and the building itself looked neglected and ramshackle.

1959-60

The thorough renovation and repair of the main hospital building was organized and implemented so the professional work continued. Surgery was performed at the Department of Orthopedics and Traumatology in General Hospital of Novi Sad. In the following time period the number of patients who were hospitalized decreased as a result of systematic use of powerful new drugs – tuberculostatic drugs.

A new complex for tuberculosis treatment was built in the vicinity of the hospital which became the Institute for Tuberculosis of Vojvodina and had 800 beds and necessary medical equipment, all of which resulted in significant improvements in the struggle with this disease.

1963-71

It was a period of great advances in the prevention and treatment of tuberculosis and as the number of patients with bone and joint tuberculosis declined, the former Anglo-Yugoslav hospital changed the profile of the work. It became a part of the Orthopedic Department in Novi Sad and treated only adult patients who required prolonged orthopedic treatment, postoperative recovery and rehabilitation.

In the separate building of the hospital, the Department of Experimental Surgery was established for surgical scientific research as well as practical lessons for students of the Faculty of Medicine in Novi Sad.

1975-78

In the main building of the former ''English hospital'', conservative orthopedic treatment and long-time care and rehabilitation of adult patients continued. Years of work without investing into the repairs and modernization of the hospital resulted in such great damage so that the hospital had to be closed in the first months in 1976.

When the funds were raised, the reconstruction and modernization of the entire hospital began and it was finished by the end of 1977, when the hospital resumed its work.

1984

On October 28, a ceremony was held to mark the fiftieth anniversary of the hospital and at the entrance on the wall next to the previous memorial plaque a new one was placed in memory of the founder Katherine Macphail, thus expressing the gratitude to this great woman **(Figure 5).** The hospital was renamed the Department of Orthopaedic Surgery and Traumatology "Dr. Katherine Macphail".

Figure 5. Memorial plagues (up 1954, down 1984).
Slika 5. *Memorijalne ploče (gore 1954. dole 1984).*

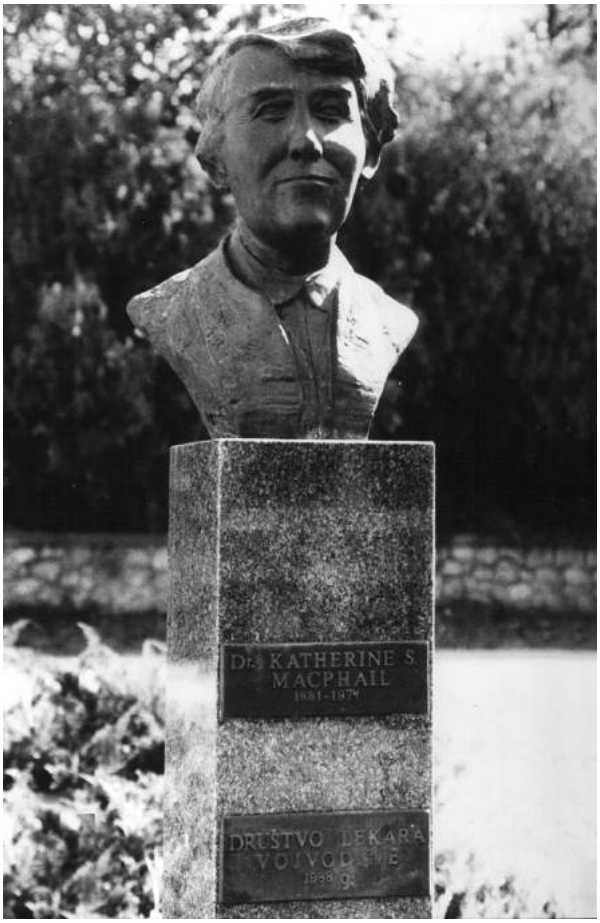

Figure 6. The monument to great benefactor of the Serbian people, Katherine Macphail (1988).
Slika 6. *Spomenik velikom dobročinitelju srpskog naroda, Ketrin Mekfejl (1988)*

1988

On June 15, a monument to the great benefactor of the Serbian people, Katherine Macphail was erected in the front of the former British hospital **(Figure 6).**

1990-92

Because of the breakup of Yugoslavia and the next war that flared up the hospital in Sremska Kamenica once again offered accommodation to the wounded and refugees from war-affected areas. However, the hospital stopped working and was closed due to the difficult economic situation and the subsequent crisis in Yugoslavia in 1992.

2014.

A street on Čardak hill, where the children's hospital used to be, is now named after Katherine Macphail. The hospital itself is now a ruined building without doors and windows. A passer-by who stops and reads the text on the memorial plaque could imagine the time when there was a place of charity and self-sacrificing labor, suffering and triumph, courage and nobility, and embracing love. This monument to the British-Yugoslav friendship now keeps only a bust of the great woman and waits for better times which are promised by the Regional Institute for Protection of Monuments of Culture.

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– Koristiti mere metričkog sistema prema Internacionalnom sistemu mera (*International System Units – SI*). Temperaturu izražavati u Celzijusovim stepenima (°C), a pritisak u milimetrima živinog stuba (mmHg).

– Ne navoditi imena bolesnika, inicijale ili brojeve istorija bolesti.

Uvod sadrži precizno definisan problem kojim se bavi studija (njegova priroda i značaj), uz navođenje relevantne literature i sa jasno definisanim ciljem istraživanja i hipotezom.

Materijal i metode treba da sadrže podatke o načinu dizajniranja studije (prospektivna/retrospektivna, kriterijumi za uključivanje i isključivanje, trajanje, demografski podaci, dužina praćenja). Statističke metode koje se koriste treba da budu jasne i detaljno opisane.

Rezultati predstavljaju detaljan prikaz podataka dobijenih tokom studije. Sve tabele, grafikoni, sheme i slike moraju da budu citirani u tekstu, a njihova

numeracija treba da odgovara redosledu pominjanja u tekstu.

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Zaključak u kratkim crtama mora da odbaci ili potvrdi pogled na problem koji je naveden u Uvodu. Zaključci treba da proizilaze samo iz vlastitih rezultata i da ih čvrsto podržavaju. Uzdržati se uopštenih i nepotrebnih zaključivanja. Zaključci u tekstu moraju suštinski odgovarati onima u Sažetku.

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Članci u časopisima:

∗ *Standardni članak*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

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∗ *Jedan ili više autora*

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Elektronski materijal

∗ *Članak u Časopisu u elektronskoj formi*

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CDI, clinical dermatology illustrated [monograph on CDROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *Kompjuterski dokument (file)*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computeried Educational Systems; 1993.

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Dozvoljeno je najviše šest priloga!

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– case reports should have the introduction, case report and conclusion

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ty and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

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Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the problem mentioned in the introduction. Conclusions must be based solely on the author's own results, corroborating them. Avoid generalised and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

5. References. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by et 'al'.

Articles in journals

∗ *A standard article*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *An organisation as the author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ *No author given*

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ *A volume with supplement*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *An issue with supplement*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *A summary in a journal*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Books and other monographs

∗ *One or more authors*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Editor(s) as author(s)*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *A chapter in a book*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ *A conference paper*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ *A dissertation and theses*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Electronic material

∗ *A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monographs in electronic format*

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *Acomputer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

6. Attachments (tables, graphs, schemes and photographs). The maximum number of attachments allowed is six!

– Tables, graphs, schemes and photographs are to be submitted at the end of the manuscript, on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG, GIF, TIFF, EPS or similar format.

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– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English language.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, ||, ¶, **, † †, ‡ ‡ .

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