ISSN 1857-0666

Curierul medical

SCIENTIFIC MEDICAL JOURNAL

Ministry of Health of the Republic of Moldova
Nicolae Testemitsanu State University of Medicine and Pharmacy

Ministerul Sănătății
al Republicii Moldova.
Universitatea de Stat de Medicină și
Farmacie „Nicolae Testemițanu"

Министерство здравоохранения
Республики Молдова.
Государственный университет медицины и
фармации им. Н. А. Тестемицану

Issued bimonthly

Vol. 59, No 1
February, 2016

Printing House "Tipografia Sirius"
2, A. Lapusneanu str., Chisinau, MD-2004
the Republic of Moldova
www. sirius.md
Phone: (+373 22) 232352

Welcome to the scientific and medical journal Curierul Medical!

From its debut in 1958 the journal has striven to support the interests of Moldovan medicine concerning the new concepts of its development. The Editorial Board warmly welcomes both the readers of and the authors for the journal, all those who are enthusiastic in searching the new and more effective ways of solving numerous medicine problems. We hope that those who want to make their contribution into the science of medicine will find our journal helpful and encouraging.

The journal is accredited by the National Council for Accreditation and Attestation. The journal publishes official papers, scientific articles, editorials, clinical studies and cases, lectures, methodological guides, reviews, brief reports and correspondence. The journal welcomes articles in English, Romanian and Russian. The journal editorial policy provides the prompt publication of papers within 12 weeks after receiving them.

Bine ați venit la revista științifică medicală Curierul Medical!

De la prima apariție în 1958, revista susține și dezvoltă noile idei în domeniul medicinii, în Republica Moldova. Colegiul de redacție agrează cu multă considerație atât cititorii cât și autorii articolelor, pe toți acei care cu mult entuziasm caută noi și mult mai efective metode de soluționare a multiplelor probleme ale medicinii. Sperăm, că toți acei care doresc să-și aducă aportul la dezvoltarea științelor medicale, vor găsi revista noastră utilă și atractivă.

Revista este acreditată de către Consiliul Național de Acreditare și Atestare. Revista publică comunicări oficiale și, totodată, sunt editate diverse publicații, inclusiv independente: articole științifice, editoriale, cercetări și prezentări de cazuri clinice, prelegeri, îndrumări metodice, articole de sinteză, relatări scurte, corespondențe și recenzii. Revista publică articole în limba engleză, română și rusă. Politica de editare a revistei prevede examinarea operativă și publicarea articolelor timp de 12 săptămâni după înaintare.

Добро пожаловать в научно-медицинский журнал Curierul Medical!

С первого дня своего выпуска в 1958 году журнал стремится поддерживать и развивать новые идеи в области медицины в Молдове. Редакционная коллегия всегда рада как читателям, так и авторам статей, всем тем, кто с энтузиазмом ищет новые, более эффективные способы решения многочисленных задач медицины. Мы надеемся, что все те, кто хотят внести свой вклад в медицинскую науку, найдут наш журнал полезным и вдохновляющим.

Журнал аккредитован Высшей Аттестационной Комиссией Республики Молдова. В журнале печатаются официальные материалы, научные статьи, наблюдения из клинической практики, обобщающие статьи, краткие сообщения, методические указания, рецензии и корреспонденция. В журнале публикуются статьи на английском, румынском и русском языках. Издательская политика журнала предусматривает оперативное рассмотрение и публикацию статей в среднем в течение 12 недель после поступления.

Address of the Editorial Office
192, Stefan cel Mare Avenue, Chisinau, MD-2004
the Republic of Moldova
Phone: (+37322) 244751, (+37322) 205209
Fax: (+38322) 295384
www.curierulmedical.org
editor@curierulmedical.org, secretary@curierulmedical.org
Index for subscription – 32130

CONTENTS • CUPRINS • СОДЕРЖАНИЕ

RESEARCH STUDIES

REVIEW ARTICLES

ANNIVERSERIES

RESEARCH STUDIES

Intensive phase efficacy of injected drugs – isoniazid and rifampicin in the treatment of patients with lung tuberculosis and hepatobiliary pancreatic comorbidities

***E. Lesnic[1], L. Todoriko[2], I. Semianov[2]**

[1]Department of Pneumophthisiology, Nicolae Testemitsanu State University of Medicine and Pharmacy Chisinau, the Republic of Moldova

[2]Department of Phthisiology and Pulmonology, Bucovinian State University of Medicine, Chernivtsi, Ukraine

*Corresponding author: evelinalesnic@yahoo.com. Received November 23, 2015; accepted February 08, 2016

Abstract

Background: One of the most important tuberculosis control action represents the effective anti-tuberculosis treatment. The standard regimens are associated with high level of side effects, especially at patients with hepatobiliary and pancreatic co-morbidities.

Material and methods: There were studied clinical and laboratory indices of a total number of 60 new pulmonary tuberculosis cases, with proved hepatobiliary and pancreatic comorbidities, distributed in the 1st study group, consisted of 30 patients treated with the standard anti-tuberculosis treatment, all drugs being administrated orally and the 2nd control group, consisted of 30 patients, treated with the standard anti-tuberculosis treatment with injected forms of first line anti-tuberculosis drugs isoniazid and rifampicin.

Results: The clinical improvement of the patient's general state under the influence of intravenous use of isoniazid and rifampicin was confirmed by a lower expressiveness of intoxication and bronchopulmonary syndroms, as well as by a better radiological dynamics and higher rate of microscopic convertion at the end of intensive phase of the tuberculosis treatment. Biochemical disturbances due to tuberculosis treatment were less evident at the patients treated with intravenous isoniazid and rifampicin, confirmed by a better rehabilitation of mathematic indices of endogenous intoxication.

Conclusions: Assessing the differences between the clinical and laboratory tolerance of tuberculosis drugs according to the way of administration, it was proved the importance of individualization of the standard treatment at patients with hepatobiliary and pancreatic disorders by intravenous use of isoniazid and rifampicin in intensive phase of the treatment, for improving the therapeutical effectiveness.

Key words: tuberculosis, comorbidities, treatment, injected drugs.

Background

One of the most important tuberculosis control action represents the effective anti-tuberculosis treatment that is the most important tool for interrupting the epidemiological chain of infectious transmission. As well as, other aims of specific treatment represent: the restoring of health, quality of life and patient's productivity, prevention of death due to tuberculosis (TB) and relapse, and prevention of acquiring of drug resistance [9, 15]. According to World Health Organization (WHO) Treatment Guidelines anti-TB drugs are classified into five groups, based on evidence of efficacy, potency and drug class. First-line anti-TB drug, also called essential first-line drugs, are recommended in a four-drug regimen, containing: isoniazid, rifampicin, pyrazinamide, etambutol for the treatment of drug-susceptible TB in the frame of so-called Directly Observed Therapy (DOT) [15]. DOT by definition means watching the patients swallowing each dose of anti-TB drugs [9]. In the frame of actually used Directly Observed Treatment Short Course Chemotherapy strategy (DOTS), the anti-TB treatment is standardized, meaning that all patients receive the same regimens, being included in well-defined groups. The standard treatment has advantages over individualized treatment by preventing prescription errors, appropriate appreciation of drug needs, distribution and monitoring. By economical mean, standard treatment shows reduced costs and permits a comparable evaluation of treatment outcomes [9]. For standard treatment, the patients are grouped according the prior anti-TB treatment course: new patients are the cases who have no history of a prior TB treatment or who received less than 1 month the anti-TB drugs and previously treated patients, includes patients who relapsed, who failed the prior treatment and patients returned after default. The total duration of the drug susceptible treatment at new patients is 6 months and consists of intensive phase, lasting 2 months and continuous phase (ambulatory phase), lasting 4 months. During the intensive phase 4 first-line TB drugs (IHN, RIF, PZA, EMB) are recommended and during the continuous phase 2 drugs are used (IHN, RIF). The main form of first line TB-drug administration is oral solid form that is used in most of cases. Oral administration is the most simple, has a lower price, but is associated with a higher rate of side effects in cases with associated gastro-intestinal disorders [13]. Despite simple administration, the oral form of some drugs can determine from minor to major side effects in certain medical conditions (patients with liver, kidney diseases, gastro-intestinal disturbances) or associated harmful habits (alcohol abuse). Actually used anti-TB standard regimens, established according to WHO recommendations are associated with a variable rate of adverse drug reactions (10–15%) diminishing their effectiveness, due to treatment individualization according to clinical and laboratory tolerance [14]. In most cases

the treatment does not show significant (major) adverse drug effects. Clinical monitoring of the treatment is essential for recognizing adverse drug effects [9]. As well as, it permits the prompt and correct management of disturbances appeared due to the TB treatment. Minor side effects (jaundice, nausea, vomiting) permit the continuation of TB treatment with an associated symptomatic treatment. If the patient develops a major side-effect, the responsible drug is stopped and the patient is referred to a specialized health care facility for further management [14]. The most frequent major side effect of the anti-TB drugs is skin rash (itchy rash) that can be developed by any drug: isoniazid, rifampicin, pyrazinamide, or streptomycine. Jaundice (without laboratory evidence of hepatitis) and toxic hepatitis can be induced by isoniazid, rifampicin, or pyrazinamide [14]. Drug-induced hepatotoxicity appears more often in multi-drug TB regimens [13]. The single formulated isoniazid - rifampicin form reports more numerous side effects than the form with one agent used alone [13]. The risk of drug-induced hepatitis is increased by the associated gastrointestinal disorders, liver and kidney diseases, alcohol abuse, and wrong diet [13]. As well as, confusion and nervous impairment can indicate drug-induced acute liver failure, if it is associated with jaundice. The development of acute renal failure, purpura, as major side effects and nausea and abdominal pain, distinguished as minor side effects permits to suspect the involvement of rifampicin in adverse drug reaction [14]. For the detection of the drug which induced hepatotoxic effects, all anti-TB drugs must be stopped, and then reintroduced one by one, at lower dosage till the establishment of the clinical and laboratory tolerance [9]. The mechanism of liver injury is the induction of cytochrome P450 enzyme by isoniazid and/or rifampicin, which increases the quantity of toxic metabolite formed by another drug. In addition to this, rifampicin impairs bilirubin uptake, resulting in elevated bilirubin levels without elevation of transaminases [13]. For clear reasons, patients with hepatobiliary and pancreatic disorders have an increased susceptibility to develop drug-induced injury that permits the individualization of the standard regimen. Individualization of standard regimens determines reducing of dosage, increasing of treatment duration that impairs the efficacy and predisposes to non-adherent patient's behavior [10]. Spectacular, in some cases the anti-TB treatment can cause the enlargement of lung inflammation and progression of parenchymal destructions [6]. Such side effects are probably due to the development of hypersensitivity to mycobacterial antigens and development of immune disturbances, during the first weeks of the treatment [6].

For the treatment of drug-resistant tuberculosis are used second line anti-TB drugs. It requires extensive chemotherapy for two years, shows a higher rate of side effects, and a lower effectiveness. Intensive phase lasts 6 months and requires injected drugs, such as aminoglycosydes and injected fluoroquinolones [14]. Only streptomycin, the component of aminoglycoside class is used in injected form for the treatment of drug-susceptible tuberculosis in certain conditions (children less than 7 years old, disseminated TB), other aminoglycosides (kanamycin and amikacin) are used in the treatment of multidrug-resistant TB. Fluoroquinolones expose high bactericidal activity, used in oral, as well as in injected form in the frame of standard regimens of multidrug-resistant TB and poli-resistant TB [14].

Despite important financial resources involved, the treatment effectiveness in Eastern European States is lower than the European average [2, 8, 10]. Due to this, two injected forms of first – line anti-TB drugs: isoniazid and rifampicin are currently in the course of implementation for the treatment of susceptible TB in the intensive phase performed in hospital conditions. According to the published data, average of maximum concentration of 450 – 600 mg of intravenous injected rifampicin is 22,9 ±2,3 μg/ml, that is 2,5 times higher than the same dose administrated orally 8,9 ±1,3 μg/ ml [7]. As well as, the minimal inhibitory concentration of injected rifampicin is 10 times lower than the oral form (0,03 and respectively 0,3 μg/ml). Considering all scientific review data, it was identified a limited number of studies, exposing the comparative rate of effectiveness and tolerability of first-line injected and oral drugs in the treatment of TB in cases with associated gastro-intestinal disorders.

Aim of the study represented the assessment of treatment efficacy of injected forms of isoniazid and rifampicin at patients with hepatobiliary and pancreatic comorbidities.

Material and methods

A prospective, descriptive, case-control study was realized including 60 new pulmonary infiltrative drug-susceptible cases, with hepatobiliary and pancreatic comorbidities. The study was performed during the period 1.1.2013 – 1.1.2014. Patients were hospitalized in the Chernavtsy Regional Clinical Phtysiopneumological Dispensary. All selected patients were microscopically positive for acid fast bacilli and were treated according to the established new case category. Patients were distributed in a study group, composed of 30 cases treated with oral forms of isoniazid and rifampicin and the control group, composed of 30 cases treated with injected forms of first-line anti-TB drugs (isoniazid and rifampicin). The rest of associated first-line anti-TB drugs (pyrazinamide 2000 mg and ethambutol 1200 mg) were used in oral form. First-line injected drugs were rifampicin (Ріфонат, «Юрія-Фарм» [Rifonat, «Uriya-Pharm»], Ukraine) 30 mg/ml (600 mg) solved in 100 ml of physiological solution of NaCl and injected intravenous; isoniazid (Бітуб, «Юрія-Фарм», [Bitub, «Uriya-Pharm»], Ukraine) 100 mg/ml (300 mg) solved in 100 ml of physiological solution of NaCl and injected intravenous. General established results: men vs women rate was 3/1, with predominance of men in both groups and a medium age of patients was established 39,6 ± 1,3 years old in SG and 38,7± 1,6 years old in CG. So, according to age and sex distribution, the patients were similarly distributed, that permitted a comparable assessment of selected groups. Hepatobiliary and pancreatic disorders were diagnosed using abdominal echography and liver functional tests: serum albumin, bilirubin (direct and indirect), transaminases (ALT, AST), serum creatinine and urea, timol test. The level of endogenous intoxication was

appreciated according to Intoxication Leucocytaire Index (ILI) Kalf-Kalif (1) and Leucocytaire Shift Yabluchianskii Index (LSYI) (2), using the formulas [1, 5]:

ILI Kalf-Kalif = (4M+3Y+2P+S)*(P+1)/Ly+M+E+B (1)

Normal value = 0,3-1,5 Conventional Units (c.u.).

LSYI = E+B+P+S/limphocytes +monocytes (2)

Where: M – monocytes, Y – young neutrophyles, P – plasmocytes, S – segmented neutrophyles, Ly – lymphocytes, E – eosinophyles, B – basophyles. Normal value = 1,5 – 2,2 Conventional Units (c.u.).

Hematological Index of Intoxication (HII) was calculated according to the formula (3) [4]:

HII = ILI * KESR *KL (3)

Where KESR is the correctional coefficient calculated according to erythrocyte sedimentation rate: KESR = 1, if the ESR is < 5 mm/hour, KESR increases by 0,1 unit for each 5 mm/hour if the ESR is between 5 mm/hour and 30 mm/hour, increases by 0,2 unit for the each 5 mm/hour if the ESR is above 30 mm/hour. KL is the correctional coefficient calculated according to leucocytes quantity. If the leucocytes quantity is till 5 * 106/ml the KL is 1 unit and increases by 0,1 unit if the leucocytes quantity is more than 8 * 106/ml.

Lymphocytes Index was approved as being the report of lymphocytes to neutrophyles: LyI=Ly/N; Normal value = 0,5-0,65 Conventional Units (c.u.).

For statistical assessment were used the methods of: comparision, synthesis and discriminant analysis. Microsoft Excel XP and SPSS were used for performing quantitative and qualitative assessment. The degree of conclusion was established to be <0,05.

Results and discussion

Clinical efficacy of injected/oral forms of first-line anti-Tb drugs isoniazid and RIF was assessed after 2 months of treatment according to specially developed symptomatology scale of intoxication syndrom (included such clinical signs: asthenia, anorexia, loss of weight, underweight/cachexia, fever/subfebril temperature, night sweats) and bronchopulmonary scale (included: cough, expectorations, hemoptysis, dyspneea grade according to MRC scale, thoracic pain). The clinical expressiveness was distributed in levels: high, moderate, low and light. It was established that clinical state evaluated through intoxication symptomatology of patients with pulmonary TB and hepatobiliary/pancreatic comorbidities at the end of intesnive phase was better in CG than in SG (table 1). As well as, the bronchopulmonary symptomatology was less expressed in the same group after 60 days of intensive therapy.

Despite a non-significant difference of endogenous intoxication biomarkers between groups of the patients at the onset of the study, the specific treatment changed significantly their state. So, at the end of intensive phase of the treatment, the intoxication index ILI K-K was lower in CG. The rest of indices (HII and LSYI) increased in the SG due to more important immune disturbances developed at those patients (table 2).

Table 1

Expressiveness of the clinical state at the end of intensive phase of TB treatment

Index	Intoxication sdr		Bronchpulmonary sdr	
	SG (n=30),%	CG (n=30), %	SG (n=30), %	CG (n=30), %
Light	56,7	73,3*	50	80*
Low	33,3	26,7	36,7	13,3*
Moderate	10	-	10	6,7
High	-	-	3,3	-
Average t°C	37,4±1,1	37,1±0,4		

Legend: * - statistical difference between SG and CG, n – number of cases.

Radiological dynamics under the influence of different forms of anti-TB drugs and duration (60, 90, 120 days of intensive phase) showed a more evident difference between groups of patients. So, the injected first-line drugs (RIF and HIN) established a conclusive positive dynamics (resorbtion of parenchimal infiltrates, reduction of lung tissue destructions) in CG than in SG after 2 and 3 months of the treatment (table 3).

Table 2

Comparative expressiveness of the endogenous intoxication biomarkers

Index	Sample group (n=20) M±m	Study group (n=30) M±m		Control group (n=30) M±m	
		1	2	1	2
ILI K-K c.u.	1,3±0,5	1,6±0,05	1,8±0,07	1,55±0,07	1,5±0,05*
HII c.u.	1,9±0,46	2,1±0,06	2,99±0,07#	2,13±0,07	2,3 ±0,07*
LSYI c.u.	1,8±0,05	2,1±0,06	2,83±0,05#	1,95±0,05	2,1±0,05*
LyI c.u.	0,6±0,76	0,55±0,06	0,38±0,05	0,46±0,06	0,43±0,05

Legend: ILI K-K – Intoxication Leucocytaire Index Kalf-Kalif, HII – Hematological Index of Intoxication.
LSI – Leucocytaire Shift Index M.I.Yabluchyanskiy, LyI – Lymphocytes Index.
Statistical difference between the index before (1) and at the end (2) of the intensive phase of the treatment within the group.
* – Statistical difference between SG and CG, sample group – group of healthy individuals.

Table 3

Radiological evolution under different forms and duration of TB treatment

Groups	60 days (n=60)		90 days (n=31)		120 days (n=6)	
	Positive	Negative	Positive	Negative	Positive	Negative
	%	%	%	%	%	%
Study group	23,3	3,3	50	21,4	50	25
Control group	47,3*	13,3*	72,7*	45,4*	100	100

Legend: * - statistical difference between SG and CG, n – number of cases.

Table 4

Microbiological dynamics under different forms and duration of TB treatment

Groups	60 days (n=60)	90 days (n=31)	120 days (n=6)	Treatment failure
	%	%	%	%
Study group	36,7	73,7	75	6,7
Control group	60*	91*	100	-

Legend: * – statistical difference between SG and CG, n – number of cases.

Table 5

Biochemical dynamics under different forms and duration of TB treatment (M±m)

Biochemical Indices	Groups	1	2
Albumine (g/)l	SG	72,1±0,59	64,8±0,41
	CG	72,4±0,81	71,7±0,67*
Bilirubine (μmol/l)	SG	15,1±0,46	20,3±0,91#
	CG	14,9±0,44	16,8±0,48
ASAT (mmol/l)	SG	0,41±0,015	0,58±0,016#
	CG	0,40±0,011	0,45±0,013
ALAT (mmol/l)	SG	0,48±0,014	0,63±0,019
	CG	0,45±0,012	0,51±0,018
Urea (mmol/l	SG	5,2±0,22	5,4±0,11
	CG	5,1±0,18	5,2±0,15
Creatinine (kmol/l)	SG	83,5±0,85	91,8±1,23
	CG	81,4±0,53	89,1±1,02
Timol test (c.u.)	SG	3,45±0,22	5,10±0,21#
	CG	3,7±0,29	4,31±0,32*#

Legend: # statistical difference between the index before (1) and at the end (2) of the intensive phase of the treatment within the group, * – statistical difference between SG and CG.

Microbiological assessment, through smear microscopy is essential tool for the treatment monitoring according to DOTS strategy. So, a conclusive difference between the groups was obtained at the end of 2nd and 3rd months of treatment, with a higher microbiological convertion in CG than in SG (table 4). After 3 months of intensive phase, treatment failure was established at 6,7% of patients of SG.

Impact on the general state and laboratory tolerance of TB-drugs used by different ways (injected or orally) at patients with hepato-biliary and pancreatic comorbidities was assessed through serological indices of albumine, bilirubine, transaminases, urea, creatinine and timol reaction. No differences were assessed before starting the treatment.

At the end of the intensive phase a higher level of albumine was established in CG. Timol test established a more elevated result in SG than in CG and indicated a higher drug-induced hepatotoxicity of oraly adminstrated TB drugs. The established fact was proved by the conclusive elevation of bilirubine and transaminases in SG at the end of intensive phase. In CG elevation of serological biomarkers was established, but the statistical threshold was not achieved.

Imagistic exploration of the hepatobiliary system established increasing of the right liver lobe at 80,0% of all investigated patients by 0.7 ± 0,71 mm and resulted in a total length 15,1 ± 1,21 mm, the left liver lobe increased at 73,3% cases by 0,82 ± 0,12 mm with a total length 11,2 ± 2,7 mm, the signs of diffuse liver damage, expressed as hyperechogenic changes and increase of the portal vein size were identified at 68,3% cases.

Conclusions

Assessing the differences between the clinical and laboratory tolerance of TB drugs according to the way of administration, it was proved the importance of individualization of the standard treatment at patients with hepatobiliary and pancreatic disorders by intravenous use of isoniazid and rifampicin in intensive phase, for improving the quality of the TB treatment.

The clinical improvement of the patient's general state under the influence of intravenous use of isoniazid and rifampicin was confirmed by a lower expressiveness of intoxication and bronchopulmonary syndroms, as well as by a better radiological dynamics and higher rate of microscopic convertion at the end of intensive phase of the TB-treatment.

Biochemical disturbances due to TB treatment was less evident at the patients treated with intravenous isoniazid and rifampicin, confirmed by a better rehabilitation of mathematic indices of endogenous intoxication.

References

1. Kalf-Kalif YaYa. О лейкоцитарном индексе интоксикации и его клиническом значении [Leucocyte intoxication index and its clinical value]. Врачебное дело [Vrachebnoie delo]. 1941;1:31-36.
2. Krujko MM, Klimenko MT, Gulchuk NM, et al. Можливості фармакотерапії туберкульозу легень [Efficacy of pharmacotherapy in pulmonary tuberculosis]. Туберкульоз, легеневі хвороби, ВІЛ-інфекція [Tubelculioz, legenibi hvorobi, VIL-infectsia]. 2012;4:57-64.
3. Unified protocol for primary, secondary and tertiary health care. Tuberculosis at adults. Order of Ministry of Health of Ukraine No 620 of 04.09.2014.
4. Ostrovskiy VK, Svitich UM, Veber VR. Лейкоцитарный индекс интоксикации при острых гнойных и воспалительных заболеваниях легких [Leucocyte intoxication index in acute purulent and inflammatory diseases]. Вестник хирургии. им. И. И. Грекова [Vestnik khirurgii im. I. I. Grekova]. 1983;11:21-24.
5. Yabluchinskiy NI, Pilipenko VA, Kondratenko PG. Индекс сдвига лейкоцитов крови как маркер резистентности организма при остром воспалении [Leucocyte shift index as marker of organism resistance in acute inflammation]. Лабораторное дело [Laboratornoyie delo]. 1983;1:60-61.
6. Todoriko LD. Синдром системної запальної відповіді при поширених формах туберкульозу легень [Immune deficiency syndrome in extensive forms of tuberculosis]. Укр. пульмон. журн. [Ukr. Pulmonol. Jurn.]. 2013;3:229-231.
7. Pyatnochka IT. Біохімічні показники крові у хворих на туберкульоз легень у процесі хіміотерапії [Biochemical indices at patients with pulmonary tuberculosis during the chemotherapy. Туберкульоз, легеневі хвороби, ВІЛ-інфекція [Tubelculioz, legenivi hvorobi, VIL-infectsia]. 2012;2:46-49.
8. Bivol S, Scutelniciuc O, Soltan V. Factorii de risc asociaţi cu abandonul şi eşecul tratamentului tuberculozei în R. Moldova [Risk factors associated with default and failure of antituberculosis treatment in R. Moldova]. Chisinau, 2009;37.
9. International Standards for Tuberculosis Care. The Hague. Tuberculosis Coalition for Technical Assistance. 2009:260.
10. Langendam MW, van der Werf MJ, Huitric E, et al. Prevalence of inappropriate tuberculosis treatment regimens: a systematic review. Eur. Respir. J. 2011;26-28.
11. Manissero D. Analysis of tuberculosis treatment outcomes in the European Union and European Economic Area. Euro Surveillance. 2010;18:195-199.
12. Smailova G, Sagintaeva G. Cauzele prelungirii fazei intensive a tratamentului la cazurile noi detectate cu tuberculoză pulmonară [The causes of prolongation of the intensive phase in regimens with chemotherapy for newly detected patients with pulmonary tuberculosis]. Bull. Acad. Science Moldova. 2011;4(32):43-44.
13. William M.Lee. Drug induces hepatotoxicity. North England Journal. 1995;333:1118-27.
14. World Health Organization. Global tuberculosis control. Epidemiology, strategy, finances. WHO Report, Geneva. 2014.
15. World Health Organization. Treatment of tuberculosis. Geneva, 2014.

Young obstetrics and gynecology doctors – a valuable potential in overcoming the deficiency of specialists and decreasing of the maternal mortality rate in the districts of the Republic of Moldova

***Iu. Dondiuc, A. Ushanly**

Department of Obstetrics and Gynecology
Nicolae Testemitsanu State University of Medicine and Pharmacy, Chisinau, the Republic of Moldova
*Corresponding author: iurie_dondiuc@yahoo.com.

Received December 01, 2015; accepted February 01, 2016

Abstract

Background: Synthesis of opinions about the quality of the professional training, barriers encountered in career growth and existing motivational factors for young specialists, provided by the residents in the field.
Material and methods: The study involves 80 residents of obstetrics and gynecology. A 31-item questionnaire was elaborated to conduct the study. The answers that participants provided were processed with the following software: Statistical Package for the Social Sciences (SPSS 20) and Microsoft Office Excel 2010.
Results: Most of the young specialists that have received a professional training, which relies in considerable amounts on public financial resources, do not want to be employed in district-level medical institutions, in spite of the fact that these institutions are in urgent need of medical specialists. This is a difficult situation which can cause major problems in providing medical assistance to the citizens. The reduced possibilities of administrating highly qualified medical assistance will eventually increase the maternal and prenatal mortality.
Conclusions: The career prospects of the residents in the public health system are highly insufficient and the employments in the rural areas are not enough attractive. As a consequence, it makes it challenging to assure an even repartition of young specialists in the obstetrics and gynecology field, in the most of the country's districts.

Key words: resident, district, medical institutions, employment, prospect.

Introduction

In the Republic of Moldova exists a collection of documents, which are predestinated to help manage the needs and evolution of the public health services. The following documents focus particularly on controlling the sufficiency of medical staff in order to meet the expected performances and increase the accessibility to highly qualified medical services. The documents under consideration are the following: "Strategy for the development of Nicolae Testemitsanu State University of Medicine and Pharmacy for 2011–2020"; "The plan of improving the medical and pharmaceutical education

in the Republic of Moldova for 2011-2020"; "National Health Policy for 2007–2021"; "Strategy for developing the health system for 2008–2017" and others [1, 2, 3, 4, 5].

Nevertheless, in the recent years, the assistance of the Mother and Child healthcare department encounters permanent decrease of obstetrician-gynecologists. The level of sufficiency of these specialists for the entire population is below the average level of the European countries. An increasing migration of personnel out of the medical system and an uneven repartition of medical specialists in the districts have been established in the prejudice of rural areas [6].

It is well known that the potential staff of the institutions consequently determines the quality of health services and therefore the rate of maternal mortality, which in the recent years has no tendency of diminishing [7].

The professional training of obstetrician-gynecologists in the Republic of Moldova takes place during the postgraduate studies, according to the system of residency that lasts 4 years and is provided by Nicolae Testemitsanu State University of Medicine and Pharmacy. In the period of 2009–2014, 75 young specialists (men 10, women 65) were trained to become obstetrician-gynecologists, which represents an average of 12,5 per year. 39 (52%) fresh graduated specialists were hired in the public medical institutions, 26 (67%) of them in the Municipality of Chisinau. The actual demand for obstetrician-gynecologists, in the public medical institutions, for the year of 2014 was a total number of 80 specialists, as reported by the Ministry of Health [8].

Material and methods

The study involves 80 residents of obstetrics and gynecology, who were divided into 4 groups in different years of study. A 31-item questionnaire was elaborated to conduct the study. The answers that participants provided were processed with the following software: Statistical Package for the Social Sciences (SPSS 20) and Microsoft Office Excel 2010.

Results and discussion

A total amount of the obstetrician-gynecologists residents, in different years of study, participated in the research: 1st year – 27 (34.0%), 2nd year – 16 (20.0%), 3rd year – 21 (26.0%), 4th year – 16 (20.0%). The proportion of male and female participants is 1:8; the repartition on the gender criteria is represented in fig. 1.

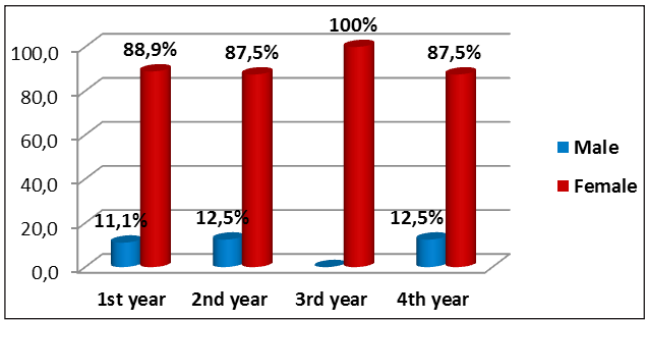
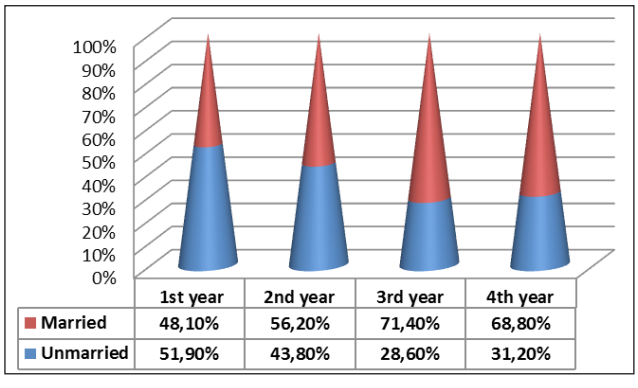


Fig. 1. Data are structured, considering the gender of the resident in correlation with the year of residency (%).

The average age of participants is 29.5 ± 1.25 years. It is important to remark, that by the time of graduation, every 5th resident will reach the age of 35.

In the first year of residency, the rate of married respondents is 48.1 ± 5.59%, while by the the 4th year of residency this percentage increases up to 68.8 ± 5.18% (t = 2.7172, p < 0.01). Regarding the year of study the proportion of married and unmarried residents is the following: for the 1st year – 1.0:1.1, for the 2nd year – 1.3:1.0, for the 3rd year – 2.5:1.0 and the 4th year – 2.2:1.0. Figure 2 demonstrates the correlation between marital status of the resident and the year of study.



	1st year	2nd year	3rd year	4th year
Married	48,10%	56,20%	71,40%	68,80%
Unmarried	51,90%	43,80%	28,60%	31,20%

Fig. 2. The correlation between marital status of the resident and the year of residency (%).

The rate of respondents having children is higher in the first 2 years of residency (1st year – 40.7% and 2nd year – 37.5%), with an average of 36.2 ± 1.88%.

Another interesting aspect to be analyzed is the residence of the participants, hence the 1st year residents have their residence in the rural areas of the country – 33.0 ± 5.26%; by the 4th year of study the rate decreases insignificantly to 24.5 ± 4.81% (t = 1.1931, p > 0.05). It is necessary to add that 58.0% of the residents in the 1st year have their residence in the Chisinau Municipality and 8.0% in the Balti Municipality (fig. 3).

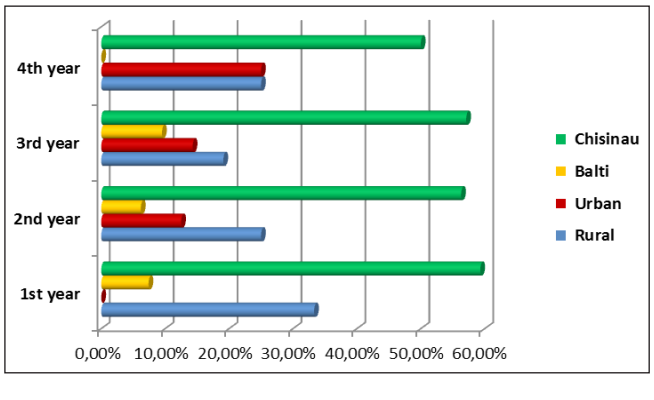
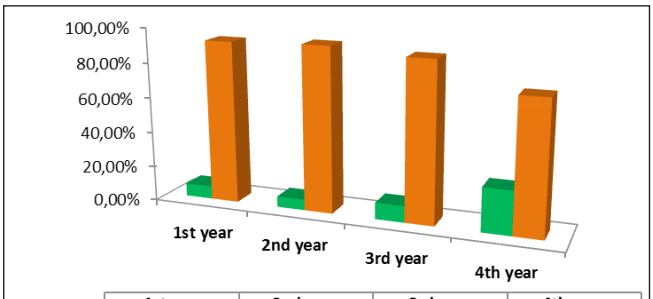


Fig. 3. Respondents are structured, considering the place of residence and the year of residency criteria (%).

The rate of students practicing their residency at the district-level institutions grows significantly: between the 1st year (33.3 ± 5.27%) and the 4th year (56.3 ± 5.55%) (t = 3.0067, p < 0.01); the rate of those practicing the internship in the medical institutions of Chisinau Municipality, declines from

66.7 ± 5.27% (in the 1st year) to 12.5 ± 3.69% (the 4th year) (t = 8.4199, p < 0.001).

Analyzing the data from the questionnaires, one concludes that the majority of participants, independently of the year of study, prefer the tuition at the medical institutions of Chisinau Municipality to the one at the district-level institutions. The resulted situation can be qualified as a "scissors phenomenon": the further one advances in the residency period, the more rises the positive consideration of the district-level institutions (the 1st year – 7.40 ± 2.85% , the 4th year – 25.0 ± 4.84%, t = 3.2033, p < 0.01) and vice versa for the municipality-level medical institutions (the 1st year – 92.6 ± 2.93%, the 4th year – 75.0 ± 4.84%, t = 3.1111, p < 0.01) (fig. 4).



	1st year	2nd year	3rd year	4th year
District	7,40%	6,20%	9,50%	25%
Chisinau	92,60%	93,80%	90,50%	75%

Fig. 4. The evaluation of the participants on quality of studies in correlation with the location of the medical institutions (%).

When asked to evaluate the main cause for choosing the obstetrician-gynecologist carrier, residents of all 4 groups of participants mentioned the humanity asset of this profession (96.3%; 87.4%; 90.4% and 62.4% as it follows) and only few ones spoke of other reasons and motivations like: family tradition (6.3% – the 4th), need of becoming a specialist (6.3% – the 2nd; 12.5% – the 4th), advice of the relatives (6.3% – the 2nd; 4.8% – the 3rd; 12.5% – the 4th), random choice (3.7% – the 1st; 4.8% – the 3rd; 6.3% – the 4th) (fig. 5).

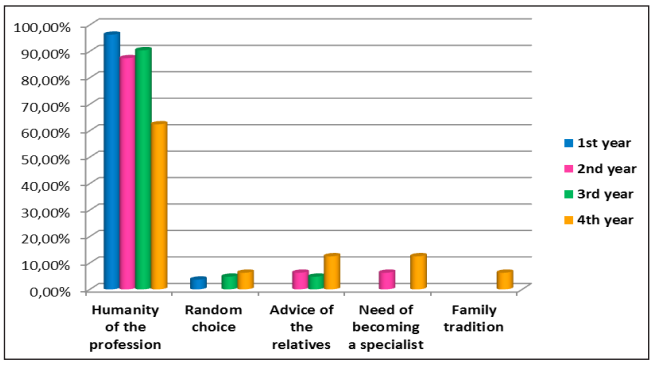
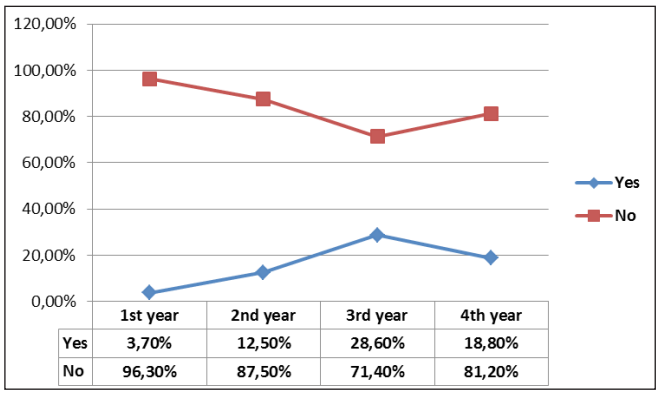


Fig. 5. Reasons for choosing the obstetrician-gynecologist career, according to the answers of the participants (%).

The majority of participants (84.1 ± 4.09%) do not regret choosing this profession. But the rate of those eventually regretting the choice tends to increase, starting from the 1st year (3.7 ± 2.11%) until the 4th year (18.8 ± 4.37%) (t = 3.1125, p < 0.01), with the highest rate for residents in their 3rd year of study (28.6 ± 5.05%) (fig. 6).



	1st year	2nd year	3rd year	4th year
Yes	3,70%	12,50%	28,60%	18,80%
No	96,30%	87,50%	71,40%	81,20%

Fig. 6. Participants confessing regret for choosing the obstetrician-gynecologist profession in correlation with the year of residency (%).

The participants in the study stated explicitly the causes for regretting studying the obstetrician-gynecologist profession. It must be mentioned that these causes have high rates which have been prioritized as follows: on the first place is the difficulty of assuring a decent life standard (r_n = 0.958), on the second place are the long and irregular hours of work, especially at night shifts (r_n = 0.929), on the third place are the causes related to personal health disturbances (r_n = 0.913), and on the fourth place are the highly stressed situations encountered in the professional activity (r_n = 0.845) (table 1).

Table 1

Main reasons for regretting the chosen career in opinion of residents of obstetrics and gynecology

	Abs.	λ	rn	Place
At this moment I am not able to assure a decent living	9	11.3	0.958	I
Psychological difficulties (stressful situations)	2	2.5	0.845	IV
Physical overload (especially the night duty)	5	6.3	0.929	II
Risks for personal health	4	5.0	0.913	III

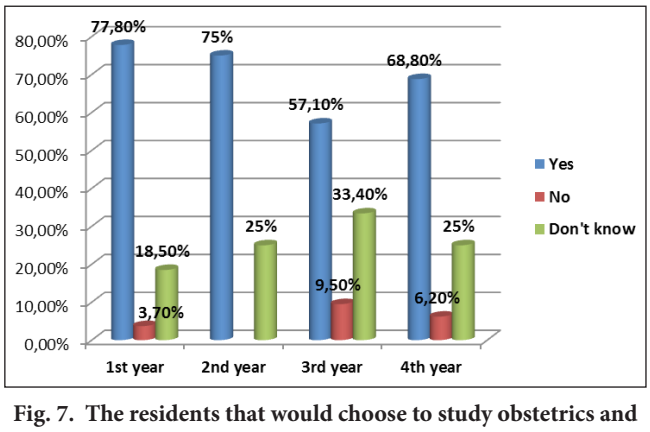
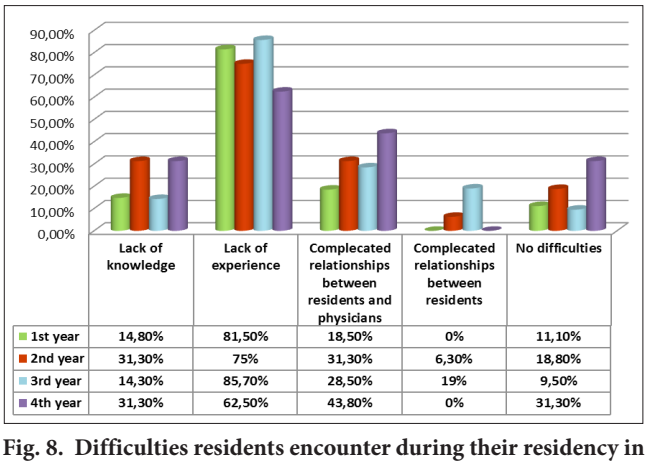


Fig. 7. The residents that would choose to study obstetrics and gynecology again, if they had the chance to.

Approximately 70.0% of the respondents confirmed that they would choose the same career if they got to choose again. Among them, the highest rate of 77.8 ± 4.65% is represented by the residents in the 1st year of study and the lowest, of 57.1

± 5.53%, by the residents in the 3rd year (t = 2.8648, p < 0.01). However every 4th participant was not able to give a concrete answer, most of them – residents of the 3rd year (33.4 ± 5.27%). A categorical negative answer came from an average of 6.5 ± 2.76% residents participating in the questionnaire, the highest rate of 9.5 ± 3.28% being observed by the residents in the 3rd year (fig. 7).

The participants specified as well other difficulties they encounter during the time of their residency. Every 3rd resident in the 2nd and 4th year of study (31.3 ± 5.18%), identified their lack of knowledge as an obstacle. Another difficulty is related to the lack of experience and some curious questions arise from this problem, according to the year of residence. When 81.5 ± 4.34% of the participants in the 1st year encounter this problem, there is, however, a simple explanation to that – they are at the beginning of their path, but if residents in the 3rd year (85.7 ± 3.91%) and the 4th year (62.5 ± 5.41%) complain of insufficient practical experience, the situation becomes confusing. The third problem pointed out by the participants has to deal with the relationships between residents and physicians; average rate amounts 30.5 ± 5.15% , with the highest rate of 43.8 ± 5.55% for the residents in the 4th year and the lowest rate of 18.5 ± 4.34% for residents in their 1st year of study. Each third resident in the 4th year of tuition answered that they encountered no difficulties (31.3 ± 5.18%) (fig. 8).



	Lack of knowledge	Lack of experience	Complecated relationships between residents and physicians	Complecated relationships between residents	No difficulties
1st year	14,80%	81,50%	18,50%	0%	11,10%
2nd year	31,30%	75%	31,30%	6,30%	18,80%
3rd year	14,30%	85,70%	28,50%	19%	9,50%
4th year	31,30%	62,50%	43,80%	0%	31,30%

Fig. 8. Difficulties residents encounter during their residency in the obstetrics and gynecology field.

The residents in the 4th year of tuition are 1.7 times more likely to assess the theoretical preparation of residency as *insufficient* to function independently in a medical institution (62.5 ± 5.41%) rather than *satisfactory* (37.5 ± 5.41%) (t = 3.2659, p < 0.01). Among residents in the 3rd year, the same situation has a rate that is 1.8 times higher: *insufficient* (52.4 ± 5.58%), *satisfactory* (28.6 ± 5.05%) (t = 3.1606, p < 0.01). Every second participant (50.0 ± 5.59%), in his/her 2nd year of residency, considers that the practical provided preparation, in order to perform an independent activity in the future, is adequate enough. Each second participant (55.6 ± 5.55%), in his/her 1st year of residency couldn't select the adequate answer to the question. Figure 9 illustrates all the possible given answers.

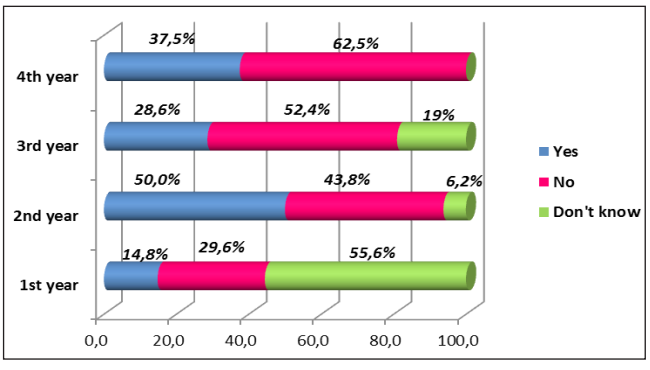


Fig. 9. Evaluation of the quality of the theoretical preparation during residency, regarding the opinion of the residents (%).

The answers provided by the participants evoked alarming results, considering the practical preparation during the residency. Every second respondent in the 2nd, 3rd and 4th year of residency (43.8 ± 5.54% in the 2nd, 3rd and 56.3 ± 5.55% in the 4th year) finds the practical preparation incomplete for an independent future activity as a physician. Up to 20.0% of residents in the 2nd, 3rd year of study have selected the "don't know" answer to this question (18.8 ± 4.37%) (fig. 10).

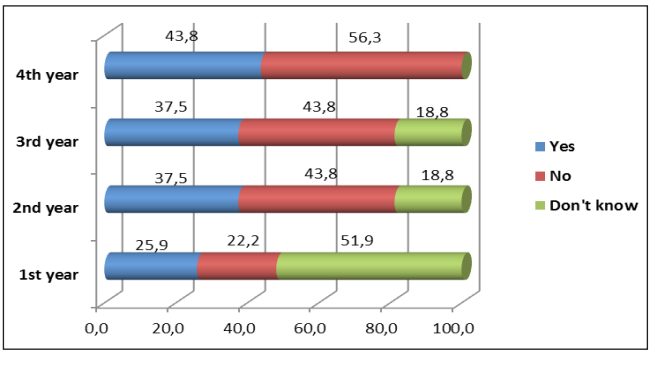


Fig. 10. Estimation of the quality of practical preparation of students during residency regarding the opinion of the residents (%).

The situation regarding the tuition of medical specialists during their residency turns out to be pessimistic as long as the "lack of motivation and the incertitude for the future" constitutes an average of 55.3 ± 5.56%, with the highest rate for the residents in the 2nd year of tuition (67.0 ± 5.26%) and the lowest rate for those studying in the 1st year of residency(46.0 ± 5.57%). Lack of confidence in one's own abilities is characteristic for 10.5 ± 3.43% of the residents, with more detailed classification depending on the year of studying: the 1st year – 4.0 ± 2.19%, the 2nd year – 17.0 ± 4.19%, the 3rd year – 16.0 ± 4.09% and the 4th year – 5.0 ± 2.44%.

The residents have selected the following strengths of the educational system, concerning the residency programs: management of theoretical seminars, involvement in practical activities, and positive attitude of the medical staff. A great number of participants picked out the "involvement in practical activities" answer, with an average rate of 90.5 ± 3.28%. This statistics is almost equal for all residency periods. Every second participant, studying in the 2nd and 4th year (52.3 ± 5.58%), considers that the program's strength relies on the theoretical seminars and among the participants studying in

the 1st and 3rd year only 31.6 ± 5.19% (t = 2.7133, p < 0.01). The positive attitude of the medical staff towards the residents is however decreasing: for the students attending the 1st and the 2nd years of residency the rate is 43.0 ± 5.54%, comparing to those attending years the 3rd and the 4th 11.0 ± 3.49% (t = 4.8871, p < 0.001). The participants that expressed the need for a new-elaborated and simplified program for the residency period constitute an average of 13.2 ± 3.78% (fig. 11).

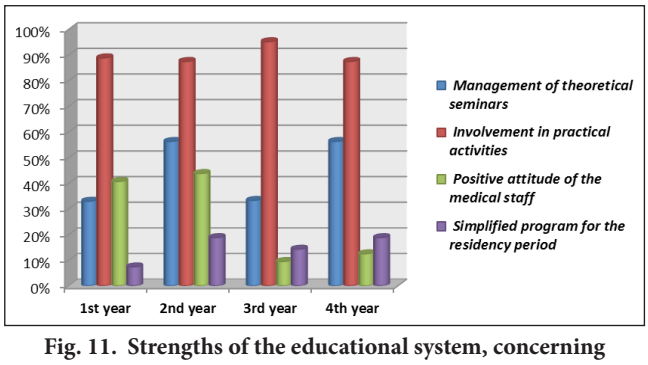


Fig. 11. Strengths of the educational system, concerning the residency programs, regarding the answers of the participants in the questionnaire (%).

An average of 43.0 ± 5.54% respondents, attending the 1st year of study, believe that 3.5 years is a sufficient time for the duration of residency in order to become a qualified medical specialist in the field; the participants attending the 2nd year of study – 4 years (61.0 ± 5.45%); the residents attending the 3rd year of study –3 years (48.0 ± 5.59%); the residents in their last year of tuition think that 2 years of residency would be sufficient (42.0 ± 5.52%).

Attitude of the participants towards an eventual proceeding to the doctoral – high level studies appears to be positive for the average of 69.0 ± 5.17%, with the highest rate among residents in the 4th year (87.5 ± 3.69%) and the lowest rate (56.3 ± 5.55%) among participants in the 2nd year of their studies.

Only residents in the 2nd year (12.5 ± 3.69%) and 3rd year (28.6 ± 5.05%) of residency do not express interest in scientific researches. Figure 12 illustrates all the possible given answers.

During the process of questionnaire we analyzed with an increased interest the future orientation of the residents regarding their professional activity. Consequently we structured the data as it follows: participants that prefer to work further in Chisinau Municipality (63.5 ± 5.38%) regarding their year of residency, have the highest rate for residents in the 1st year – 77.8 ± 4.65% and in the 4th year – a percentage of 56.3 ± 5.54% has been registered. No participants in the 3rd year of residency opted to continue their carrier in district-level medical institutions, while for residents in the 2nd and 4th years, 6.3 ± 2.72% of students would work in district-level institutions. Every second participant in the 2nd year of residency is planning to work as a medical specialist abroad (50.0 ± 5.59%), following every third participant in the 4th year (37.4 ± 5.41%) and every fifth resident in the 3rd year (24.0 ± 4.77%), this summarizing makes up an average of 30.6 ± 5.15% of the residents (table 2).

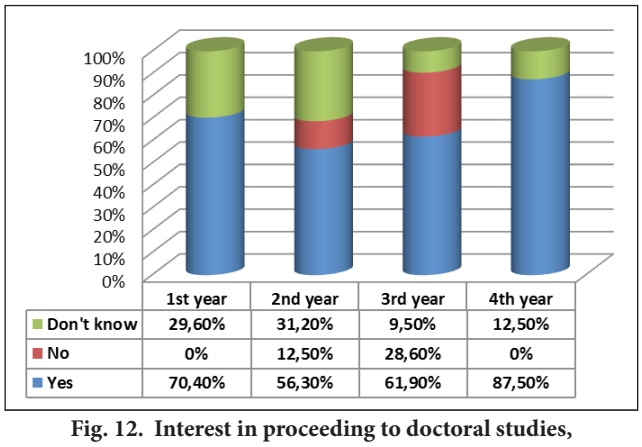


Fig. 12. Interest in proceeding to doctoral studies, according to the year of residency (%).

Aspects and factors that have caused the lack of eagerness when it comes to working in district-level medical institutions, which are in urgent need of medical specialists, arises interest for a thorough research. Residents of the 4th year, in 80.0 ± 4.47% of cases pointed on the lack of broad opportunities for carrier growth, followed by the inferiority of medical equipment at the district-level medical institutions and the low earnings (58.0 ± 5.52%); 54.0 ± 5.57% of the respondents emphasized the absence of living conditions and (42.0 ± 5.51%) the unemployment of the husband/wife. The answers provided by the residents between the 2nd and the 4th years of tuition have the equal hierarchy, but lower rates, which are represented in figure 13.

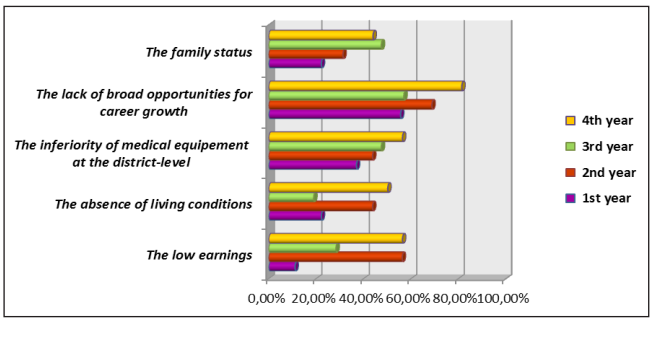


Fig. 13. Main factors that have caused the reluctance towards working in district-level medical institutions in the opinion of respondents (%).

Table 2

Future plans and orientation of the participants regarding their professional activity (%)

	1st year	2nd year	3rd year	4th year	χ2, gl, p
In Chisinau	77.8±4.65	43.7±5.55	76.0±4.77	56.3±5.54	21.7 gl=3.0 p<0.001
In the district-level medical institutions	11.1±3.51	6.3±2.72	0.0±0.00	6.3±2.72	6.2 gl=3.0 p>0.05
Abroad	11.1±3.51	50.0±5.59	24.0±4.77	37.4±5.41	18.2 gl=3.0 p<0.001

Conclusions

The career prospects of the residents in the public health system are highly insufficient and the employments in the rural areas are not enough attractive. As a consequence, it makes it challenging to assure an even repartition of young specialists in the obstetrics and gynecology field, in the most of the country's districts.

Most of the young specialists that have received a professional training, which relies in considerable amounts on public financial resources, do not want to be employed in district-level medical institutions, in spite of the fact that these institutions are in urgent need of medical specialists. This is a difficult situation which can cause major problems in providing medical assistance to the citizens. The reduced possibilities of administrating highly qualified medical assistance will eventually increase the maternal and prenatal mortality.

The health system in the Republic of Moldova lacks good functioning methodology in plan development, monitoring and controlling of human resources. The system confronts the absence of a realistic motivation for the medical specialists and the existing professional preparation demonstrates insufficiency.

All of the mentioned above implies some reorganizational proceedings in the tuition system of medical specialists as well as in the management of medical staff. It requires the implementation of special methodologies in planning and foreseeing the evolution of medical staff availability, in correlation with the socio-economic development of the country. Creating a multidimensional system of monitoring the medical staff, would allow controlling the professional development of medical specialists in the fields which will allow a prolific activity of the health system and a good operating assistance of the Mother and Child healthcare department.

References

1. Strategia de dezvoltare a sistemului de sănătate în perioada 2008-2017 [The development strategy of the health system during 2008 – 2017]. *Monitorul Oficial [Official Gazette]* 15.01.2008, nr. 8-10 art №:43.
2. Politica Națională de Sănătate 2007 – 2021 [National Health Policy 2007 – 2021]. *Monitorul Oficial [Official Gazette]*. 17.08.2007 nr.127 – 130 art №:931.
3. Programul de dezvoltare a învățământului medical și farmaceutic în Republica Moldova pe anii 2011 – 2020 [The development program of medical and pharmaceutical education in the Republic of Moldova during 2011 – 2020]. *Monitorul Oficial [Official Gazette]*. 05.11.2010 nr. 214-220 art №:1126.
4. Strategice de dezvoltare a Universității de Stat de Medicină si Farmacie „Nicolae Testemițanu" din Republica Moldova în perioada 2011 – 2020 [The strategics of development of the State University of Medicine and Pharmacy "Nicolae Testemitsanu" from the Republic of Moldova during 2011–2020]. https//www.usmf.md.
5. Concepția – cadru de dezvoltare a resurselor umane în sistemul sănătății și planul de acțiuni de implementare [Concept – the development framework of the human resources in the health system and action plan of implementation]. https//www.old.ms.md/-files/11843.
6. Dondiuc Iu. Asigurarea populației Republicii Moldova cu cadre de medici obstericieni – ginecologi [Ensuring the population of the Republic of Moldova with the staff of obstetrician-gynecologists]. *Buletin de perinatologie*. [Bulletin of Perinatology]. Chisinau, 2015;3:25-30.
7. Dondiuc Iu. Kadrowyy potentsial spetsialistov akusher-ginekologov rodovspomogatelnykh uchrezhdeniy Respubliki Moldova [The personnel potential of specialists obstetrician-gynecologists in the maternity hospitals of the Republic of Moldova]. Materialy XV Vserossiyskogo nauchnogo foruma Mat i Ditya. Moskva [Materials by the XV all-Russia scientific forum Mother and Child. Moscow]. 2014;403-404.
8. Dondiuc Iu. Evaluarea potențialului de cadre de medici obstericieni-ginecologi din maternitățile Republicii Moldova [Evaluation of the potential for obstetricians and gynecologists in the maternity hospitals of the Republic of Moldova. *Buletin de perinatologie* [Bulletin of Perinatology]. Chisinau, 2015;3:13-18.

Curierul medical, February 2016, Vol. 59, No 1

Influence of polymorphic variants of serotonin receptor 5-HTR2AT 102C gene on mental status of patients with rheumatic arthritis depending on sex

***L. A. Protsiuk, N. A. Stanislavchuk**

Department of Internal Medicine No 1, N. I. Pirogov National Medical University of Vinnitsa, Ukraine

*Corresponding author: rossata@yandex.ua. Received December 12, 2015; accepted February 02, 2016

Abstract

Background: In this study was determined the frequency of T102C polymorphism of the 5-HTR2A gene and its impact on the mental state of the patients with RA according to sex and gene variant polymorphism.

Material and methods: Molecular genotyping was performed using the technique of polymerase chain reaction. The degree of depression severity in the examined according to the Hamilton Anxiety Rating Scale was assessed. The levels of reactive and personal anxiety were defined according to the scale of Spielberger.

Results: In the study, we found that in women with RA was significantly less common homozygous CC as compared to male patients ($p < 0.05$), and the clinical picture of patients with RA women with TT and TC genotypes there were significantly more frequent symptoms of fatigue, autonomic anxiety and depressive disorders (DS), high state, trait anxiety and symptoms of severe depression ($p < 0.001$), whereas in women with CC genotype were found mild symptoms of DS. Our results showed that patients with RA men with genotype TC and TT, compared with women's characteristics, revealed mild to moderate severity of DS, and RA men patients with genotype CC did not demonstrate the symptoms of depression ($p < 0.05$).

Conclusions: Depressive disorders with high levels of state and trait anxiety that affect significantly the course and manifestations in women with genotype TC and TT were detected in the vast majority of patients with RA.

Key words: rheumatic arthritis, polymorphism, serotonin receptor gene 5-HTR2A T102C.

Introduction

Prolonged course of rheumatic arthritis (RA) leads to changes in life style and interests of patients, decrease of social and material status as well as the development of mental disorders [1]. It is demonstrated in the work of Y. K. Sikalo and N. A. Stanislavchuk [2] that patients with RA have complicated dynamics of mental disorders adversely influencing the course and prognosis of underlying disease. Depression and anxiety are the main manifestations of mental disorders. The most common conception of anxiety and depressive disorders is serotonin theory. Serotonin plays the major role in regulation of neuroendocrine rhythms, vascular tone, mood, sleep, appetite; it influences the behavior (including social), mood and emotions of a person [3]. Recent studies showed the disturbances in serotonergic system status to be associated with a number of psychopathologic phenomena [4]. The current knowledge of such mental disorders as depression and anxiety in RA patients demonstrates their significance in decrease of social adaptation of these patients, worsening of their social functioning. At the same time the relationship between mental disorders and clinical and social-psychological characteristics of RA patients is studied insufficiently [5].

The object of this work was to study the influence of polymorphic variants of serotonin receptor 5-HTR2AT 102C gene on mental status of patients with rheumatic arthritis depending on sex.

Material and methods

120 RA patients, 90 females (75.0%) and 30 males (25.0%) were studied. Their age ranged from 18 to 75 years, the mean age being 51.5±12.04 years. The distribution of genotype frequency of 2A serotonin receptor HTR2A T102C gene was determined in 100 patients taking a course of treatment at N. I. Pirogov Regional Clinical Hospital of Vinnitsa, Ukraine. Clinical characteristics of patients depending on genotype and sex are given in table 1.

Clinical diagnostics was made on the basis of ACR/EULAR criteria of 2010 [6]. Polymorphic sites of T102C in promotor regions of 5-HTR2A gene were determined by isolating genomic DNA with phenol-chloroform method using the kit for DNA/RNA isolation from blood serum or plasma (SPF "Li-Tech", Russia). Polymorphic sites of T102C gene were amplified with polymerase chain reaction.

Table 1

Clinical characteristics of RA patients, included in the study, depending on genotype and sex

Sign	RA patients (n=100)	TC (n=53)	TT (n=28)	CC (n=19)
Females, n (%)	73 (73.0)	42 (79.2)	21 (75.0)	10 (52.6)
Average age, females, years (M±SD)	51.6±12.0	49.5 ±10.8	55.6±13	51.7 ±12.2
Males, n (%)	27(27.0)	11 (20.8)	7 (25.0)	9 (47.4)
Average age, males, years (M±SD)	49.2±11,8	51.7±14.9	50.0±5.0	45.6±11.5
Seropositive RF, females, n (%)	45 (61.6)	19 (45.2)	17 (80.9)	9 (47.4)
Seropositive RF, males, n (%)	23 (85.2)	9 (81,8)	6 (85.7)	8 (88.8)

Examination of patients included: study of complaints, medical history and anamnesis vitae as well as the factors influencing psycho-emotional status of patients. Objective study of RA patients was done according to routine methods. Anxiety level was assessed by Spielberger State-Trait Anxiety Scale (STAI) [7]. Depressive status and depression severity were evaluated by Hamilton Depression Rating Scale (HDRS) [8]. Statistical data processing was done with Statistical package for Windows v. 8.0 using parametric and nonparametric methods. Modified Pearson's Chi-Squared criterion (p) was used to check the correspondence of empiric distribution of genotype frequency to theoretically expected Hardy-Weinberg equilibrium (steady distribution). Yates' continuity-corrected Shi-Squared test for small samples as well as two-tailed Fisher's exact test (F) was used in pair-wise comparison of allele and genotype frequencies in studied groups. Differences were considered significant if significance value was 95% ($p<0.05$).

Results and discussion

Study of genotype frequencies of polymorphic loci T102C of 5-HTR2A gene in RA patients depending on sex and according to Hardy-Weinberg distribution demonstrated heterozygous TC genotype to occur in 57.5% of females and 40.8% of males, homozygous TT genotype – almost with the same frequency in both sexes while homozygous CC genotype – more frequently in males than in females ($p<0.01$, respectively). The data are presented in table 2.

According to data received by Spielberger questionnaire among RA patients only 9 patients (7.5%) showed low level of state anxiety (SA) and 14 patients – low level of trait anxiety (TA) while moderate anxiety, both state and trait, was determined in 47 (39.2%) and 42 (35.0%) patients, respectively. The majority of patients (64 -53.3%) demonstrated high level of anxiety, both state and trait.

The analysis of SA and TA levels showed that irrespective of patients' genotype average indices of state 47.0[41.0;51.0] scores and trait 44.0[36;48] scores anxiety appeared to be higher in females than those in males – 38.0[32;45] and 38.0[34;44] scores, respectively – with no significant difference between them. High level of anxiety, both state and trait was observed significantly more frequently in females than in males: SA – 58.9% and 36.7% of patients ($\chi_1^2=4.46$, $p=0.0346$); TA – 63.3% and 23.3% of patients ($\chi^{2Y}=12.9$; $p=0.0003$), respectively.

The analysis of SA and TA indices in groups of patients with different variants of polymorphic sites of T102C gene depending on sex showed that average values of state ($p=0.0006$) and trait ($p=0.0135$) anxiety in females with TC, were significantly higher than those in male patients with TC genotypes. At the same time in groups of male patients with TC and CC genotype there was a tendency to the increase of average value of SA in male patients with TC ($p=0.085$) in comparison with males CC. Besides in women with TC genotype there was significantly higher of SA values ($p=0.0007$) as compared to female patients with CC and TT ($p=0.002$) genotype. The data are presented in table 3.

Table 3

Indices of state and trait anxiety in RA patients with different variants of polymorphic sites of T102C gene depending on sex Me [LQ;UQ]

Genotype	Sex	TC	TT	CC
State anxiety (scores)	F	49.0 [46.0;54.0]**	42.0 [37.0;48.0]*	33.5 [30.0;42.0]**
	M	36.0 [32.0;45.0]	41.0 [38.0;45.0]	38.0 [30.0;45.0]
Trait anxiety (scores)	F	45.0 [36.0;48.0] #	44.0 [39.0;48.0]*	37.0 [32.0;42.0]*
	M	36.0 [34.0;39.0]	42.0 [34.0;48.0]	41.0 [37.0;44.0]

Notes: * - confidence level $p<0.01$ between groups of female and/or male patients; # - confidence level $p<0.05$;
** confidence level $p<0.001$.

The data received in the course of study provided evidence that women with TC genotype had high SA levels significantly more frequently than moderate levels – 71.4±7.0% versus 28.6±6.9%, ($p<0,001$), and there were no cases of low anxiety levels among women with this genotype. Among male patients with TC genotype there was a tendency to the increase of the number of patients with high SA level ($p=0.092$) as compared to those with low SA level. There were no significant differences in this index between RA patients, both women and men, with TC genotype. Among women with TT genotype moderate and high SA levels occurred with similar frequency -42.9% and 57.1% ($p>0.05$), respectively, and there were no patients with low anxiety level. At the same time 71.4% of men with TT genotype showed the signs of moderately evident SA and the tendency ($p=0.052$) to decreased number of patients with high and low SA levels by contrast to patients having moderate anxiety levels which occurred with similar frequency

Table 2

Genotype frequency of polymorphic loci T102C of 5-HTR2A gene in RA patients depending on sex (%)

Locus	Sex	n	Genotypes			Alleles	
			TC	TT	CC	T	C
T102C	M	27	40.8 %	25.9 %	33.3%	53.7 %	46.3%
	$\chi2$ =0.88; p = 0.348; Fisher's exact test: p = 0.348 | F(ST) = 0.330						
	F	73	57.5%	28.8%	13.7%	57.5%	42.5%
	$\chi2$ = 2.3; p= 0.129; Fisher's exact test: p = 0.125 | F(ST) = 0.411						

in 14.3%, respectively. Significant increase of the number of female patients with high anxiety level in comparison with male patients was established between female and male groups with TT genotype - 57.1% and 14.3% (p<0.05), respectively.

High SA level was determined in 50.0% of women and 33.3% of men with CC genotype while low and moderate levels – in 20.0% and 30.0% of women and 22.2% and 44.4% of men, respectively. No significant difference of this index between the groups of female and male patients with CC genotype was detected.

High TA level was diagnosed in women with TC genotype significantly more often than low one – 52.4% versus 16.7% (p<0.001) and moderate – 52.4% versus 30.9% (p<0.05), respectively, while 54.5% of men with TC genotype had low TA level, 27.3% and 18.2% - high and moderate levels, respectively. The tendency (p=0.092) to the increase of number of patients with low TA level was observed between the groups of patients with high and moderate TA levels.

No patients had low TA level both among women and men with TT genotype while in women with TT genotype high TA level was seen significantly more often than moderate one – 85.7% versus 14.3% (p<0.001), and in men moderate TA level was detected significantly more often than high one – 71.4% versus 28.6% (p>0.05). Between the groups of female and male patients there was significant increase of male patients with TT genotype and moderate TA level in comparison with female patients (p<0.01) as well as significant increase of female patients with high TA level by contrast to men (p<0.01).

Among female patients with genotype CC high TA level was detected in 50.0%, moderate – in 40.0% and low – in 10.0% of women. There was a tendency to the increase of the number of women with high TA level (p=0.062) as compared to patients with low TA level. Among men with CC genotype there were no patients with low TA level while patients with moderate TA level occurred significantly more often than those with high TA level – 88.9% versus 11.1% (p<0.01). Moderately evident TA was detected significantly more often in men with CC genotype than in women – 88.9% versus 40.0% (p<0.05) while women showed the tendency to the increase of the number of patients with high TA level by contrast to men (p=0.086), respectively.

The results obtained showed depressive disorders (DD) of various degree of severity in 105 (87.5%) RA patients by Hamilton depression scale. According to this scale 55 patients (45.8%) had mild manifestations of DD, 33 patients (27.5%) - moderately severe, 11 patients (9.2%) – severe and 6 patients (5.0%) – extremely severe signs. Incidence of DD in patients with RA depending on sex was determined, it being significantly higher in women than in men – 83 (92.2%) versus 22 (73.3%).

Average values of depression by Hamilton scale in women and men ill with RA with TT and CC genotypes appeared to be nearly identical without any significant differences in the values (p>0.05). The corresponding data are given in table 4.

The analysis of depressive disorders indices in groups of patients with different variants of polymorphic sites of T102C gene depending on sex showed that average values of depression by Hamilton scale (p=0.0001) in females with TC, were significantly higher than those in male patients with TC genotypes. At the same time in the group of female patients with CC genotype there was significant decrease of DD as compared to female patients with TT (p=0.02) and TC (p=0.015) genotype. The analysis of depression by Hamilton scale indices in groups of patients with different variants of polymorphic sites of T102C gene depending on sex showed that average values DD in male patients with TT genotype (p=0.0036 and p=0.0004, respectively), were significantly higher than those in male patients with TC and CC genotypes.

In female patients with TT genotype moderately severe DD occurred significantly more often (42.9±10.8%) than in patients with no signs of depression (4.8±4.7%, p<0.01), patients with signs of severe depression (14.2±7.6%, p<0.05) and extremely severe depression (9.5±6.4%, p<0.05). There was no significant difference in values between groups of female and male patients with TT genotype. No signs of extremely severe DD were found among men with TT genotype.

In female patients with CC genotype mild DD occurred significantly more often (70.0±14.5%) than in patients with no signs of depression, patients with signs of mild and severe depression having similar frequency -10.0±9.5% (p<0.05). In 66.7% of RA male patients with CC genotype signs of mild depression occurred and 33.3% of patients had no signs of depression. There was no significant difference in values between groups of female and male patients with CC genotype. No signs of extremely severe DD were found among men and women with CC genotype. Besides, no signs of mild and moderately severe DD were detected in men with CC genotype.

Conclusions

The study found out that RA female patients with TC genotypes had high levels of state and trait anxiety indicating evident psychoemotional stress with development of persistent anxiety as a trait of character. The presence of psychoemotional stress in female and male patients with CC genotype

Table 4

Indices of depressive disorders in RA patients with different variants of polymorphic sites of T102C gene depending on sex Me [LQ;UQ].

TC genotype		TT genotype		CC genotype	
F	M	F	M	F	M
14.0 [11.0;17.0]	8.0 [6.0;8.0]**	15.0 [12.0;18.0]	16.0 [12.0;18.0]	10.0 [8.0;13.0]	9.0 [7.0;12.0]*

Notes: * - confidence level p<0.001 between groups of female and/or male patients.

was suggested by signs of moderately severe anxiety were detected. Moderately severe and severe depressive disorders were common in women with TT genotype while the majority of women with TC and CC genotypes as well as men with CC genotype had mild depressive disorders.

References

1. Moll LT, Gormsen L, Pfeiffer-Jensen M. Higher prevalence of depression in patients with rheumatoid arthritis - a systematic review. *Ugeskr Laeger.* 2011;173(41):2564-8.
2. Sikalo YuK, Stanislavchuk MA. Psikhoemotsionalnye rasstroystva u bolnykh revmatoidnym artritom [Psychoemotional disorders in patients with rheumatoid arthritis and correction of them by paroxetine]. *Ukrainskiy revmatologicheskiy zhurnal [Ukrainian Rheumatology Journal*]. 2014;3(57):54-58.
3. Christian P. Handbook of the Behavioral Neurobiology of Serotonin. First edition / P. Christian, J. Barry. USA: Elsevier BV, 2010;833.
4. Mbemba J, Korf J, Ormel J, et al. Investigating the Molecular Basis of Major Depressive Disorder Etiology: a Functional Convergent Genetic Approach. *Stress, Neurotransmitters, Hormones Neuroendocrine, Genetic Mechanisms*. 2008;1148:42-56.
5. Smulevich AB. Psychological disorder in clinical practice. M: Medical 4. press inform, 2011;720.
6. Aletaha D, Neogi T, Silman AJ, et al. Rheumatoid Arthritis Classification Criteria: An American College of Rheumatology and European League Against Rheumatism Collaborative Initiative. *Arthritis Rheum*. 2010;62:2569-2581.
7. Hamilton MA. Rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*. 1960;23:56-62.
8. Spielberger ChD. Theory and research on anxiety. Jn Ch.D.Spielberger (Ed.). Anxiety and Behavior. New York: Acad. Press, 1966;240.

Possibilities of telemedicine in work to improve survival in multiple trauma victims

S. O. Gurjev*, A. Y. Fil, Y. Y. Fil, B. B. Lemishko

Department of Traumatology and Ortopaedics, Danylo Halytskiy National Medical University of Lviv, Ukraine

*Corresponding author: adrian-fil@yandex.ru.

Received December 04, 2015; accepted January 25, 2016

Abstract

Background: World experience in providing medical assistance to victims of trauma indicates high efficiency of telemedicine methods in organization of medical care to trauma victims and an effective and adequate implementation of therapeutic and diagnostic measures.

Material and methods: We made some analyses of the necessity of the telemedicine consultation and control in 1150 patients with multisystem injuries which assisted 1000 victims in the medical institutions of the second level and 150 victims in the third level institutions. We studied the necessity for the assistance in the diagnosis, recommendations for treatment, and dynamic control. We explored the effectiveness of telemedicine on the example of 110 patients.

Results: The use of telemedicine technology in the process of care in patients with polytrauma is appropriate in medical institutions of the second level. There is a difference between the need and feasibility of telemedicine technology in institutions of the 2nd and the 3rd levels with the second level there is a need for treatment guidelines. The use of telemedicine technology can increase the survival of the affected by 14.5% by optimizing the provision of emergency medical care.

Conclusions: Conditions of Ukraine's health care system, do not allow providing full medical and diagnostic care in all medical institutions of Ukraine. Therefore, there is request to continue consulting practitioners in damage control specialty, dynamics of treatment, as well as providing opportunities to discuss and select the optimal therapeutic and diagnostic management.

Key words: telemedicine, multiple traumas, victims.

Introduction

World experience of care to trauma victims demonstrates the high efficiency of the methods of telemedicine in the organization of care to trauma victims, and effective and adequate implementation of therapeutic and diagnostic activities [1].

The actual conditions of the health system of Ukraine do not allow a full medical diagnostic aid in all medical institutions of Ukraine [2, 3].

There is therefore a need for constant consultation practitioners majoring in damage control dynamics of treatment, as well as providing opportunities to discuss and select the optimal therapeutic and diagnostic activities [4].

The increase in the number of severity and types of injuries leads to the necessity of highly skilled, highly specialized and high-tech medical care for patients with polytrauma.

World experience in providing medical care to victims of trauma indicates high efficiency of telemedicine methods in the organization of medical care to victims of trauma and effective and adequate implementation of therapeutic and diagnostic measures.

In fact, the current situation of the health system of Ukraine does not allow for a full medical and diagnostic care in all medical institutions of Ukraine [5]. Therefore, there is a need for constant counseling practitioners with specialty in damage control dynamics of treatment and who enable discussion and selection of optimal therapeutic and diagnostic measures. The above is only possible when using telemedicine techniques, which ensure interoperability of health care institutions at various levels.

Material and methods

We made some analyses of the necessity of the telemedicine consultation and control in 1150 patients with multisystem injuries which assisted 1000 victims in the medical institutions of the second level and 150 victims in the third level institutions. We studied the necessity for the assistance in the diagnosis, recommendations for treatment, and dynamic control. We explored the effectiveness of telemedicine on the example of 110 patients.

All calculations were conducted according to the criteria and requirements of evidence-based medicine by using computer technology, with all provisions and findings being within probabilities.

Results and discussion

The study found that the advice actually require 82% of the victims who were given medical treatment in medical institutions of the second level, and 36% of victims who received assistance in the third level institutions (tab. 1).

Table 1

The victims who were given medical treatment

Events	The share in the array of needs (%)	The share of the total array (%)	Rank
Help in diagnosis	52,56	45,10	1
Recommendations for treatment	35,24	25,13	2
Dynamic control treatment	19,02	10,78	3

Advisory services to provide recommendations on treatment of victims are needed at the second level and it is near 35.24%. Additional help for the dynamic control is 19.02% or 10.78% of the total array and is ranked on the third place. Thus, it should be noted that the main problem can be solved by consultation with highly qualified specialists in the field of injury problems. Recommendations for treatment take 1.5 times less, when this technology is used and in a dynamic control 2.7 times less. Expert analysis of cases showed, that the vast majority of aid could be accelerated and provided by using telemedicine technology.

Analysis of the data presented in table 2 indicates that the vast majority of consultative and diagnostic assistance could be provided via telemedicine technology. While studying the need for advisory assistance in the third level institutions we found that this was required only by 20.06%. The distribution of aid is given in table 3.

As seen from table 3, the structure needs to conduct additional measures. Level 3 is different from the establishments of the 2nd level. Firstly, only 20.06% need additional advice, secondly, first is the need for consultative assistance for the treatment of victims who make up 90.32% or 18.67% of the array.

Diagnostic measures constitute only 35.48% of the array needs or 7.33% of the array.

Almost 19.35% of the panel needs dynamic control of the treatment, or 4% of the array.

Telemedicine techniques can be applied to a limited extent. As shows the data from the table 4, the use of telemedicine technology as a method to perform additional advice is only for 20% of diseases. The most necessary substitution is in the

Table 2

Consultative and diagnostic assistance that could be provided via telemedicine technology

Events	Need		Expert possibility for such measures		The possibility of using telemedicine	Rank
Diagnostic	52,56	45,10	37,80	31,06	68,74	2
Treatment	35,24	28,90	26,10	21,40	74,05	1
Dynamic observation	19,02	15,60	15,12	12,40	65,19	3

Table 3

The need for advisory assistance in the third level institutions

Events	The share in the array of needs (%)	The share of the total array (%)	Rank
Help in diagnosis	35,48	7,33	2
Recommendations for treatment	90,32	18,67	1
Dynamic control treatment	19,35	4.00	3

Table 4

Comparative characteristics of the use of telemedicine technology in diagnosis and treatment

Events	Need		Experts taking action		The possibility of using telemedicine	Rank
	The needs	Gen.	The needs	Gen.		
Diagnostic	35,48	7,33	12,9	2,67	36,36	1
Treatment	90,32	18,67	12,9	2,67	14,29	2
Dynamic observation	19,39	4,00	16,66 0,322	0,6	16,67	3

diagnosis of injuries. The therapeutic assistance was needed in half of cases. Therefore, there is a real need for consultant call in the third level structures. Analysis indicates that the use of telemedicine technology is most appropriate in health care institutions of the second level.

The use of telemedicine technology to provide health care, organization and implementation of therapeutic and diagnostic measures in 110 patients with polytrauma, who was given medical care in the second level institutions, has proven that expert estimated figures are fully confirmed. The use of telemedicine technology enhanced the survival of victims by 14.55% due to the improvement of the quality of diagnosis, optimization of the characteristics of therapeutic techniques, reduction of clinical decision-organizational solutions for conducting Clinical Diagnostic measures.

Conclusions

1. The use of telemedicine technology in the process of care in patients with polytrauma is appropriate in medical institutions of the second level.
2. There is a difference between the need and feasibility of telemedicine technology in institutions of the 2-nd level, and the 3-rd level. There is a need for a correction and guidelines of the treatment and diagnostics principles at the third and the second levels.
3. The use of telemedicine technology can increase the survival of affected by 14.5% by optimizing the provision of emergency medical care.

References

1. Loane MA, Loane MA, Bloomer SE, et al. A comparison of real time and store and forward teledermatology: a cost benefit study. *Br. J. Dermatol.* 2000;143:1241-47.
2. Mintser OP, Mintser OP, Tsarenko AV, et al. Model to improve the accessibility and quality of health care to the rural population with the use of telemedicine technology: guidelines. K., 2012;26.
3. Better, Sooner, More Convenient Primary Health Care. New Zealand Ministry of Health, Primary Health Care. http://www.moh.govt.nz/moh.nsf/indexmh/phcs-bsmc.
4. Krupinskiy E, Krupinskiy E, Barker G, et al. Telemedicine versus in-person dermatology referrals: an analysis of case complexity. *Telemed. J.* 2002;8:143-147.
5. Popchenko TP. Regarding the status and future directions of reform financing and management of health care in Ukraine. A snapshot of the National Institute for Strategic Studies under the President of Ukraine. 2012;717. http://www.niss.gov.ua/articles/.

Microsurgical denervation at focal muscular dystonia, in torticollis patients

V. I. Tsymbaliuk[1], I. B. Tretyak[1], *M. Yu. Freydman[2]

[1]Department of Restorative Neurosurgery, A. P. Romodanov State Institute of Neurosurgery, Kiev, Ukraine
[2]Department of Neurosurgery, Hospital No 2, Belaya Tserkov, Ukraine

*Corresponding author: mf86neuro@gmail.com. Received December 15, 2015; accepted February01, 2016

Abstract

Background: Surgical treatment of focal muscular dystonia, despite all achievements of modern neurosurgery, and auxiliary methods of diagnostics, continues to cause more questions, than gives answers. The main challenge for all who uses denervation techniques in treatment of spastic wryneck (SW) is accurate identification and the fullest exclusion of the dystonic muscles which take part in the formation of complex of symptoms of SW.
Material and methods: 32 patients with torticollis were enrolled into the study. All enrolled patients underwent 75 microsurgical denervations of dystonic muscles, including 32 selective denervations of contrlateral sternocleidomastoid muscle, 28 selective posterior ramisectomy of C1-C6 roots (Bertrand's procedure), 15 denervations and myotomias of dystonic muscles of omo-trapezoid triangle (DMOTT).
Results: The outcome evaluation was conducted via neurological examination and Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) questionnaire. The outcomes showed decrease of severe torticollis (up to 0%), severe disability decreased to 0%, light disability increased from 0% to 60.71%. DMOTT strongly affected, thus improved, the outcomes.
Conclusions: Initial indicators of weight of a current of SW with torticollis decreased to zero that once again emphasize efficiency and adequacy of the interventions chosen the denervation and surgical targets. Easy severity prevailed at all patients in the remote terms of supervision – 60.71% that managed to be reached performance of DMOTT. Thus, the carried-out microsurgical interventions, in particular DMOTT, allowed us to reach positive result (in the context of decrease in weight of a course of a disease) at 100% of patients with T.
Key words: muscular cervical dystonia, spastic wryneck, torticollis, microsurgical denervation.

Introduction

According to Sitthinamsuwan B. et al. [8] the resection of peripheral nerves has to be the main, primary method of surgical treatment of uncomplicated cases of the spastic torticollis (ST).

Spastic wryneck (SW) – a focal form of muscular dystonia (D) which is shown by the tonic, clonic or tonico-clonic spasms of muscles of a neck which lead to temporary or continuous compelled position of the head and neck.

Prevalence of focal forms of muscular dystonia by results of the conducted researches in the countries of the European

Commonwealth makes up from 5,7 to 29,5 cases per 100 thousand population [2,6,1]. SW belongs to the most widespread forms of focal dystonias. According to Kandel E. I. [3] idiopathic SW makes up to 63% of all cases of SW. On average from 8 to 10 new cases of SW per 100 thousand populations are registered yearly. [4].

Conservative therapy of SW is directed first of all at the restoration of neyrotransmitery balance in subcrustal structures of a brain. Therapy by botulinum toxin – a hemodenervation of muscles which take part in the formation of complex of symptoms of SW – is effective in 70-85% of cases, despite quite unstable and, sometimes, quite short-term effect [5, 9].

Surgical treatment of focal muscular dystonia, despite all achievements of modern neurosurgery, and auxiliary methods of diagnostics, continues to cause more questions, than gives answers. The main challenge for all who uses denervation techniques in treatment of SW, is accurate identification and the fullest exclusion of the dystonic muscles which take part in the formation of complex of symptoms of SW. It is considered that exactly those surgeons who take into account all variety of features of an innervation of back group of muscles of a neck and their role in realization of turn of the head, achieve the best results [7].

The main approaches and the list of denervation procedures are known for a long time: the purpose is formulated, targets are defined, and surgical interventions are developed and introduced in practice [7]. The extensive experience of treatment of patients with the SW various forms is saved up, the list of complications was considerably decreased. Despite all aforesaid, results still remain far from an ideal: there is a high risk of the residual phenomena and, sometimes, even recurrence of a disease [9, 7]. Having analyzed own accumulated experience, we developed essentially new approach to staging (sequence) of surgical interventions and expanded not only the range of targeted muscles, but also significantly improved a denervation technique. Such approach to treatment of SW allowed us to improve significantly results of microsurgical denervation at patients with torticollis (T).

Material and methods

The study is based on the analysis of surgical treatment of 32 patients with torticollis who stayed for treatment in restorative neurosurgery department of A. P. Romodanov State Institute of Neurosurgery (Kiev, Ukraine) from 2002 to 2014.

The total of patients with torticollis that took part in research made up 32 patients. Age groups of patients looked as follows: patients of young age (21-44 years) – 0, average (45-59 years) – 24 (75%), and advanced age (60-74 years) – 8 (25%). Prevailed the male patients: 24 men (75%) and 8 women (25%). According to the duration of the existing disease patients were distributed as follows: 9 (28.1%) patients – more than 5 years, 21 (65.6%) – from 5 to 2 years, 2 (6,25%) – less than 2 years suffered from T. To 14 patients (43.75%) with T at a pre-hospital stage therapy botulinum toxin with insignificant and/or temporary effect was prescribed. Easy initial severity of SW by Toronto Western Spasmodic Torticollis Rating Scale I (TWSTRS (I)) we observed at 2 (6.25%) patients, moderate severity – at 22 (68.75%) and extrem severity – at 8 (25%). 26 patients (81.25%) at the time of inclusion in research considered themselves people with hard T invalidization, 6 (18.75%) – with the average level of an invalidization (by TWSTRS (II)).

To patients with T 75 surgical interventions of denervation of spasmodic muscles were executed. Out of them 32 (42.66%) – denervation contralateral (in relation to turn of the head) a sternocleidomastoid muscle, 28 (37.33%) – an ipsilateral back cervical ramisectomy of C1-C6 of backs (BCR) and 15 (20%) – contralateral denervation of muscles of omo-trapezoid triangle (DMOTT).

DMOTT – implies a denervation and a miotomy of a muscle which raises a corner of a shovel (LS) and m. splenius capitis (MSC). Forward branches of C3-C4, derivatives of a cervical texture were the main sources of an innervation of the muscles stated above. DMOTT was developed in our clinic, and its efficiency is confirmed with results of the conducted research.

Collecting primary results of surgical treatment began not earlier than in 14 days (early results) after the termination of all planned stages of a surgical denervation that corresponded to the moment of the patient's leaving the hospital, and included an assessment of clinical and neurological data, questioning on TWSTRS. When collecting late results (till 1 year after carrying out the denervation interventions) and remote results (2 years after carrying out the denervation interventions) we performed careful clinical and neurological examination and questioning on TWSTRS. Moreover, clinical and neurological inspection and collecting of biographical particulars were carried out at any moment of the patient's addressing the clinic. The maximum term of supervision over the patient after performance of all stages of denervation of microsurgical interventions made up11 years, on average 5 years ± 2 months.

Questioning provided determination of the severity of SW (TWSTRS (I)) and invalidization level (TWSTRS (II)) – collecting the early, late and remote results of microsurgical denervation interventions.

Assessment of the severity of SW by (TWSTRS (I)) envisaged questioning of the patient and assessment by himself his own state on the basis of 6 indicators: the maximum excursion of the head and neck in 3 main planes; duration of pathological installation/tension of muscles for 24 hours; existence or absence of trigger points which are capable to facilitate the patient's condition; shoulder elevation degree, active volume of movements; time throughout which the patient is able to hold a head/neck in neutral situation. The score of indicators defined severity of SW: 0-10 points – easy severity, 11-25 points – average, 26-35 points – heavy degree of SW.

Assessment of the level of an invalidization of the patient (TWSTRS (II)) implied an assessment by himself of own state by score system – activity in 6 typical environments: work, daily activity, and reading, driving, and watching of the TV, activity outdoors. The score of indicators determined invalidization level: 0-10 points – easy invalidization, 11-20 points – average level, 21-30 points – heavy invalidization.

Statistical data processing, received as a result of the conducted research, was carried out as follows: criterion χ2 Pearson was determind for the purpose of detection of a link between factorial and productive signs. So, terms during which the analysis of results was carried out (before and after carrying out interventions of microsurgical denervation) were factorial signs in our research. Productive – 3 degrees/levels of the severity of invalidization while the assessment of the early, late and remote results.

All statistical calculations were made by means of the Excel program from the software package of "Microsoft Office 2003".

Results and discussion

All denervation interventions at patients with T were followed by 2 main types of complications: a dysesthesia in a dermatome which autonomous innervation is provided by C2 spinal nerve; infectious complications from an operational wound.

The total complications accounted for 26 cases: among them the dysesthesia in a zone of an innervation of C2 of a spinal nerve after carrying out BCR – 24 considerably prevailed (92.3%). Infectious complications in the postoperative period were observed at 2 patients (7.69%).

In the analysis of early results (till 14 days), we observed at 12 patients (37.5%) with T clinical and neurological regress of SW symptomatology: the tone of dystonic muscles which had been denervated was absent, position of the head and neck was approaching the physiological one. At 7 patients (21.87%) the clinical and neurological picture was followed by the expressed pains in postoperative wounds (in particular after BCR) that considerably complicated the assessment of regress of SW symptomatology – patients tried to keep compelled postures. The number of T patients who in the analysis of early results considered that degree of a course of their disease decreased, made up 2 (6.25%) patients. It should be noted that 4 T patients (12.5%) with initial average severity of SW refused to undergo further stages of surgical denervation, considering that their state considerably improved after a denervation of a contralateral sternocleidomastoid muscle.

In the analysis of late results at 15 T patients we noted only insignificant regress of clinical and neurological symptomatology of SW: the tone of ipsilateral denervated dystonic back cervical and paravertebral muscles (BCPVM) was raised, rotation of the head and neck in the direction of muscles with the raised tone, an elevation of a shovel and shoulder was observed. EMG investigation revealed pathological dystonic activity of ipsilateral LS and, in general, muscles of omo-trapezoid triangle of a neck. We suggested carrying out DMOTT to all 15 patients for the decrease in the tone of the dystonic muscles of omo-trapezoid triangle – all patients agreed to undergo denervation surgery.

At 12 patients (50%) at the time of discharging from the hospital the dysesthesia in C2 innervation zone was observed, but we didn't observe full regress of sensitive deficiency. At 3 patients (12.5%) out of 24 who at the time of discharging still had the dysesthesia in C2 innervation zone, we observed considerable, though partial regress of sensitive deficiency. At 5 patients (45.83%) the dysesthesia considerably worsened the quality of life and it significantly reflected in indicators an invalidization. The number of patients who in the analysis of late results considered that the severity of the course of their disease decreased, made up 1 patient. It should be noted that in the analysis of late results, we didn't observe a clear tendency to the reduction of the severity of the disease course at patients with T. The analysis of late results on the basis of data of questioning patients with T allowed to determine the following changes in invalidization levels. 6 patients with the initial grave level of invalidization moved to group with the average level of invalidization. It is necessary to emphasize that we observed an accurate tendency of decrease in the level of invalidization at patients with T in dynamics: so, the initial grave level of invalidization was observed at 81.25% of patients, in the analysis of late results – at 71.48%. In the analysis of late results, the average level of invalidization made up already 28.57% at initial indicators of 18.75%.

In the analysis of the remote results at 15 T patients (all those who underwent DMOTT) we noted essential regress of clinical and neurological symptomatology of SW: the tone of denervated muscles was absent, position of the head and neck came nearer to the physiological. EMG investigation didn't find pathological dystonic activity of denervated muscles. At all 12 (50%) patients at the time of discharging from clinic was observed dysesthesia in C2 innervation zone, though we didn't observe full regress of sensitive deficiency. At 3 patients (12.5%) out of 24 at the time of discharging the dysesthesia in C2 innervation zone remained, and we observed considerable, but, nevertheless, partial regress of sensitive deficiency. At 5 patients (45.83%) the dysesthesia considerably worsened the quality of life that was reflected in invalidization indicators. The number of patients, who in the analysis of the remote results considered that severity of their disease decreased, made up 17 patients. So, 7 patients with an initial grave course of SW moved to the group of patients with an easy course of SW. 10 patients with moderate severity of SW course moved to the group of patients with an easy course of SW. It is necessary to emphasize that namely 15 patients with T for whom DMOTT was carried out, constituted the largest group that had the cource of SW considerably decreased: 7 patients with initially heavy and 8 with moderate severity of SW course. Thus, we observed a precise tendency of decrease in severity of a disease at patients with T in dynamics: so, initial heavy degree was observed at 25% of patients, average – at 68.75%, and in the analysis of the remote results of heavy degree of SW course wasn't observed – 100% decrease in the indicator. Moderate severity accounted for already 39.28%, the light course was observed at 60.71% – the group increased by 17 patients (fig. 1.). In the analysis of the remote results, we found close statistical connection between the change of gravity of the course of the disease and the carried-out surgical interventions ($\chi 2=21,465$; $\chi 2 critical=9,21$; $p<0,01$). In other words, in the analysis of the remote results we found statistically considerable influence of the carried out surgical denervation interventions on the reduction of severity of the disease in patients with T.

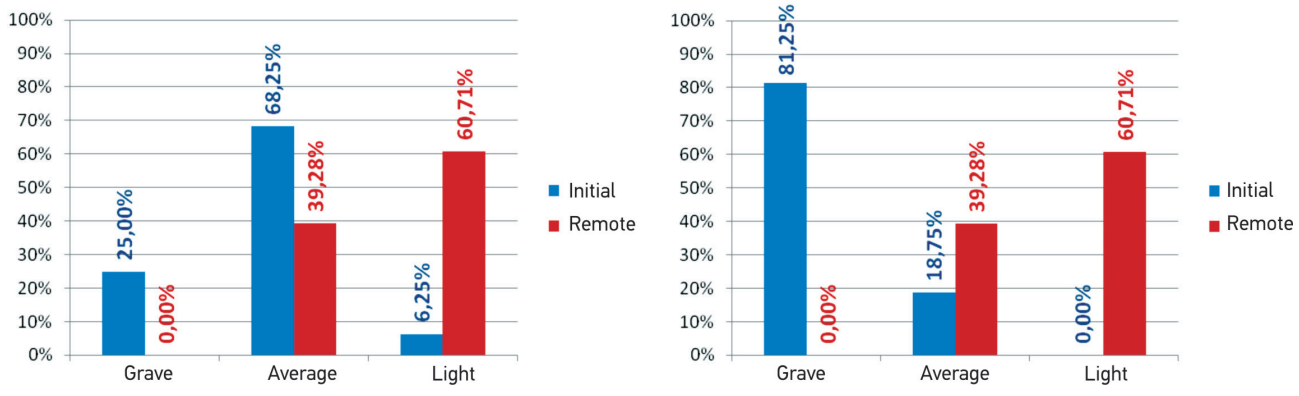


Fig. 1. Dynamics of change of severity of the course and levels of invalidization at patients with torticollis.

It is necessary to emphasize that we found statistically significant connection between the gravity of a course of a disease and the late and remote results ($\chi2=27,125$; $\chi2critical=9,21$; $p < 0,01$). It means that we observed statistically reliable reduction of disease severity in the remote terms of follow-up in comparison with late terms of it. In a time interval between the follow-up terms stated above, 15 patients underwent DMOTT that allowed reducing statistically authentically the severity of SW course with T. Relative indicators prove that carrying out DMOTT allowed reducing the gravity of the course of the disease at 100% of patients. The analysis of the remote results allowed us to determine the following changes in invalidization levels at patients with T: 16 patients with the initial grave level of invalidization moved to the group of patients with the light level of invalidization. 4 patients with the initial grave level of invalidization moved to the group of patients with the average level of invalidization. 1 patient with the initial average level of invalidization moved to the group of patients with the light level of invalidization. All 15 patients to whom DMOTT was carried out, were included into the group of patients whose initial heavy level of invalidization changed for the light one. We observed a distinct tendency of decrease in the level of invalidization at patients with T in dynamics: initial grave level of invalidization was observed at 81.25%, in the analysis of the remote results – the grave level of invalidization after all carried-out stages the denervation interventions wetre not realized any more. We didn't observe the initial light level of invalidization among patients; in the analysis of the remote results it made up 60.71% that meant more than by 60 times exceeded initial indicators. In the analysis of the remote results, we found close statistical connection between levels of invalidization and the carried-out surgical interventions ($\chi2=44,401$; $\chi2critical=9,21$; $p < 0,05$). In other words, we found statistically significant influence of the denervation interventions on the decrease in the level of invalidization in patients with T. Also we found statistically significant link between invalidization levels, the late and remote results of surgical treatment of T ($\chi2=37,474$; $\chi2critical=9,21$; $p < 0,01$). It means that statistically reliable decrease in the level of invalidization in the remote terms in comparison with late terms of follow-up was observed – DMOTT to 15 patients was carried out at the time interval stated above.

Conclusions

Initial indicators of gravity of SW course with T decreased to zero; this once again emphasizes the efficiency and adequacy of the chosen denervation interventions and surgical targets. Light severity prevailed at all patients in the remote terms of the follow-up – 60.71% that was managed to be achived by the performance of DMOTT. Thus, the carried-out microsurgical interventions, in particular DMOTT, allowed us to get positive results (in the context of the decrease in the severity of the course of the disease) at 100% of patients with T.

References

1. Collaborative Group. The Epidemiological Study of Dystonia in Europe (ESDE). A prevalence study of primary dystonia in eight European countries. *J. Neurol.* 2000;247:787-792.
2. Nult J, Muenter V, Aronson A, et al. Epidemiology of focal and generalized dystonia in Rochester, Minnesota. *Mov. Disod.* 1988;3:188-194.
3. Kandel EI. Funktsionalnaya i stereotaksicheskaya neurokhirurgiya [Functional and stereotaxic neurosurgery]. AMN SSSR [USSR Academy of Medical Sciences]. M, 1981;368.
4. Lees AJ. Tics. M: Medicine, 1989;336.
5. Ondo WG, Krauss JK. Surgical Therapies for Dystonia. In: *Dystonia: Etiology, Clinical Features, and Treatment*, M.F. Brin, C. Comella, J. Jankovic (Ed.). Philadelphia: Lippincott Williams & Wilkins, 2004;125-148. ISBN: 0-7817-4114-9.
6. Defazio G, Berardelli A, Abbruzzese G, et al. Possible risk factors for primary adult-onset dystonia: a case–control investigation by the Italian Movement Disorders Study Group. *J. Neurol. Neurosurg. Psychiatry*. 1998;64:25-32.
7. Cohen-Gadol AA, Ahlskog JE, Matsumoto JY, et al. Selective peripheral denervation for the treatment of intractable spasmodic torticollis: experience with168 patients at the Mayo Clinic. *J. Neurosurg.* 2003;98:1247-1254.
8. Sitthinamsuwan B, Nunta–Aree S. Dystonia — The Many Facets — Changhai, China: InTech, 2012;220.
9. Poewe W, Deuschl G, Nebe A, et al.. What is the optimal dose of botulinum toxin type A in the treatment of cervical dystonia? Results of a double blind, placebo controlled dose ranging study using Dysport. *J. Neurol. Neurosurg. Psychiatry.* 1998;64(1):13-17.

Peculiarities of acute rotavirus infection in infants with perinatal exposure to human immunodeficiency virus

***H. Trotskyy[1], Y. Pakulova-Trotska[2]**

[1]Department of Pediatrics and Neonatology, Faculty of Postgraduate Education

[2]Department of Pediatrics, Faculty of Medicine No 2, Danylo Halitskiy National Medical University of Lviv, Ukraine

*Corresponding author: gtrotskyy@mail.ru. Received December 03, 2015; accepted February 5, 2016

Abstract

Background: The number of children with perinatal exposure to human immunodeficiency virus (HIV) in Ukraine is increasing, and the problems of nursing and treatment of those children are important. Rotavirus intestinal infections are common among young children and also children with perinatal exposure to HIV (PEH), and may have a hard course and negative influence on child's development.

Material and methods: We examined 40 children with PEH and 20 children without HIV and the features of their physical, psychomotor development and the course of acute intestinal infections in those groups.

Results: There was found that intestinal rotavirus infection had heavier and longer course for children with PEH, and it aggravated the underlying disease. We tested changes in medical diagnostic algorithm, including the determination of procalcytoninum, the use of lactose mixtures and antibiotics. There was found significantly positive impact on the course of intestinal infection and recovering process.

Conclusions: Feeding with high adapted mixture the children with PEH reduced the risk of acute intestinal infections (AII). Using of antibiotics on the basis of determining the level of procalcytoninum for treatment of AII in children with PEH may improve the course of AII and accelerate their recovery.

Key words: children, perinatal exposure to HIV, procalcytoninum, rotavirus.

Introduction

There are more than 50 000 children in Ukraine with intestinal infections per year. At least 25 to 50% of gastroenteritis in children under five years old was caused by rotavirus (RVI) [2, 7, 11, 12]. Therefore, more pediatricians in their practice are faced with the problem of treatment of diarrheal syndrome in children with human immunodeficiency virus (HIV). Recently, more attention is paid to the defeat of the digestive tract in HIV-infected children [1, 5, 7]. As shown in several studies of HIV-uninfected children of HIV-positive women they had significantly more common intestinal infections compared with the control group [13, 14, 16]. But if the correction with probiotics is possible in group of HIV-negative children [1], for the HIV - positive children and children with HIV with not yet certain status it creates a problem.

Objective: To increase the efficiency of differential diagnosis, treatment and prevention of diarrhea syndrome in children with perinatal exposure to HIV by studying the most common etiology, clinical course, characteristics of nutrition.

Material and methods

We examined 40 infants with perinatal exposure to HIV (PEH) and 20 infants without exposure to HIV and the features of their physical, psychomotor development and the course of acute intestinal infections in those groups. The children with PEH were treated in Lviv regional center for the control and prevention of HIV-AIDS from 2010 to 2013. The control group consisted of 40 children aged 1 to 2 years (mean age, 18 ± 3 months.) without PEH. Children of the control group were hospitalized in the Uzhgorod infectional hospital with RVI diagnosed from 2010 to 2013.

We interviewed parents of children in both groups. Also, children from both groups held general clinical examination, evaluation of physical and psychomotor development, diet and laboratory tests (general blood analysis, blood chemistry analysis, scatoscopy, a rotatest, the determination of procalcitoninum (PCT)).

Results and discussion

The physical development of children born to HIV-infected mothers at birth is primarily responsible for gestational age. Then the number of children with low and very low physical development increased.

We found by comparing the anthropometric parameters, such as height, weight, perimeter of the chest, of children with PEH and healthy children that apparently healthy children developed normally, with a tendency to the formation of excess weight (25%) or carrying excess weight (7.5%). At the same time, children with PEH had a lack of body weight (60%) or extremely underweight (27.5%) (fig. 1).

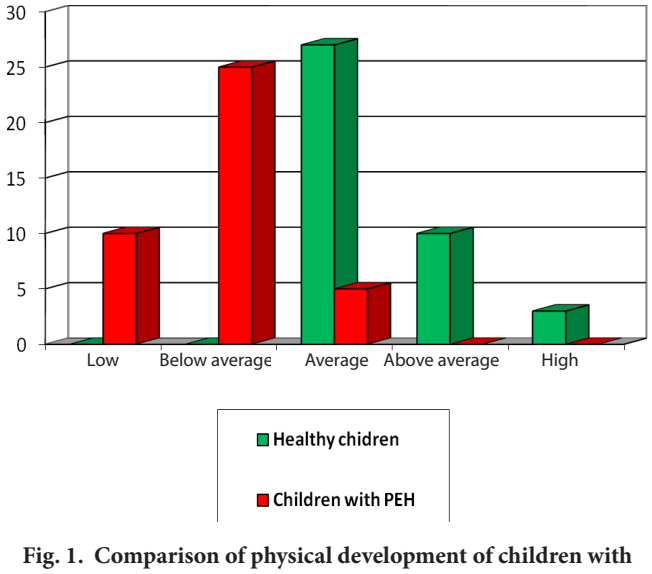


Fig. 1. Comparison of physical development of children with PEH and children without PEH (abs).

At the same time, the study of feeding the children with PEH showed that their nutrition was significantly different from nutrition of healthy children and recommendations on nutrition for young children. All the children with PEH according to the protocol were bottle-fed. A large proportion of children were fed by non-adapted formula milk (72.5%), which was accompanied by an increase in the frequency of functional disorders of the digestive system (constipation, flatulence, regurgitation and vomiting). Those disorders were observed in all children with PEH during the first year of life.

Another feature of the feeding of children with PEH was later introduction of complementary foods. The introduction of complementary foods was carried out after proper terms by an average of 5,2 ± 0,6 months. Children with PEH during the first year of life obtained mainly milk or infant formula, milk porridge and mashed potatoes. Meat products, fresh fruits and vegetables, even in the form of mashed potatoes were introduced in 12 children (30%) from the tenth to twelfth month of life, in 28 children (70%) - during the second year of life. The parents attributed this difficulty in cooking such consistency that the child is able to consume, as well as significant problems with child addiction to the new taste sensations (the introduction of new food). According to the qualitative and quantitative composition of solid food it usually does not comply to the needs of the child, in addition, the consistency of the food was liquid, rubbed (homogenized), the food is subjected to prolonged mechanical and thermal processing, which could result in lost large amounts of vitamins and trace elements.

When analyzing the cases of diseases of children with PEH, we found that 29 (72.5%) children can be attributed to a group of sickly ones. Thus, during the first year of life, 16 children (40%) were sick for 5 times, 15 ones (37.5%) – for 6 times, 9 children (22.5%) – for 7 times. There were 52 acute respiratory infections cases, 34 cases of bronchitis and 28 cases of pneumonia.

Usually regurgitation appears in the second half of the 1st month of life, on the 2nd month of life the intensity and the frequency increase and are held at the maximum level of up to 5-6 months of age. After 6-7 months of age the prevalence of regurgitation intensity gradually decreases, but in part it can be kept in 10% of children aged 12-13 months. In healthy children the frequency of symptoms of functional gastrointestinal tract is significantly reduced after the first year of life, in children with PEH we saw a different picture. In the second year of life in 26 children with PEH there were complaints of recurrent abdominal pain (65%), in 24 children (60%) was observed a tendency to constipation, 12 children (30%) had regurgitation during each meal, in 4 children (10%) there was periodic (1-2 times a day) vomiting.

We have observed that children who were fed with adaptable mixture had episodes of acute intestinal infection (AII) with a light and shorter course.

The evaluation of intestinal infections in young children was carried out by a 20-point Vesikari scale, taking into account the full clinical picture of viral gastroenteritis (severity and duration of diarrhea, vomiting, fever, dehydratation, the need for treatment). It was found that in children with PEH, compared with those born to mothers without HIV the AII preceded longer and harder. Thus, the duration of diarrhea in the main group by Vesikari scale is estimated at an average of 2.7 points, in the control group – 1.2 points. The number of defecations per day – 2.4 and 1.3 points in accordance. The duration of vomiting – 2.8 and 1.1 points, the hyperthermia – 2.6 and 1.8 points, the dehydration – 2.2 and 0.8 points ($p < 0.05$).

Almost half of the children (49 %) were noticed to have a poor appetite. It is evident that such disorders are not contributing to the full nutritional welfare of children with PEH.

In assessing the neuropsychiatric performance using modified maps formalized study of neuropsychiatric function in children during the first 7 years of his life to the creation of the profile of the psychomotor development of the child we found in children with PEH the gap in the development of motor skills, intelligence, expressive speech; as to the self-service and gaming skills at 2 months – 11 children (27.5%), at 3 months – 7 children (17.5%), at 4 months or more – in 3 children (7.5%). At the same time, the lag formation of visual and auditory perception and emotion was smaller.

Thus, the backlog of these functions in an average of 3 months we have observed in 7 children (17.5%), 4 months – in 5 children (12.5%), at 5 months or more – in 3 children (7.5%). In 12 children (30%), we noticed a slight delay in psychomotor development (1-2 months of age norms).

In assessing neuropsychiatric development of healthy children we established that it corresponded to the age in all cases.

We analyzed the illness of infants with PEH and compared it with the degree of psychomotor retardation. We found that sickly children had a greater degree of psychomotor retardation. The defeat of the respiratory system was the most common illness among young children with PEH, such as bronchitis (37.5%) and pneumonia (30%), as well as functional disorders of the gastrointestinal tract, such as abdominal pain (67.8%), constipation (60%), frequent regurgitation (30%), vomiting (10%).

On the basis of correlation analysis we have established a strong direct correlation between the degree of neurodevelopmental disability and transferred somatic diseases ($r = + 0,95$; $p < 0.01$). It was determined that frequent and prolonged physical illness intensified neuropsychiatric delay of the child's development.

Laboratory studies in the group of young children with PEH revealed that nearly half of these children (45 %) had mild anemia, mean hemoglobin levels in children of this group were 111,7 ± 6,6 g/l.

The data of biochemical blood analyses revealed that the level of total protein ranged from 66,8 ± 3,75 g/l and posted lower limit of normal, not correlated with the severity of the general condition and of nutritional status that corresponds with data of other authors. Indicators of electrolyte metabolism (K +, Na +, Cl-) corresponded to age norm indicators, the level of K + 5,1 ± 0,2 mmol/l (normal 4,14-5,75 mmol/l), Na + 136 ± 2 mmol/l (normal 133-141 mg/dl), Cl- 101 ± 2 mmol/l (normal 98-107 mg/dl). The level of glucose on

average matched normal controls and was 4,6 ± 0,4 mmol/l. The level of total bilirubin and fractions were within the age norm: total bilirubin 14 ± 0,7 mm/l (normal 8,5-20, m/l), free 1,7-17,1; associated 0,86-5 1 mm/l). Urea and creatinine also correspond to the normal indicators (3,3-5,6 mg/dl, creatinine – 18-35 m/l).

HIV polymerase chain reactions (PCR) were performed in a group of children with PEH to determine their status at the age of 3 months. All 40 children had the negative results, and in 4 children they were positive. Children whose at the age of 18 months PCR was positive for HIV had lower rates of physical development, psychomotor development and significantly lagged behind the main group of children on those parameters. Obviously, those data can be used as an aid in predicting the HIV status of a child less than 18 months of age. We made rotatest in both groups as a screening, and the result (positive) was one of the criteria for inclusion in the study.

PCR for RVI also were performed in both groups, with a view to final confirmation of the presence of RVI in children included in the study.

Determination of procalcytoninum (PCT) in the blood plasma we carried out with the purpose of its using as a marker of inflammatory activity. We noticed that in the group of children with PEH compared to healthy children, the level of PCT in serum was increased. Thus, in the group of healthy children PCT level in the serum was 0,08-0,43 ng/ml, while in the basic group - 0,31-1,02 ng/ml. The difference between groups was significant ($p \leq 0,05$).

In addition, children with PEH with severe diarrhea by the Vesikari scale have higher plasma levels of PCT that may be used to predict the course of disease and recovery. This parameter may be important in the management of the patients with acute intestinal infection (AII), as it gives the opportunity to decide if they have need in the prescription of an antibiotic. According to a number of studies [17], the optimal value of PCT for the decision on the prescription of an antibiotic is the concentration of > 0.4 ng/ml. Of course, these are only recommendatory numbers that belong to groups with inflammatory processes but not bacterial and inflammatory processes associated with local bacterial infections. The final decision on the administration of an antibiotic should take the doctor, taking into account other laboratory and clinical parameters. As for the group with a severe bacterial infection, all patients in it had higher levels of PCT – 1 ng/ml. For this reason, in inflammatory processes with severe clinical course, in case a blood concentration of PCT is more than 1 ng/ml, are recommended unequivocally antibiotics [17]. These researchers believe that when the concentration of biomarkers is less than 0.25 ng/ml antibiotics are not needed. The use of antimicrobials is recommended to start from the time when the level of PCT in the blood increases to 0.25-0.5 ng/ml. It is known that the concentration of PCT in patients with inflammatory processes is not dependent on age [18]. Taking into account this laboratory value may reduce the excessive use of antibiotics, have a positive impact on the prevention of the emergence of resistant strains of micro-organisms, and also reduce treatment costs. At the same time it significantly accelerates antibiotic treatment of infectious and inflammatory processes.

For children with AII there were characteristic signs of maldigestion and malabsorption that manifested by amylorrhea, steatorrhea, kreatoreya for 82% of children in coprograms. There were clinical signs of transient lactase deficiency after RVI in children, stool pH less then 5.5.

The protocol treatment of rotavirus infection involves the following basic therapy such as low / lactose-free diet, sorbents, enzymes, eubiotiks, oral rehydration, nifuroxazide. The application of eubiotics in children with PEH was excluded, but taking into account the reduced protective functions of the body and the possible frequent juxtaposition of a bacterial infection, children with PEH and AII may need antibiotics. On the other hand, it is known that antibiotics can worsen the clinical course of viral AII inhibiting own intestinal flora. Therefore, given the level of PCT, it was formed a group of children who need antibiotics (ceftriaxone 50 mg/kg 2 times a day intramuscular for 7 days), on the one hand, and the group of children that do not need. Also the children of the main group (20 persons) in addition to the basic therapy and antibiotics received the enterosorbent dioctahedral smectite (Neosmektin – children up to one year – 1 bag per day (3 g), 1-2 years – 2 bags per day (6 g), more than two years – 2-3 sachets per day (6-9 g)) to normalize stool frequency. The course of treatment lasted for 3.5 days. The control group (20

Table 1

Comparative characteristics of clinical symptoms of acute intestinal infections in children, depending on the assigned treatment (M ± M), days

Criteria of efficiency		The main group, = 40	Control group, n=40	P
Intoxication		2,4 ±0,51	4,1±0,63	<0,05
Fever	2,6 ±0,87	4,2±1,11	>0,05	
Vomiting	1,9 ±0,67	2,9±0,77	>0,05	
Normalization of appetite	3,6 ±1,12	5,5±1,34	>0,05	
Exsicosis	2,1 ±0,46	3,6±0,69	>0,05	
Duration of diarrhea	3,1 ±0,68	6,2±0,84	<0,01	
Duration of intensive care	1,45 ±0,51	3,2±0,71	<0,05	
Duration of hospitalization	5,1 ±0,73	7,4±0,82	<0,05	

persons) were children, matched by age and severity of the disease, but received only the basic therapy (table 1).

A comparative analysis of the elimination of the main symptoms of the disease in the group of children who received treatment with dioctahedral smectite and antibiotics, symptoms of intoxication in 14 children (70 %) disappeared on Day 2, and Day 3 – in 17 patients (85 %), while in the comparison group only 6 children ($\chi 2 = 6,54$, $p = 0,016$). In children who received enterosorbent stopped vomiting and diarrhea. On the 3-day of treatment vomiting ceased in 85 % of patients of the main group, while in the comparison group vomiting disappeared only in 70% ($p < 0,05$). In the control group of patients who did not receive dioctahedral smectite in the treatment, the average stool frequency on the first day of treatment remained the same, and the improvement of stool has been reported. On 4-5 days of treatment with dioctahedral smectite, clinical recovery with normalization of the stool occurred in all patients, while in the comparison group clinical recovery occurred only in 80% of cases.

Conclusions

Children with PEH, although according to the protocol are treated as practically healthy children, but actually they are not. For children with PEH was inherent the delay in physical and neuropsychological development and eating disorders. All those features affected the formation of the child's resistance to pathogens. Feeding with high adapted mixture the children with PEH reduced the risk of AII. Children with PEH are classified as sickly children. For children with PEH the course of the disease with longer and severe duration with lengthened period of convalescence was typical. Consequently, those children required special attention in terms of primary and secondary prevention of the most common pathologies of childhood, as well as considering the peculiarities of the period of reconvalescence. The use of antibiotics on the basis of determining the level of PCT for treatment of AII in children with PEH may improve the course of AII and accelerate their recovery.

References

1. Assefa S, Erko B, Medhin G, et al. Intestinal parasitic infections in relation to HIV/AIDS status, diarrhea and CD4 T-cell count. *BMC Infect Dis*. 2009;9:155-64.
2. Chandran A, Heinzen M, Santosham G. Nosocomial rotavirus infections: a systematic review. *J Pediatr*. 2006;149:441-47.
3. Jennifer S, Zeichner L. Steven. Textbook of Pediatric HIV Care. Cambridge: University Press, 2005;784.
4. Joel Gallant. 100 Questions & Answers About HIV and AIDS. Jones and Bartlett Publishers, 2008;398.
5. Katabira E. Epidemiology and management of diarrheal disease in HIV-infected patients. *International Journal of Infectious Diseases*. 2003;3:164-67.
6. Madhi S, Cunliffe N, Steele D. Effect of human rotavirus vaccine on severe diarrhea in African infants. *N Engl J Med*. 2010;362:289-98.
7. Malek M, Curns A, Holman R. Diarrhea- and rotavirus-associated hospitalizations among children less than 5 years of age. *Pediatrics*. 2006;117:1887-92.
8. Neveli ML, Coovadia H, Cortina-Borja M. Mortality of infected infants born to HIV-infected mothers in Africa: a pooled analysis. *Lancet*. 2004;364:1236-43.
9. Newell ML. Mortality of infected and uninfected infants born to HIV infected mothers in Africa: a pooled analysis. *Lancet*. 2004;364(9441):1236-41.
10. O'Reilly Ciara E. Diarrhea-caused significant morbidity in children born to mothers with HIV in Kenya. *Infectious Diseases in Children*. 2009;60:529-36.
11. Parashar U, Burton A, Lanata C, et al. Global mortality associated with rotavirus disease among children in 2004. *J Infect Dis*. 2005;200(Suppl 1):9-15.
12. Parashar UD, Gibson CJ, Bresse JS, et al. Rotavirus and severe childhood diarrhea. *Emerg. Infect. Dis*. 2006;12:304-6.
13. Payne D, Staat M, Edwards K. Active population-based surveillance for severe rotavirus gastroenteritis in children in the United States. *Pediatrics*. 2008;122:1235-43.
14. Podder G. Rotavirus-specific subclass antibody and responses in Bangladeshi children with rotavirus diarrhoea. *J. Medical Virology*. 2003;69:286-95.
15. Saiada F, Rahman G, Moni S. Clinical presentation and molecular characterization of group B rotaviruses in diarrhoea patients with HIV in Bangladesh. *J Med Microbiol*. 2000;12:289-95.
16. Soriano-Gabarro M, Mrucowicz J, Vesicari T. Burden of rotavirus disease in European union countries. *Pediatric Ivfect. Dis*. 2006;25:7-11.
17. Ugarte H, Silva E, Mercan D, et al. Procalcitonin used as a marker of infection in the medical intensive care unit. *Crit Care Med*. 2000;28:977-83.
18. Wanner GA, Keel M, Steckholzer U, et al. Relationship between procalcitonin plasma levels and severity of injury, sepsis, organ failure, and mortality in injured patients. *Crit Care Med*. 2000;28:950-957.
18. Zanorec R, Misianik J, Setvak D. Early changes of neutrophil and lymphocyte counts and serum procalcitonin following surgery, SIRS and sepsis. *Intensive Care Med*. 2000;26(suppl. 3):227.

Antibiotics consumption evaluation in reanimation department

E. P. Bernaz

Business Administration Office, Emergency Medicine Institute, Chisinau, the Republic of Moldova

Corresponding author: bernaz_e@yahoo.com. Manuscript received December14, 2015; accepted February 12, 2016

Abstract

Background: Unnecessary use of anti-infectives for systemic use is a major global issue and often results in too many problems such as: ineffective treatment and side effects in patients, increase of the risk of development of pathogen microbial resistance and treatment costs. Defined daily doses (DDD) is a method that integrated the evaluation of drugs consumption of worldwide hospitals, giving the possibility of comparison, improving the rational use, optimizing the possibility of coherent planning of antibiotics necessities.

Material and methods: The data of this study represents a six-year (2009-2014) period in Reanimation Department, which describes the consumption dynamics of anti-infectives for systemic use of drugs in natural and value indexes.

Results: The defined daily doses (DDD) per 1000 occupied-bed days (DDD/1000) of antibiotics in Reanimation Department has decreased from 3270.17 in 2009 to 1664.99 in 2014 and is by 22.76% higher than medium consumption of 1286.11 DDD/1000 in 1134 intensive care units from international hospitals. The value indexes per DDD/1000 declined from 87860 in 2009 to 54307 lei in 2014 or by 38.19%, when the cost of one medium DDD increased from 26.87 in 2009 to 32.62 lei or by 21.40% in 2014. The pharmacoeconomy from 2010 to 2014 increased more than by 3 times.

Conclusions: The stated decrease in DDD/1000 OBD and the obtained pharmacoeconomy characterized the measures taken to improve the rational use of antibiotics. The increase of one DDD cost, shows the increase in the price of antibiotic medical remedies for the evaluated period.

Key words: antibiotics, defined daily dose, consumption, rational use, hospitals, occupied-bed days, indices.

Introduction

The unnecessary use of antibiotics is a major global issue and often results in a great deal of problems, such as: ineffective treatment and side effects in patients, increased risk of development and dissemination of pathogen microbes resistance, triggered super infections and the increased treatment costs [1-6]. The data about morbidity and mortality, as well as unnecessary or inappropriate consumption of antibiotics in acute care hospitals of The United States, caused Centers for Disease Control and Prevention to recommend all acute care hospitals to implement Antibiotic Stewardship Programs [7].

It is known that in the Republic of Moldova drugs consumption analysis in defined daily doses (DDD) per 1000 occupied-bed days (DDD/1000), is an important objective indicator of drugs consumption evaluation, the result of which is serving as real database for optimizing the rational use and planning the medical necessities in health care institutions. This issue is not taken seriously enough and highlighted in the national scientific research literature.

The primary aim of this study is directed to determine the value of DDD/1000 in accordance with World Health Organization (WHO) requirements [8, 9] based on the evaluation of antibiotics consumption of the institutional representative data in Reanimation department for a six-year period (2009-2014). The obtained results from Reanimation department, in comparison with the published ones in intensive care units from worldwide hospitals, will permit to recommend measures to ensure the rational use and optimization of planning the annual necessities of anti-infectives for systemic use.

The Emergency Medicine Institute of the Republic of Moldova (EMI) was founded in 1959. The clinical services of EMI include: Orthopedic-Traumatology for 150 beds, Surgery for 140 beds, Neurosurgery for 80 beds, Neurology for 70 beds, Maxillofacial for 30 beds, Urology for 40 beds, Gynecology for 30 beds, Microsurgery for 30 beds, Municipal center for hemodialysis with 8 seats and 9 beds, Clinical Intensive Care Unit for 30 beds and Reanimation department for 23 beds. The above-mentioned clinical services include 600 beds overall. In addition to the above-mentioned services, there are 4 more outpatient Departments of traumatology and orthopedics [10].

Material and methods

The study uses data of a six-year period (2009-2014), from EMI Reanimation Department for 23 beds that shows the dynamics of consumption of anti-infectives for systemic use, in accordance with Anatomical Therapeutic Chemical (ATC) classifications system of World Health Organization, indicated in natural and value indexes. Statistical, analytical, mathematical, comparative, logical and descriptive methods were used in the study.

Results and discussion

To evaluate the consumption of anti-infectives for systemic use, were taken 10 steps necessary to determine the DDD/1000 [11], the statistics data concerning the number of treated patients (only patients with health insurance and other free treated by the state categories of citizens) and occupied bed-days/per year: (2009 = 3990; 2010 = 6551; 2011 = 6985; 2012 = 9051; 2013 = 7384; 2014 = 7361), as well as the data related to the total annual consumption of antibiotics were used.

All in all, 50 antimicrobial remedies (both for parenteral and enteral use) for hospitalized patients' treatment in the evaluated period were used: 12 enteral forms; 18 parenteral forms and 10 names of both forms, which represent 40 active antimicrobial substances.

Rate of antibiotics subgroups consumption of parenteral forms evaluated in DDD/1000 during 2009-2014 period is shown in figure 1.

In figure 1 is demonstrated the average consumption annual rate of parenteral forms for the evaluated period for all antibiotic subgroups that recorded a decline from 3172 in 2009 to 1629 DDD/1000 in 2014 or by 48.64%. The main consumption of 2369.42 DDD/1000 or 74.70% from the total in 2009 to 1244.67 or 76.41% from the total in 2014, shows a decrease from the mentioned period of 47.47% for other beta-lactam antibacterials (Cefazolinum 3.0, Cefuroximum 3.0, Cefotaximum 4.0, Ceftazidimum 4.0, Ceftriaxonum 2.0, Cefoperazonum 4.0), aminoglycoside antibacterials (Streptomycinum 1.0, Gentamycinum 0.2, Kanamycinum 1.0, Amikacinum 1.0) and other antibacterials (Vancomycinum 2.0, Metronidazolum1.5, Dioxydinum 0.7, Nitroxolinum 1.0). The mean consumption with a decrease in the mentioned period by 52.16%, from 770.43 DDD/1000 or 24.29% of the total in 2009 to 368.56 or 22.63% of the total in 2014 was recorded by beta-lactam antibacterials, penicillins, quinolone antibacterials and antimycotics for systemic use. Macrolides, lincosamides and streptogramins (Clarithromycinum 0.5, Azithromycinum 0.5, Lincomycinum 1.8) and amphenicols (Chloramphenicolum 0.3) showed a decline in consumption by 51.50%, from 32.08 DDD/1000 or 1.01% of the total in 2009 to 15.56 or 0.96% of the total in 2014, and were placed on the last third position.

In figure 2 is shown the consumption rate of enteral forms of antibacterials for systemic use subgroups in DDD/1000, during 2009-2014.

Figure 2 shows the average consumption annual rate of antibiotics for oral use that recorded an instable rate and is more appropriate to 80-100 DDD/1000 during four years: 2009, 2011, 2012 and 2013. The consumption of 80.45 DDD/1000 or 81.88% of the total in 2009 to 33.28 or 92.45% of the total in 2014 was registered by the antimycotics for systemic use (Ketoconazolum 0.2, Fluconazolum 0.2), they showed a decrease by 58.63%, when other subgroups registered only an episodic consumption for the same period. Figure 3 shows the total (parenteral and enteral forms) antibiotic subgroups usage rates.

Figure 3 states the average consumption annual rate of parenteral and enteral forms for all antibiotic subgroups that recorded a decline from 3270 in 2009 to 1665 DDD/1000 in 2014 or by 49.08%. The main consumption of 2369.42 DDD/1000 or 72.46% of the total in 2009 to 1244.67 or 74.76% of the total in 2014 with a decrease of 47.47% during the evaluated period, was registered for other beta-lactam antibacterials,

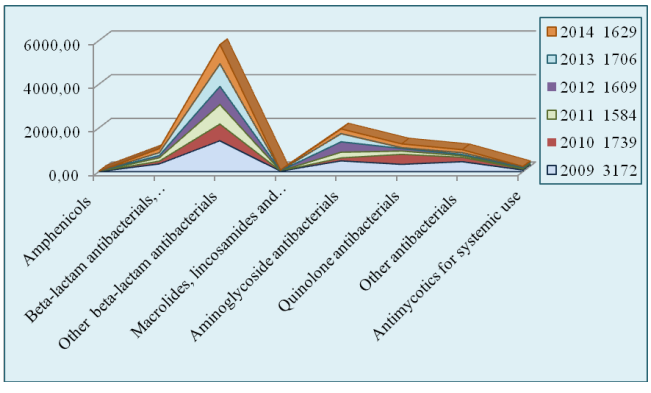


Fig. 1. Parenteral consumption forms of antibacterials for systemic use in DDD/1000.

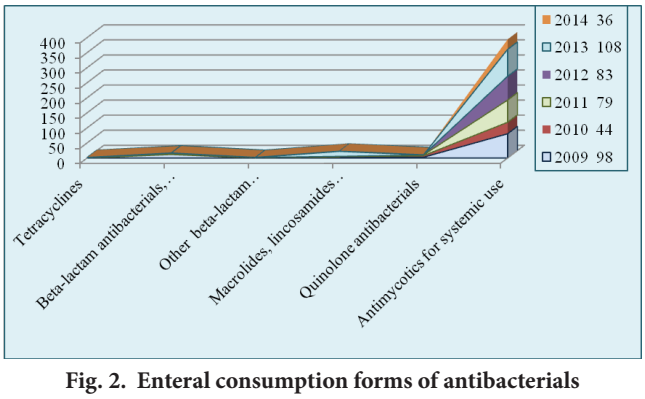


Fig. 2. Enteral consumption forms of antibacterials for systemic use in DDD/1000.

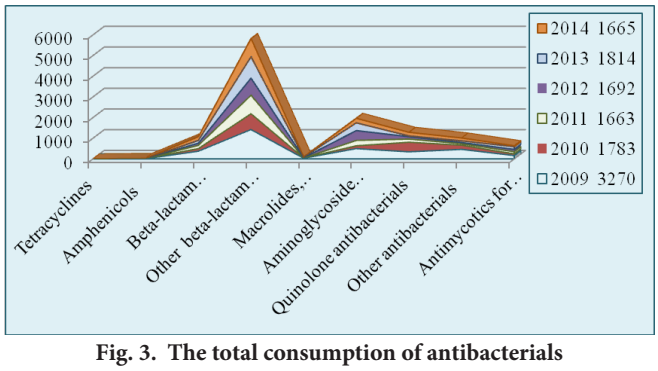


Fig. 3. The total consumption of antibacterials for systemic use in DDD/1000.

aminoglycoside antibacterials and other antibacterial. The mean consumption with a decrease by 53.55% from 865.17 DDD/1000 or 26.46% of the total in 2009 to 401.84 or 24.14% of the total in 2014 was recorded by beta-lactam antibacterials, penicillins, quinolone antibacterials and antimycotics for

Table 1

The ratio between DDD/1000 for parenteral to enteral antibiotics forms

Years		2009	2 010	2011	2012	2013	2014
Parenteral		3171.9	1739.4	1583.5	1609	1706.4	1629
Enteral		98.25	43.51	79.36	83.31	107.67	36
The ratio of parenteral to oral		32.28	39.98	19.95	19.31	15.85	45.25
Total		3270.5	1782.1	1662.6	1692.1	1814.7	1665
Percentage forms from total	Parenteral	97.56	95.23	95.08	94.06	97.84	97.84
	Enteral	2.44	4.77	4.92	5.94	2.16	2.16

systemic use. Macrolides, lincosamides and streptogramins (Clarithromycinum 0.5, Azithromycinum 0.5, Lincomycinum 1.8) and amphenicols (Chloramphenicolum 0.3) were placed on the last position with a decline of 51.90% consumption from 35.59 DDD/1000 or 1.09% of the total in 2009 to 17.12 or 1.03% of the total in 2014. Table 1 demonstrates the ratio DDD/1000 of parenteral to enteral use forms and percentage from the total.

As stated in table 1 for the evaluated period, the ratio between antibiotics DDD/1000 parenteral to enteral forms recorded an instable report between 15 and 20 times during three years (2011-2013), as well as from 30 to 45 times during other three years (2009-2010; 2014). From the total DDD/1000, the percentage of parenteral forms of antibiotics, was more or less the same in the mentioned period with the annual average of 96%, as well as the enteral forms from 2% to 6%. Similar data of DDD/1000 for the entire institution can be found in recent publications [12].

The comparison of total consumption data of the anti-infectives for systemic use, evaluated in DDD in 1576 international hospitals and their intensive care units with the similar data in the EMI and Reanimation department, is presented in table 2.

Table 2 states the average annual rate for total-hospital antibiotics utilization period in EMI that decreased from 662.4 in 2009 to 464.1 DDD/1000 in 2014 or by 30%. The overall medium consumption in 1706 international hospitals, constituting 459.20 DDD/1000, was lower than the consumption of 464.1 DDD/1000 in EMI in 2014 by 4.90 DDD/1000, and, lower by 121.1 comparatively to medium global annual hospital antibiotics consumption of 343 DDD/1000 or by 20.09% [13].

The Reanimation department registered a decrease of antibiotics consumption from 3270.17 in 2009 to 1664.99 DDD/1000 in 2014 or by 49.09% respectively. An approximate calculation of DDD/1000 was conducted for 1134 intensive care units of international hospitals that resulted in an average consumption of 1286.11 DDD/1000{[(10x1013.1 + 2x1762.3 + 1x982 + 38x1016 + 38x1143 + 35x1254 + 1x1761 + 1x683 + 43x1156 + 34x1110 + 58x1400 + 38x1335 + 8x1223 + 744x1332 + 1x1260 + 40x1169 + 40x1127 + 1x1109 + 1x1052) = 1458445 : 1134] = 1286.11DDD/1000}, which was 1984.06 in 2009 or by 60.67% and 378.88 DDD/1000 in 2014 or by

Table 2

Surveillance studies of antibiotics use in international hospitals, comparing with the similar data in Emergency Medicine Institute and Reanimation department

Setting	Surveillance time-period	Data source	Frequency of data collection	Use of antibiotics in DDD/1000
Emergency Medicine Institute	6 years (2009– 2014)	Pharmacy dispensing records (PDR)	Annual	662.4 in 2009; 464.1 in 2014.
Reanimation departmnent of EMI	6 years (2009–2014)	(PDR)	Annual	3270.17 in 2009; 1664.99 in 2014.
10 primary and 2 secondary acute care hospitals in the Canton of Zurich in Switzerland [14]	in 2006	(PDR)	Annual	1013.1 to 1762.3
1 university hospital in Greece [15]	5 years (1998-2002)	(PDR)	Annual	982.0
54% of the national acute care hospitals in Switzerland [16]	5 years (2004- 2008)	(PDR)	Annual	1016.0 to 1143.0
38 ICUs providing services to a population of approximately 6 million in Sweden [17]	in 1999	(PDR)	Annual	1257.0
35 European Intensive Care Units [18]	in2005	(PDR)	Annual	1254.0
Spanish general hospital [19]	5 years (1996–2000)	(PDR)	Annual	1761.6
Geneva University Hospital and its adult ICUs [20]	5 years (1996–2000)	(PDR)	Annual	683.0
43 intensive care units in Germany [21]	in 2005	(PDR)	Annual	1156.0
2 cohorts of intensive care units (ICUs) in Germany (N=34), (N=58) [22]	in the 2005	(PDR)	Annual	1110.0 and 1400.0
38 German general, surgical, and interdisciplinary ICUs in [23]	4 years (2000- 2003)	(PDR)	Annual	1335.0
8 German University Hospitals [24]	3 years (1998-2000)	(PDR)	Annual	1223.0
744 reported ICU in Germany [25]	3 years (2000-2002)	(PDR)	Annual	1332.0
The main university clinic for medical emergencies from Bucharest municipality[26]	in 2008	(PDR)	Annual	1260.0
40 non–university regional general hospitals in southwestern Germany [27]	2 years (2001- 2002)	(PDR)	Annual	1169.0 and 112.7
Military Medical Academy hospital of Bulgaria [28]	in 2011	(PDR)	Annual	1109.0 and 1052.0

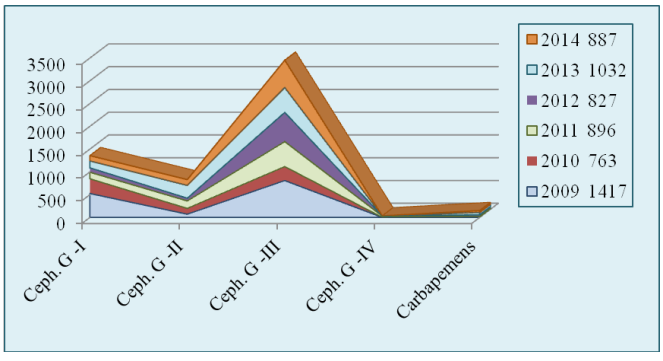


Fig. 4. Total consumption of other beta-lactam antibacterials for parenteral use in DDD/1000.

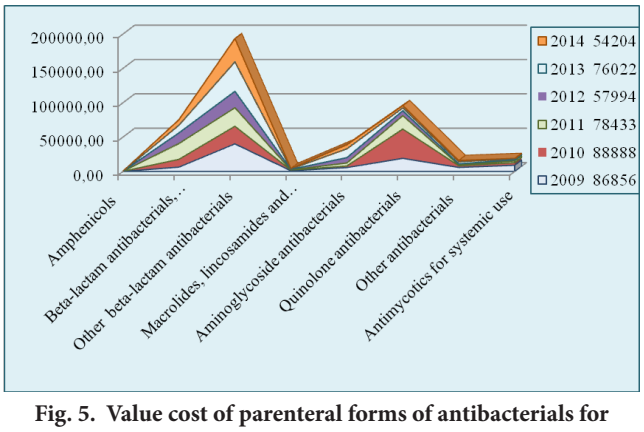


Fig. 5. Value cost of parenteral forms of antibacterials for systemic use per DDD/1000 in lei.

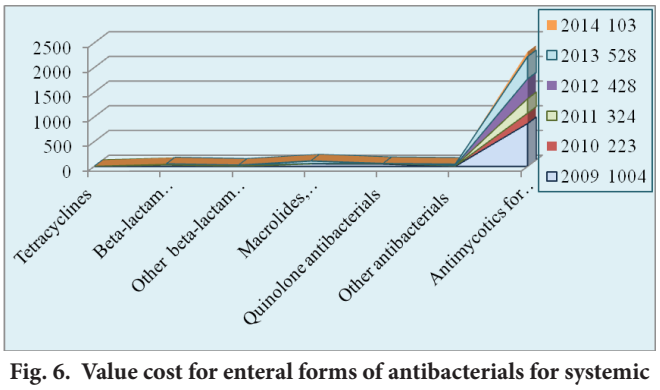


Fig. 6. Value cost for enteral forms of antibacterials for systemic use per DDD/1000 in lei.

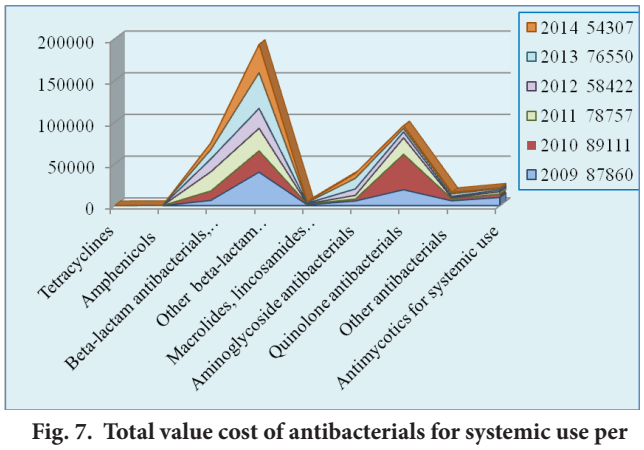


Fig. 7. Total value cost of antibacterials for systemic use per DDD/1000 in lei.

22.76% that was more than the results recorded in Reanimation department of EMI. In figure 4 the total consumption of other beta-lactam antibacterials for parenteral and enteral use in DDD/1000 is demonstrated.

The chart states a registration of a total stable consumption of parenteral forms during the years of 2010, 2011, 2012 and 2014 from 763 to 887 DDD/1000, which is more characteristic for all the evaluated period, with high records of 1417 in 2009 and 1032 DDD/1000 in 2013. The cephalosporin's G-I (Cefalexinum and Cefazolinum) consumption has visibly decreased from 525.06 DDD/1000 in 2009 to 116.56 in 2014 or by 77.8%. The cephalosporin's G-II (Cefuroximum, Cefaclorum) and G-III (Cefotaximum, Ceftazidimum, Ceftriaxonum, Cefixim, Cefoperazonum, Cefoperazonum + Sulbactamum) consumptions show a slow decrease from 880.2 (70.68+809.52) in 2009 to 730.20 DDD/1000 (127.56+602.64) or by 17.04%. The carbapemens (Meropenemum, Imipenemum+Cilastatinum) recorded an increment from 11.28 DDD/1000 in 2010 to 39.94 in 2011 that was by 3.54 times more. The cephalosporins G-IV registered the only consumption in 2011. Figure 5 shows the value cost of DDD/1000 in lei for parenteral forms of antibacterials for systemic use during 2009 - 2014.

Figure 5 demonstrates that the cost of DDD/1000 in value indexes (lei) of subgroups with antibiotics for parenteral use, recorded a decline from 86856 in 2009 to 54204 lei in 2014 or by 37.59%. The increment in cost per DDD/1000 of 2146.52 from 11865.96 lei (6246.62 + 5587.22 + 32.12) in 2009 to 14012.48 lei (8041.70 + 5879.70 + 91.08) in 2014 or by 18.09% was recorded by 3 subgroups: beta-lactam antibacterials, penicillins, aminoglycoside antibacterials and amphenicols. The following subgroups: other beta-lactam antibacterials, quinolone antibacterials, antimycotics for systemic use, other antibacterials, macrolides, lincosamides and streptogramins recorded a decline of cost per DDD/1000 from 74990 (40122.89 + 19035.30 + 8977.57 + 5826.32 + 1027.92) in 2009 to 40191 lei (33981.3 + 3366.60 + 458.56 + 1793.70 + 591.22) in 2014 or by 46.41%. Figure 6 shows the consumption rate in value indexes in lei, for subgroups with antibiotics for enteral forms per DDD/1000, during 2009-2014.

Figure 6 shows an unstable amount of lei spent per DDD/1000 during 2009 to 2014, recording the highest in 2009 and abrupt decline in 2014, that amounted to 103 lei per DDD/1000 or by 9.70 times. The main annual consumption rate per DDD/1000 in value indexes of all antibiotic subgroups recorded antimicotics for systemic use with a decline from 866.05 or 86.29% of the total in 2009 to 98.42 lei or 95.71% of the total in 2014 or by 8.80 times.

The total institutional antibiotics consumption in value indexes varied from 1562575 in 2009 to 1500888 lei in 2014, which represents respectively 17% and 14% from whole amount of drugs [29]. The same data for Reanimation department was 341581 in 2009 and 399754 lei in 2014 or 22.34% and 20.03% respectively from the whole amount of drugs, and 21.88% and 26.63% from the total institutional antibiotics consumption. Figure 7 states the consumption rate in value indexes (lei) of subgroups with antibiotics for parenteral and enteral forms in DDD/1000 during 2009-2014.

In chart 7 the presented data demonstrates that in the evaluated period total annual antibiotics consumption in value indexes per DDD/1000, recorded a decline from 87860 in 2009 to 54307 lei in 2014 or by 38.19%. In figure 8 is presented the total value cost of other beta-lactam antibacterials for parenteral use of DDD/1000 in lei.

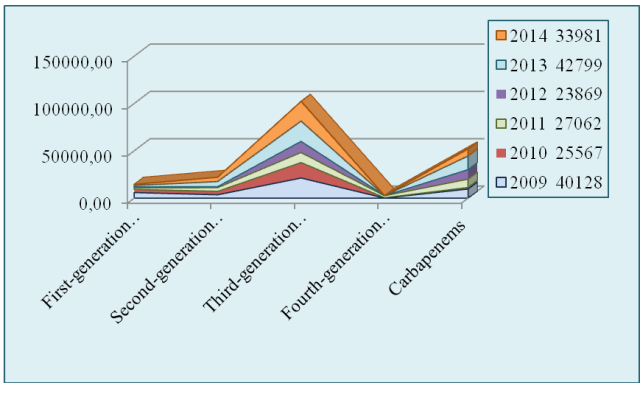


Fig. 8. Total value cost of other beta-lactam antibacterials for parenteral use of DDD/1000 in lei.

Figure 5 shows that the cost of DDD/1000 in value indexes (lei) of subgroups with antibiotics for parenteral use recorded a decline from 40128 in 2009 to 33981 lei in 2014 or by 15.32%. An exceptional decline was in 2013 year with the higher consumption of 42799 lei per DDD/1000. The increment in cost per DDD/1000 was recorded by the second generation of cephalosporin from 3481.95 in 2009 to 4528.20 lei in 2014 or by 30.05%. First and third cephalosporin generations and carbapenems, recorded a decline from 36646.19 (5856.39 + 21224.8 + 9565) in 2009 to 29453.10 lei (1124.1 + 20913 +7416) in 2014 or by 19.63%.

To determine the cost of one medium DDD of antibacterials for systemic use separately for parenteral and enteral forms, the value cost of DDD/1000 to DDD/1000 was divided respectively. The medium cost of one antibiotic DDD in lei for parenteral and enteral forms is shown in tables 3 and 4

Table 3 states that in the evaluated period the total cost of one medium DDD increased from 26.87 in 2009 to 32.62 lei in 2014 or by 21.40% and of parenteral forms from 27.38 to 33.27 lei or by 21.51%. For enteral forms this cost registered a significant decrease from 10.22 to 2.86 lei or by 3.57 times. The ratio between the cost of one medium DDD of parenteral and enteral forms was respectively 2.68:1; 9.96:1; 12.14:1; 7.01:1; 9.09:1 and 11.63:1 for the evaluated years.

The calculation of one medium DDD costs in lei of parenteral forms of other beta-lactam antibacterials is shown in table 4. As stated in the table for the evaluated period, the cost of one medium DDD of parenteral forms increased from 12.65 to 20.86 lei or by 35.10%.

The periodical evaluation and presentations of antibiotic consumption in DDD led to making practical decisions on rational use of this group of drugs. In table 5 are presented the results of pharmacoeconomy in the Reanimation Department of intensive care.

As stated in table 5, starting from 2009 and taking into consideration the exchange rate, the pharmacoeconomy increased from 14046 in 2010 to 45407 lei in 2014 per DDD/1000 that amounted to 3.32 times, corresponding to the annual savings from 92015,3 to 334241 lei. In case of not taking into

Table 3

Cost of 1 (one) DDD antibiotics in lei for parenteral and enteral forms

Reanimation department intensive care unite						
	2009	**2010**	**2011**	**2012**	**2013**	**2014**
Parenteral cost in lei DDD/1000	86856	88888.10	78432.60	57993.60	76022.00	54204.00
Enteral cost in lei DDD/1000	1003.66	223.05	323.93	428.13	527.47	102.83
Parenteral and enteral cost of DDD/1000 in lei	87859.66	89111.15	78756.53	58421.73	76549.47	54306.83
Parenteral DDD/1000	3171.90	1739.40	1583.50	1609.00	1706.40	1629.00
Enteral DDD/1000	98.25	43.51	79.36	83.31	107.67	36.00
Parenteral and enteral DDD/1000	3270.15	1782.91	1662.86	1692.31	1814.07	1665.00
Total cost of one DDD in lei	26.87	49.98	47.36	34.52	42.20	32.62
Parenteral cost of one DDD in lei	27.38	51.10	49.53	36.04	44.55	33.27
Enteral cost of one DDD in lei	10.22	5.13	4.08	5.14	4.90	2.86

Table 4

Cost of one DDD other beta-lactam antibacterials in lei of parenteral and enteral forms

Reanimation department						
	2009	**2010**	**2011**	**2012**	**2013**	**2014**
Parenteral cost in lei DDD/1000	40122.89	25566.49	27043.07	23869.4	42798.9	33981.3
Parenteral DDD/1000	3171.90	1739.40	1583.50	1609.00	1706.40	1629.00
Parenteral cost of one DDD in lei	12.65	14.70	17.08	14.84	25.08	20.86

Table 5

Departmental pharmacoeconomy in the period of 2009 - 2014

Years and DDD/1000	2009 3270	2010 1783	2011 1663	2012 1692	2013 1814	2014 1665
Cost of DDD/1000 (lei)	87859,6	89111,2	78756,5	58421,7	76549,7	54307
National Bank of RM exchange rate, of February 20th ($US)	10,5672	12,7572	12,0338	11,8977	12,1176	13,5178
Pharmacoeconomy to DDD/1000 exchange rate, starting from 2009	0	14046	18701	35971	21104	45407
Annual pharmacoeconomy taken into consideration, according to 2009 exchange rate	0	92015,3	130626	325574	155832	334241
Pharmacoeconomy to DDD/1000, 2009 as the reference point, without exchange rate	0	-1251,6	9103,1	29437,9	11309,9	33552,6
The annual number of thousands occupied beds	3,99	6,551	6,985	9,051	7,384	7,361
Annual pharmacoeconomy not taken into consideration 2009 exchange rate	0	-8199,2	63585,2	266442	83512,3	246981

consideration the exchange rate, the amount was from 63585.2 to 246981 lei.

Conclusions

1. The DDD/1000 OBD of antibiotics in Reanimation department decreased by 49.09% or from 3270.17 in 2009 to 1664.99 in 2014 and was by 22.76% higher than the medium consumption of 1286.11 in 1134 intensive care units of international hospitals.

2. The value indexes per DDD/1000 declined from 87860 in 2009 to 54307 lei in 2014 or by 38.19%. The cost of one medium DDD increased from 26.87 in 2009 to 32.62 lei in 2014 or by 21.40%. The pharmacoeconomy increased yearly and in 2014 was more than 3 times, comparatively with 2009.

3. The average annual institutional rate for the total antibiotics consumption for the stated period decreased from 662.4 in 2009 to 464.1 DDD/1000 OBD in 2014 or by 30%. The overall medium consumption in 1547 international hospitals constituting 425.81 DDD/1000 was less than 38.29 DDD/1000 or by 8.25% than the consumption in 2014 in EMI.

4. The parenteral use forms recorded a decline from 3172 in 2009 to 1629 DDD/1000 in 2014 or by 48.64% and with an unstable consumption for the ones with enteral use forms, varying from 38 to 108 DDD/1000 in different years.

5. The total institutional antibiotics consumption in value indexes varied from 1562575 in 2009 to 1500888 lei in 2014 that represents 17% and 14% from the whole amount of drugs. The same data for Reanimation department was 341581 in 2009 and 399754 lei in 2014 or 22.34% and 20.03% from the whole amount of drugs, and 21.88% and 26.63% from the total institutional antibiotics consumption.

6. The cost of DDD/1000 declined from 87860 in 2009 to 54307 lei in 2014 or by 38.19%, and vice versa the cost of one medium DDD increased from 26.87 in 2009 to 32.62 lei in 2014 or by 21.40%, when the cost of one medium DDD of parenteral forms of other beta-lactam antibacterials increased from 12.65 to 20.86 lei or by 35.10%.

7. The ratio between costs of one medium DDD of parenteral and enteral forms were respectively 2.68:1; 9.96:1; 12.14:1; 7.01:1; 9.09:1 and 11.63:1 for the years under consideration.

References

1. Ingram PR, Seet JM, Budgeon CA, Murray R. Point-prevalence study of inappropriate antibiotic use at a tertiary Australian hospital. *Internal medicine journal*. 2012;42(6):719-721.
2. Levin PD, Idrees S, Sprung CL, et al. Antimicrobial use in the ICU: indications and accuracy an observational trial. *Journal of hospital medicine: an official publication of the Society of Hospital Medicine*. 2012;7(9):672-678.
3. Perencevich EN, Sands KE, Cosgrove SE, et al. Health and economic impact of surgical site infections diagnosed after hospital discharge. *EmergInfectDis*. 2003;9(2):196-203.
4. Cizman M. The use and resistance to antibiotics in the community. *Int J Antimicrob Agents*. 2003;21:297-307.
5. Alberti, C, Brun-Buisson C, Burchardi H, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Medicine*. 2002;28:108-21.
6. Kunin CM, Johansen KS, Worming AM, Daschner FD. Report of a symposium on use and abuse of antibiotics worldwide. *RevInfectDis*. 1990;12:12-16.
7. Fridkin SK, Baggs J, Fagan R, et al. Vital Signs: Improving Antibiotic Use among Hospitalized Patients. *MMWR. Morbidity and mortality weekly report*. 2014;63.
8. Guidelines for ATC classification and DDD assignment WHO, 16th edition. WHO Collaborating Centre for Drug Statistics Methodology Norwegian Institute of Public Health. Oslo, 2013;284.
9. How to Calculate Antimicrobial Defined Daily Doses (DDDs) and DDDs per 1000 Patient Days.www.antimicrobialstewardship.com./how_to_calculate_ddds_final.pdf.
10. Medical and public health institution – Emergency Medicine Institute. http://urgenta.md/Index.aspx.
11. Bernaz EP. Evaluation of the antimicrobials used in defined daily doses in hospitals of the Republic of Moldova. *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale [Bulletin of the Moldovan Academy of Sciences. Medical Sciences]*. 2014;3(44):189-200.
12. Bernaz EP. Evaluation of consumption in defined daily doses of antimicrobials for systemic use in hospitals. *Curierul medical*. 2015;58(5-6):10.
13. Henard S, Rahib D, Léonand L, et al. Consommation des antibiotiques rapportée via les bilans standardisés de lutte contre les infections nosocomiales et relation avec l'ICATB. *MÃ©decine et Maladies Infectieuses*. 2010;41(4):197-205.
14. Kuster Stefan P, Ruef1 Christian, Bollinger Alfred K, et al. Correlation between case mix index and antibiotic use in hospitals. *Journal of Antimicrobial Chemotherapy*. 2008;62(4):837-842.
15. Kritsotakis EI, Gikas A. Surveillance of antibiotic use in hospitals: methods, trends and targets. *Clin Microbiol Infect*. 2006;12: 701-04.
16. Plüss-Suarda C, Pannatiera A, Kronenbergc A, et al. Hospital antibiotic consumption in Switzerland: comparison of a multicultural country with Europe. *Journal of Hospital Infection*. 2011;76:166-171.
17. Walther SM, Erlandsson M, Burman LG, et al. Icustrama Study Group. Antibiotic prescription practices, consumption and bacterial resistance in

a cross section of Swedish intensive care units. *Acta Anaesthesiol Scand*. 2002;46(9):1075-81.
18. Hanberger H, Arman D, Gill H, et al. Surveillance of microbial resistance in European intensive care units: the first report from the Care-ICU programme for improved infection control. *Intensive Care Med*. 2009;35:91-100.
19. Hermosilla Nájera L, Canut Blasco A, Ulibarrena Sanz M, et al. Trends in antimicrobial utilization at a Spanish general hospital during a 5-year period. *Pharmacoepidemiology and Drug Safety*. 2003;12(3):243-247.
20. Loeffler JM, Garbino J, Lew D, et al. Antibiotic consumption, bacterial resistance and their correlation in a Swiss university hospital and its adult intensive care units. *Scand J Infect Dis*. 2003;35(11-12):843-50.
21. Meyer E, Schwab F, Schroeren-Boersch B, et al. Diversity in antibiotic use in intensive care units in Germany. *Dtsch Med Wochenschr*. 2008;133(6):235-40.
22. de With K, Meyer E, Steib-Bauert M, et al. Antibiotic use in two cohorts of German intensive care units. *J Hosp Infect*. 2006;64(3):231-7.
23. Meyer E, Jonas D, Schwab F, et al. SARI: surveillance of antibiotic use and bacterial resistance in German intensive care units. Correlation between antibiotic use and the emergence of resistance. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. 2004;47(4):345-51.
24. de With K, Bergner J, Bühner R, et al. Antibiotic Use at German University Hospitals (Project INTERUNI-II). Results for Medical Intensive Care, Hematology-Oncology, and Other Medical Service Areas]. *Med Klin*. 2004;99(7):347-54.
25. Meyer E, Schwab F, Jonas D, et al. Surveillance of antimicrobial use and antimicrobial resistance in intensive care units (SARI): 1. Antimicrobial use in German intensive care units. *Intensive Care Med*. 2004;30:1089-96.
26. Nedelcu IN, Radu L, Firulescu S, et al. Use of systemic antibacterial agents at a university emergency clinic in Bucharest, in the year 2008. *Bacteriol Virusol Parazitol Epidemiol*. 2009;54(1):53-8.
27. Kern WV, de With K, Steib-Bauert M, et al. Antibiotic use in non-university regional acute care general hospitals in southwestern Germany, 2001-2002. *Infection*. 2005;33(5-6):333-9.
28. Savov E, Gergova I, Borisova M, et al. Consumption of antimicrobial drugs and antibiotic resistance in problematic for hospital infectious pathology bacteria. *Trakia Journal of Sciences*. 2013;11(4):338-342.
29. Bernaz EP. A six-year evaluation of antibiotics consumption in DDD in septic orthopedic-traumatology Department. *Curierul medical*. 2015;58(6):10-16.

Changes of free radical oxidation and of antioxidant defense system in peripheral blood and fluid discharged from prostate draining lodge in large transbladder adenomectomy

***V. Bobu[1], V. Gudumac[2], A. Tanase[3], Ie. Zota[4], V. Caraion[1], E. Costenco[1]**

[1]Departmet of Urology, Holy Trinity Municipal Hospital, Chisinau, the Republic of Moldova
[2]Laboratory of Biochemistry, [3]Department of Urology and Surgical Nephrology, [4]Department of Pathomorphology
Nicolae Testemitsanu State University of Medicine and Pharmacy, Chisinau, the Republic of Moldova
*Corresponding author: victor.bobu64@gmail.com. Received January 13, 2016; accepted February 05, 2016

Abstract

Background: This study is dedicated to determination of the peculiarities of the lipid peroxidation and antioxidant system processes in the patients with prostate adenoma (PA), and the correlation between blood serum and fluid draining from lodge after adenomectomy with the aim of highlighting the risk factors of this pathology.
Material and methods: There were studied 79 men aged 50-75 years, divided into two specific groups: group 1 – 49 men with PA treated surgically by transvezical method, modified by us and group 2 – 30 healthy men.
Results: The results showed that in PA the processes of lipid oxidation with production of reactive oxygen species increased, confirmed by marked increasing of hydroperoxides of lipids, keto-diene conjugates and carbonyl compounds. There had been an impressive increase of the malondialdehyde level in both blood serum at pre- and postoperative stages and in the drained fluids from the lodge in patients of group 1. A deficiency of antioxidants was demonstrated by total antioxidant reduced activity and decreased functionality of the main antioxidant enzymes – superoxide dismutase, glutathione peroxidase, catalase in pre- and post-operative periods, as well as in fluids from the drained lodge in group 2.
Conclusions: It was found that oxygen species manifested an imbalance between reactive oxygen species generation and antioxidant protective system and they are an important pathogenic cause in self-maintenance and exacerbation of inflammatory response that can influence the pre- and postoperative evolution of PA, a predictive factor in developing treatment strategies, postoperative management.
Key words: prostate adenoma, urology, oxidative and antioxidant system.

Background

One of the main problems of vital importance in the treatment of the prostate adenoma (PA) for complex intraoperative and postoperative monitoring of the patients and prophylaxis of the complications is the maintenance of body homeostasis and hemostasis in the lodge after adenomectomy.

The reactive oxygen species (ROS) have a pivotal role in maintaining homeostasis of the organism, and in modulation of the regulatory processes. Currently is known the role of ROS in signaling and control of all aspects of life, including energy regulation, cytoskeletal structure, transport of substrates, proliferation, differentiation, and apoptosis, immune modulation and inflammatory responses, etc. [8]. ROS are largely responsible for the cellular and molecular particularities of the affected tissues by various pathologies.

The biological effects of ROS are determined by the balance between their production and their inactivation rate

by antioxidant defense system (AOS). Enzymatic and non-enzymatic antioxidants act in the human organism, and their high efficiency consists in the synergy of their action, each of them acting by different mechanisms on the ROS chains in the different levels (membrane, cytoplasm, extracellular fluids, etc.) [2, 10, 11].

In recent years it has been eloquently demonstrated that activation of lipid peroxidation (LP) involves significant damage in the cell membranes and other lipid-containing structures, which may disrupt its functions. Therefore intensification of LP in pathological condition is accompanied by accumulation of biochemical products such as lipid hydroperoxides, conjugated dienes (CD), carbonyl compounds (CC) and malondialdehyde (MDA) in the tissues and body fluids [7; 4] and are hazardous for living organisms and damage all major cellular constituents.

The generation of free radicals and nonradical reactive species and the intensity of LP formation is managed and maintained within the physiological limits under the influence of AOS compounds classes with specific hydrophilic antioxidant activity in the cytosol and body fluids and with antioxidant hydrophobic activity in biological membranes. It is well known that antioxidant enzymes such as: superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPO), γ-glutamyl transpeptidase (γ-GTP), etc., play a critical role in maintaining biological redox balance and homeostasis and thus cell integrity and functions [16; 6].

According to the data from the literature the role of oxygen radicals, LP and AOS is frequently mentioned in the pathogenic mechanisms of PA onset and development. According to some authors PA development may be an alternative way to prostate carcinogenesis due to increased prostate disorders promoted by oxidative stress and inflammatory mediators [19; 12; 21]. The hypothesis is based on the role of inflammation in stimulating prostate carcinogenesis [1]. This increasing trend can result from perturbation of the DNA repairing systems and increased nitrogenous bases injuries caused by elevated levels of ROS in the prostate cells [3, 13]. Ageing, significant imbalance of oxidation/reduction (redox) status, infection and inflammation are recognized as major risk factors for the development of benign prostatic hyperplasia and prostate cancer.

Prostate chronic inflammatory processes generate significantly elevated levels of reactive oxygen species, nitrogen and halogen compounds. Oxidative stress causes changes of the DNA that can lead to genome instability and may initiate carcinogenesis. However, it was shown that oxidative damage is not sufficient to initiate this process. Peroxidation products induced by ROS appear to take part in the epigenetic mechanisms regulating genome activity.

Thus, we consider fully argumented the initiation of the detailed research on evaluation of peculiarities of intensity of LP and AOS in patients with PA and the correlation of data from blood serum and peripheral fluid from drained lodge after adenomectomy in co-report with normal particularities for revelation of the possibilities of modern diagnosis, treatment and risk factors of this disease. Despite the diagnostic performance, wide variation in surgical tactics remains quite problematic developments in the postoperative period, often triggered by various complications, which justified the need for a study on the evaluation of free radical oxidation processes in the PA.

The aim of this study was to evaluate the processes of free radical peroxidation, the state of serum antioxidant system in pre- and post-operative patients with PA in serum and fluid draining from the lodge after adenomectomy in the early post-operative stage for the assessment of their role in the pathogenesis of the lesion development and evolution in PA.

Material and methods

The research is based on a study of 79 men aged 50-75 years, and according to the aim they were divided into two specific groups:

· Group 1 (G1), study group – patients with confirmed diagnosis of PA (n = 49)

· Group 2 (G2), control group – healthy people (donors of blood) (n = 30)

49 patients from the first group with diagnosis of PA were operated on in the Department of Urology of Holy Trinity Municipal Hospital by transvezical method in our modification, with endo-urethral drainage of the lodge and Foley catheter with a triple step No 20 into sutured bladder [5].

Material for the study were 5 ml of serum collected from cubital vein preoperative one hour before surgery and 24 hours after surgery intervention and 5 ml of fluid from the lodge obtained by endo-urethral method.

Lipid peroxidation intensity was assessed by determining the level of lipid hydroperoxides, conjugated dienes, and carbonyl compounds in the polar and nonpolar phases, and malondialdehyde.

Antioxidant defense system particularity was studied by evaluating the level of following indicators: total antioxidant activity (TAA) with ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid), and TAA with DPPH (2,2-diphenyl-1-picrylhydrazyl) in both phases – hexane (lipophilic) and isopropanol (hydrophilic), and the activity of such antioxidant enzymes as: superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPO), γ-glutamyl transpeptidase (γ-GPT). Assessment of the level of total proteins was performed by biuret method with the set of Eliteh reagents, France.

The correlation of the radical oxidation processes and antioxidant system in the blood serum with the fluid eliminated from the postoperative lodge was examined by assessment of the indices of pro- and anti-oxidant systems in the supernatant obtained after centrifugation of the liquid from the lodge.

Techniques adapted for application on multi-modal microplate hybrid reader Synergy H1 (Reader Hydride) (BioTek Instruments, USA) were used for examination of free radical oxidation processes and AOS.

Biochemical investigations were conducted in the Scientific Biochemical Laboratory of Nicolae Testemitsanu State University of Medicine and Pharmacy.

StatsDirect softwear (StatsDirect Ltd, UK) (6.0 Statistics. Soft Inc., 2002) was used for calculation of t-Student criteria.

Results and discussion

Evaluation of the results of lipid peroxidation and antioxidant system in blood and in fluids from the lodge of enrolled patients are shown in the tables 1 and 2.

According to the data presented in table 1, in patients with large PA (group 1) before and after the surgery, the blood concentration of LHPO, CD and CC in both phases – hexane (lipophilic) and isopropanol (hydrophilic) significantly ($p<0.05$) exceed these values in control group. The values of malondialdehyde, the final product of lipid peroxidation processes, doubled during all the stages of the study, with serum variations from 20.9±3.52 preoperatively to 21.6±4.38 postoperatively and 22.5±5.24 in the lodge in comparison with 10.06 ± 0.148 in the group 2.

In this study, lipid peroxidation products, namely the MDA proved to be significantly increased in patients with PA at preoperative stage. Thus we concluded that MDA level was significantly higher in patients from G1 at both stages in comparison with the control one.

MDA is a derived product of polyunsaturated fatty acids peroxidation. Evaluation of serum MDA is a non-invasive biomarker of oxidative stress. Our data showed an increased MDA in the patients with PA which had a positive correlation with PSA levels. Therefore we concluded that this index could be considered a useful marker of lipid peroxidation and prostate inflammation and could be a significant predictive factor of these processes.

Highly reactive aldehydes (4-hydroxynonenal, MDA), lipid peroxidation products are able to change the structure of DNA and proteins, making them mutagenic, cytotoxic and genotoxic. We therefore believe that a high level of MDA and of other reactive aldehydes can explain the changes in nitrogenous bases of DNA not only in prostate cancer, but also in glandular epithelium of PA.

High values of oxidative stress (OS) indices in the fluids from postoperative lodge which had small difference in comparison with the values recorded in the blood at pre- and postoperative stages was another feature documented in patients of G1.

It is known that hydroperoxides have the ability to oxidize thiol group-containing compounds (cysteine, glutathione, lipoic acid). But the SH (thiol) groups are not the only unique site of peroxide oxidation. Interaction of LP and proteins results in development of specific complexes with covalent links between NH2 (amino) groups of aminoacids and aldehydes or carboxylic groups of lipoperoxides. Thus, we can conclude that MDA has a dominant role in the formation of insoluble protein polymers through the creation of links between polypeptide chains involving lysine amino-groups. Likely, that certain hydroperoxide interaction with proteins determines the biological effects of lipoperoxides on the cells, including cytolytic effect.

The biochemical investigation of the markers listed above, for the assessment of antioxidant processes peculiarities in

Table 1

Changes in lipid peroxidation processes in the serum and in the fluids from the lodge in patients with PA

Parameters	General group of study			
	G1 – study group (n=49)			(G2) Control group (n=30)
	In blood serum		Fluids of the lodge	
	Before surgery (first 60 min)	After surgery at 24 hours	After surgery at 24 hours	
Age (years)	**68,6±1,05**			**68,9 ±0,80**
MDA, nM/L	20,9±3,52* (207%)	21,6±4,38* (215%)	22,5±5,24* (224%)	10,06±0,148 (100%)
In hexane, lipophilic nonpolar phase				
LHPO, cu/ml	10,75±1,14** (279%)	10,25±1,27* (270%)	11,41±1,39** (297%)	3,84±0,09 (100%)
CD, cu/ml	7,33±0,86** (277%)	6,15±0,82* (233%)	6,40±0,77* (242%)	2,64±0,12 (100%)
CC, cu/ml	5,31±0,67*** (352%)	4,4±0,55*** (291%)	2,82±0,44** (187%)	1,51±0,02 (100%)
In isopropanolic, hydrophilic polar phase				
LHPO, cu/ml	10,67±2,03* (189%)	9,64±1,16* (170%)	11,37±2,18** (207%)	5,65±0,04 (100%)
CD, cu/ml	5,71±0,86** (198%)	4,40±0,63** (153%)	6,95±0,95*** (241%)	2,88±0,03 (100%)
CC, cu/ml	2,28±0,37* (158%)	2,30±0,26** (160%)	3,84±0,51*** (268%)	1,44±0,06 (100%)
Total protein, g/L	53,4±4,22** (78%)	49,8±6,04** (73%)	51,7±6,27* (75%)	68,6±2,45 (100%)

Note: LHPO – lipid hydroperoxides; conjugated dienes (DC), carbonyl compounds (CC) and malondialdehyde (MDA); cu - conventional units.
Statistically significant differences:
a) compared to the control group * - $p<0.05$; ** - $p<0.01$; *** - $p<0.001$;
b) compared to the group before surgery and after surgery, # - $p<0.05$; ## - $p<0.01$; ### - $p<0.001$.

Table 2

Changes of antioxidant system in serum and in fluids from the lodge in patients with PA

Parameters	General group of study			
	G1 – study group (n=49)			(G2) Control group (n=30)
	In blood serum		Fluids form the lodge	
	Before surgery (first 60 min)	After surgery in 24 hours	After surgery in 24 hours	
Age (years)	**68,6±1,05**			**68,9 ±0,80**
TAA - ABTS, mM/L	0,36±0,06 (75%)	0,37±0,04 (77%)	0,36±0,08 (75%)	0,48±0,04 (100%)
TAA - DPPH, mM /s.L, lipophilic, nonpolar phase	2,66±0,31* (78%)	2,71±0,37 (87%)	2,65±0,41 (85%)	3,42±0,19 (100%)
TAA - DPPH, mM/ s.L, hydrophilic, polar phase	1,78±0,32* (70%)	1,92±0,64 (76%)	1,91±0,77 (76%)	2,54±0,11 (100%)
CAT, nkat/L	45,9±3,72*** (67%)	44,5±4,86** (65%)	56,2±6,33 (82%)	68,5±0,85 (100%)
SOD, cu	614,8±71,3*** (55%)	795,8±68,1*** (71%)	736,9±80,9*** (66%)	1124,0±40,5 (100%)
GPx, nkat/L	84,2±9,4* (61%)	97,6±10,6 (71%)	88,4±9,1* (64%)	138,1±15,3 (100%)
γ-GPT, IU/L	29,20±3,24* (136%)	22,06±2,62 (103%)	32,04±3,64* (149%)	21,5±2,13 (100%)

Note: LP – lipid hydroperoxide; diene conjugates (CD), carbonyl compounds (CC) and malondialdehyde (DAM);
cu - conventional units; IU – international units.
Statistically significant differences:
a) compared to the control group * - p<0.05; ** - p<0.01; *** - p<0.001;
b) compared to the group before surgery and after surgery, # - p<0.05; ## - p<0.01; ### - p<0.001.

patients with PA (G1) proved a deficiency of antioxidants, by significant decrease of total antioxidant activity (TAA-DPPH) in both phases – hexane (lipophilic) and isopropanol (hydrophilic) (table 2).

It is worth mentioning that the main activity of antioxidant enzymes (SOD, CAT, and GPO) significantly decreased in serum by 33-45% at pre- and postoperative stages in patients with PA. The only exception is the important increase of γ-GPT activity at preoperative stage.

Therefore, it is to note that the cause of increased oxidative stress may be the over-production of free radicals or the decrease of the inactivation of free radicals by antioxidant enzymes SOD, CAT, GPO. Elevated levels of free radicals are also accompanied by high MDA level, a product of lipid peroxidation at preoperative stage in patients with PA in comparison with the control group.

The study results showed that oxidative stress in patients of group 1 with PA was significant in the pre-operative stage in comparison with control group G_2. Similar peculiarities were noted by other researchers. Also our results are in concordance with some studies which have established the presence of chromosomal aberrations in these patients [16].

According to Przybyszewski W.M. and Rzeszowska-Wolny J. [14] prostate inflammation can generate significantly elevated levels of ROS, reactive nitrogen species, and halogenated compounds. Neutrophils and macrophages provide a source of free radicals that can induce hyperplastic changes through oxidative stress (OS) in the prostatic tissue and DNA damage. OS can induce vascular tissue injury and damage to the structure and function of proteins, genomic damage that due to posttranslational modifications including those involved in DNA repair and apoptosis [15]. This can lead to oxidative damage of DNA by mutations, deletions or rearrangements and reduce DNA repair. OS also modifies the population of stem cells. Genomic changes result in modulation of an imbalance between cell proliferation and cell death. According to some opinions the change in normal ratio is regulated by programmed cell death that leads to hyperplasia or precancerous processes [9].

In this context, some scientific sources state that tissue of human prostate is vulnerable to DNA oxidative damage due to decreased level of DNA enzymes. In these cases OS may enable the transcription of nuclear transcription factor-kB (NF-kB) by tumor necrosis factor TNF-α pathway/AP-1 transduction and NF-kB-inducing kinase transduction pathways. It should be noted that NF-kB is known as a transcriptional regulator of the inflammatory processes and activator of the gene responsive for regulation of the immune response, inflammation, cell proliferation, cell migration and apoptosis. Thus, nuclear translocation of NF-kB can activate target genes involved in carcinogenesis. These features in particular NF-kB deregulation were proposed to be one of the supposed molecular mechanisms that induce chronic inflammation and cancer [9]. Some opinions state, that cell soluble proinflammatory mediators directly activate NF-kB and induce local production of proinflammatory factors in patients with PA, but not in the control group [22, 25].

MDA is a final product derived from peroxidation of polyunsaturated fatty acids and lipids. In contrast free radicals, aldehydes are relatively stable and, therefore, have the oppor-

tunity to broadcast within or outside the cell to attack distant objects in the place of origin initiated by free radicals. MDA not only reflects the level of lipid peroxidation, but is also a by-product of cyclooxygenase. Platelet activity, and persistent platelet activation is a common feature of many clinical syndromes associated with increasing of lipid peroxidation. According to Kulinski V. I. [23] measuring the level of MDA in plasma or serum of blood provides a suitable condition *in vivo* index of lipid peroxidation and is a biomarker, often used to investigate the radical-mediated physiological and pathological conditions. Therefore we note that circulating levels of MDA proved to be significantly higher in patients with large prostatic adenoma in comparison to healthy donors (G2). Similar results were obtained by other researchers and they are strongly correlated with the levels of prostate-specific antigen [20]. Some studies also indicate the role of lipid peroxidation that also may be a trigger in the synthesis of prostaglandins by cyclooxigenase-2 activation [17].

The products of peroxide oxidation of lipids are eliminated by superoxide dismutase, glutathione peroxidase, catalase, and such vitamins-antioxidants as α-tocopherol and ascorbic acid.

The authors noted that assessing the level of antioxidants in patients with PA can help in good management and reduce morbidity. Romanda Duru et al. [18] state that in the management of patients with PA, antioxidants supplementation is needed, because deficiency in antioxidants may be associated with cell degeneration, pathologic process and poor prognosis.

Extent of oxidative damage ROS-induced can be exacerbated by low efficiency of antioxidant defense mechanisms. Imbalance between OS and antioxidant components of the cell also plays the important role in the development of PA. Some sources of literature reveal OS growth and decreased antioxidant mechanism in prostate diseases including PA. However, data is not univocal. Low antioxidant capacity was found in patients suffering from benign prostate hyperplasia compared to controls. Negative correlation between blood serum peroxides and antioxidant capacity was observed in these patients [24].

The studies demonstrated in patients an imbalance between the production of RLO and antioxidant substances. This imbalance occurs because of excessive RLO and natural antioxidants can't cope with it, and in result appears incapable of annihilating them, as evidenced by the decreased total antioxidant activity in both phases – hexane, hydrophobic, nonpolar and isopropanol, hydrophilic, polar, both at the pre- and postoperative stages.

We note that oxidative stress is manifested by the imbalance between generations of ROS, on the one hand and protective antioxidant systems, on the other hand, forms pathogenic elements important in the self-maintaining and exacerbating the inflammatory response and influencing the development of PA patients during the study. Therefore the obtained results about oxidative processes and antioxidant correlations that reflect the current research findings open the new possibilities of drawing up strategies of medical and surgical management in patients with PA.

Conclusions

1. In the case of prostate adenoma, the processes of oxidation with production of reactive oxygen species were increasing, manifested by marked increases of the lipid hydroperoxides, conjugated dienes, carbonyl compounds and malondialdehyde in the blood and in the fluids from the lodge at the pre- and postoperative stages. Compared with G1 the recorded indices of oxidative stress were significantly higher, in particular malondialdehyde (22.5±5.24 nM/L) in blood serum, similar to pre- and postoperative 20.9±3.52 and 21.6±4.38 nM/L, respectively.

2. Deficiency of antioxidants was found in the patients with PA, as demonstrated by the important reduction of total antioxidant activity, decrease of the activities of the main antioxidant enzymes (SOD, CAT and GPO) during pre- and postoperative stages.

3. Oxidative stress is manifested by imbalances between generation of reactive oxygen species, on the one hand, and antioxidant systems protection, on the other hand, the activity of enzymes is an important pathogenic and informative marker in the self-maintenance and exacerbation of inflammatory response influencing evolution of PA at pre- and post-operative stages. Oxidative stress is a predictive element in developing treatment strategies for patients with PA at intra-operative and post-operative stages.

References

1. Adekola SA, Popoola OA, Ogundiran SM, et al. Is gamma glutamyl transferase a diagnostic marker of prostate disease? *International Journal of Medicine and Biomedical Research*. 2013;2(2). www.ijmbr.com.
2. Atasayar S, Orhan H, Özgüneş H. Malondialdehyde quantification in blood plasma of tobacco smokers and non-smokers. *FABAD J. Pharm Sci*. 2004;29:15-19.
3. Aydin A, Arsova-Sarafinovska Z, Sayal A, et al. Oxidative stress and antioxidant status in non-metastatic prostate cancer and benign prostatic hyperplasia. *Clinical Biochemistry*. 2006;39(2):176-179.
4. Baroni GS, D'Ambrosio L, Ferretti G, et al. Fibrogenic effect of oxidative stress on rat hepatic stellate cells. *Hepatology.* 1998;27:720-26.
5. Bobu V, Tanase A., Eşanu C, et al. Metodă de drenare endouretrală în operaţii urologice la organele etajului inferior. Brevet de invenţie nr 3804 AGEPI, 2008.
6. Cabre M, Camps J, Paternain JL, et al. Time-course of changes in hepatic lipid peroxidation and glutathione metabolism in rats with carbon tetrachloride-induced cirrhosis**.** *Clin.Exp Pharmacol Physiol.* 2000;27(9):694-699.
7. Casini A, Ceni E, Salzano R, et al. Neutrophil-derived superoxide anion induces lipid peroxidation and stimulates collagen synthesis in human hepatic stellate cells: role of nitric oxide. *Hepatology*. 1997;25:361-67.
8. Jones DP. Radical-free biology of oxidative stress. *Am J Physiol Cell Physiol.* 2008;295:849-68.
9. Finkel T. Signal transduction by reactive oxygen species. *Journal of Cell Biology*. 2011;194(1):7-15.
10. Gudumac V, Baciu E, Marin V, et al. Investigaţii enzimologice. Elaborare metodică. Chişinău, 2000;56.
11. Hong Yan Li, et al. Advanced oxidation protein product accelerates renal fibrosis in a remnant kidney model. *J Am Soc Nephrol*. 2007;18:528-38
12. Khandwala HM, McCutcheon IE, Flyvbjerg A, et al. The effects of insulin-like growth factors on tumorigenesis and neoplastic growth. *Endocr Rev*. 2000;21:215-244.
13. Kohnen PW, Drach GW. Patterns of inflammation in prostatic hyperplasia: a histologic and bacteriologic study. *J Urol*. 1979;121:755-60.
14. Kutdo T, Kigoshi H, Hagiwara T, et al. Cathepsin G, a Neutrophil Protease, Induces Compact Cell-Cell Adhesion in MCF-7 Human Breast Cancer Cells. In: Hindawi Publishing Corporation Mediators of Inflammation. 2009;1:11.

15. Lee KL, Peehl DM. Molecular and cellular pathogenesis of benign prostatic hyperplasia. *J Urol*. 2004;172:1784-91.
16. Olinescu R. Radicalii liberi în fiziopatologia umană. București: Ed.Tehnică, 1994;9-16
17. Przybyszewski WM, Rzeszowska-Wolny J. Oxidative stress in prostate hypertrophy and carcinogenesis. *Postepy Hig Med Dosw*. 2009;63:340-50.
18. Duru R, Obioma Njoku, Maduka I. Oxidative Stress Indicators in Patients with Prostate Disorders in Enugu, South-East Nigeria. Hindawi Publishing Corporation. *BioMed Research International*. 2014;6. Article ID 313015.
19. Suzuki S, Platz EA, Kawachi I, et al. Intakes of energy and macronutrients and the risk of benign prostatic hyperplasia. *Am J Clin Nutr*. 2002;75:689-697.
20. Tsai CC, Chen HS, Chen SL, et al. Lipid peroxidation: a possible role in the induction and progression of chronic periodontitis. *J. Periodontol. Res*. 2005;40(5):237.
21. Wang W, Bergh A, Damber JE. Chronic inflammation in benign prostate hyperplasia is associated with focal upregulation of cyclooxygenase-2, Bcl-2, and cell proliferation in the glandular epithelium. *Prostate*. 2004;61:60-72.
22. Kostyuk VA, Potapovich AI, Lunets EF. Spectrophotometric determination of diene conjugates. *Problems of Medical Chemistry*. 1984;4:125-127.
23. Kulinskiy VI, Kolesnichenko LS. Glutathione system. Other enzymes, thiol-disulfide exchange, inflammation, and immunity function. *Biomed. Chemistry*. 2009:55(4):365-380.
24. Galaktionova LP, Molchanov AV, Warsaw BJ. Status peroxidation in patients with gastric ulcer and duodenal ulcer. *Klinicheskaya Laboroatornaya Diagnostika*. 1998:6:10-14.
25. Livovskaia EI, Volchegorskiy IA, Shemyakov SE, et al. Spectrophotometric definition of end-products of lipid peroxidation. *Problems honey chemistry*. 1991;4:92-93.

Portal hemodynamics disorders severity in liver cirrhosis assessment by duplex ultrasound

***C. Tambala[1], I. Secrieru[2]**

[1]Radiology and Imaging Department, Nicolae Testemitsanu State University of Medicine and Pharmacy
[2]Laboratory of Information Systems, Institute of Mathematics and Computer Science
Academy of Sciences of Moldova, Chisinau, the Republic of Moldova
*Corresponding author: caroli@bk.ru. Received January 04, 2016; accepted February 10, 2016

Abstract

Background: The need to evaluate hemodynamics in case of portal hypertension syndrome is a current problem. Identification of portal hypertension by invasive methods is difficult, hence the logical conclusion of the need to optimize the portal hypertension diagnosis by non-invasive methods. This study aims: to identify a system of non-invasive measurements, which will permit to develop a scoring system for portal hemodynamics disorders severity in liver cirrhosis assessment by duplex ultrasound and a scoring interpretation, which allows the classification as: low severity, middle severity and high severity.
Material and methods: One hundred eleven patients who were diagnosed with cirrhosis formed the research cohort. The patients had an enhanced clinical and biological evaluation. Ultrasound examination was done by Logiq E9, Voluson E8 equipment, using linear probe of 7-10 MHz frequency and convex probe of 3.5-5 MHz frequency by the transabdominal access, in real time two-dimensional (B) regimen, with the subsequent use of color Doppler and spectral Doppler techniques. Obtained data was processed using case-based reasoning, data segmentation and clusterization.
Results: A scoring for portal hemodynamics disorders severity in liver cirrhosis assessment, based on five non-invasive measurements, obtained by doppler ultrasound imaging, was developed.
Conclusions: The scoring system can be used for a differential diagnosis of liver cirrhosis. The decision rules in the form of productions, obtained during the data clustering stage, can be used to develop medical information systems.
Key words: liver cirrhosis, portal hemodynamics, doppler ultrasound imaginghepatic.

Introduction

Liver cirrhosis is the final stage of chronic liver diseases and is usually complicated by portal hypertension, which becomes the most important cause of morbidity and mortality in these patients. Portal hypertension as a complication of liver cirrhosis, being a clinical / hemodynamic syndrome defined by gradient increase of portal venous pressure, conditions upon a positive diagnosis, the imaging examination being credited as having greater accuracy in detection of the structural hepatosplenic and hemodynamics changes on splenoportal axis.

The need to evaluate hemodynamics on splenoportal axis in case of portal hypertension syndrome is a current problem, due to the increased incidence of the given pathology and specific pathogenetic aspects. The early diagnosis and appropriate management of pathology can certainly improve the prognosis and life expectancy of patients with chronic liver diseases.

Identification of portal hypertension by invasive methods is difficult, both because of laborious processes and serious condition of the patients. Hence the logical conclusion of the need to optimize the portal hypertension diagnosis by non-invasive methods, a complicated problem recognized in numerous studies.

HVPG measuring through the hepatic veins catheterization is the gold standard for evaluation of portal pressure in cirrhosis, but it is an invasive method [1]. HVPG changes provide important information not only for positive diagnosis, but also during treatment have an important significance in guiding cirrhotic patients. However, the technique has limi-

tations in clinical practice to be invasive, with complications' potential and requires a technical expertise with limited availability and did not find a widespread use in medical practice.

It must be emphasized that none of the non-invasive methods replaces the measurement of pressure gradient in hepatic veins and endoscopic screening of esophageal varices, but they certainly facilitate clinical management of patients with liver cirrhosis and provide valuable prognostic information. Traditionally these techniques are based on scoring systems (e.g. Child-Pugh Score [2,3]), or on imaging signs analysis. The sequence of these diagnostics methods, conventional ultrasound (2D) and color duplex Doppler regimen has a number of advantages, being an accessible, non-irradiating, repeatable method it can be performed even at the patient's bedside.

Despite the fact that some techniques became conventional instruments in the estimation of portal hypertension, the search for non-invasive markers for predicting the portal hemodynamic disease severity continues and presents an interest in medical diagnostics, as well as social and economic.

In the study [4] a system of 6 criteria (sonographic signs) was proposed, which allows a differential diagnosis of liver cirrhosis and its classification into: minimal portal hemodynamic disturbances, moderate portal hemodynamic disturbances and severe portal hemodynamic disturbances.

Later this system was subjected to a complex analysis using segmentation and clusterization methods and algorithms, as well as techniques typical for case-based reasonong.

In this paper we propose a scoring system for portal hemodynamics disorders severity in liver cirrhosis assessment by duplex ultrasound and a scoring interpretation, which allows the classification of these disturbances as: low severity, middle severity and high severity.

Material and methods

It is a retrospective study realized at the Republican Clinical Hepatology Department of the University Hospital. The medical records of 111 patients in the last 36 months were studied, who were diagnosed with cirrhosis of the liver of various aetiologies (97.8% mainly of viral origin). The average age of the selected patients was 48.4 years old. The study group consisted of 46 (41.4%) men and 65 (58.6%) women, aged 20-70 years). The exclusion criteria of the research: children, pregnant women, patients with pre- and posthepatic portal hypertension, the presence of hepatocellular carcinoma.

The patients had an enhanced clinical and biological evaluation. The cytolytic, cholestatic, hepatoprive syndromes were assessed. The esophageal varices were diagnosed by upper endoscopy and classified as absent or present, and the severity of varices was described in degrees. The evaluation of severity of hemodynamic disorders was studied by duplex ultrasound, using linear probe of 7-10 MHz frequency and convex probe of 3.5-5 MHz frequency by the transabdominal access. All the patients were examined at the beginning in real time two-dimensional (B) regimen, with the subsequent use of color Doppler and spectral Doppler techniques. Through the two-dimensional exam the morphological appearance of the liver, spleen was studied, highlighting parenchymal structure, homogeneity. Dopplerography in color and power regimen was used to emphasize the portosystemic collaterals. Dopplerography in spectral regimen allowed to describe hemodynamic changes both on arterial and venous side, which included the features of the arterial and venous flows in the hepatolienal basin, by assessing the indices of impendance, congestion (CI), splenoportal (SPI), portal vascular (PVI), portal hypertension index (PHI).

From the cohort of 111 patients those with splenectomy were excluded. The remaining 101 cases were divided into three groups – patients with low, middle and high portal hemodynamics disorders severity.

The overall assessment of patients with portal hemodynamics disorders was based on 16 ultrasound and dopplerography parameters system [5, 6]. The selection of these 16 parameters was performed on the basis of statistical analysis. A set of operations carried out by specific working processes and techniques was applied during statistical processing:

- Measurement of intensity degree of statistical regularities was performed using correlation coefficient (Spearman correlation);
- Sensitivity, specificity indicators, positive and negative likelihood ratios, confidence levels, area under the ROC (AUROC) curvatures and diagnostic accuracy were calculated;
- Parameters estimation and verification of statistical hypotheses were performed by calculating errors, using t-criterion and the degree of veracity of "p".

A further analysis based on all 16 criteria segmentation [4], allowed the reduction of parameters to six: spleen area, congestion index, PHI, portal vascular index, splenoportal index, portosystemic collaterals' presence.To achieve the main aim of this research we decided to use the methods and algorithms used previously to formalize the field of ultrasound examination for pathologies of hepato-pancreato-biliary region [7, 8] and diagnosis of early stages of non-alcoholic fatty liver disease [9].

Results and discussion

Both segmentation and cluster analysis used in this research are based on the hypothesis that liver condition worsening acts specifically on each parameter. Each of the six parameters was subjected to the segmentation procedure. Initially the data about 101 patients were divided into three groups: 21 with low severity portal hemodynamics disorders; 45 with middle severity portal hemodynamics disorders; 35 with high severity portal hemodynamics disorders. Subsequently, data were selected for each parameter and arranged in increasing sets as follows:

Low_Ai = [v1, ..., Vj_low], where i = 1 ... 6; j_low = 21; V1, ..., Vj_low – i parameter values for 21 patients with low severity portal hemodynamics disorders and V1 is the minimum value, but Vj_low – maximum value.

Middle_Ai = [v1, ..., Vj_middle], where i = 1 ... 6; j_mi-

ddle = 45; V1, ..., Vj_middle - parameter values of 45 patients with portal hemodynamics middle severity disorders and V1 is the minimum value and Vj_middle – maximum value.

High_Ai = [V1, ..., Vj_high], where i = 1 ... 6; j_high = 35; V1, ..., Vj_high – i parameter values of 35 patients with portal hemodynamics high severity disorders and V1 is the minimum value and Vj_middle – maximum value.

Taking into consideration that Low_Ai, Middle_Ai, High_Ai sets are arranged in ascending order, for each parameter 2, 3 or 4 values can be emphasized, which are cut-offs:

1. Middle_Ai.V1;
2. High_Ai.V1;
3. Low_Ai.Vj_low, IF Low_Ai.Vj> High_Ai.V1;
4. Middle_Ai.Vj_low, IF Middle_Ai.Vj> High_Ai.V1;

Respectively, each range of values of six parameters can be divided into 3, 4 or 5 sub-segments.

For each sub-segment the confidence level in one of three conclusions was calculated. This confidence level corresponds to the probability of presence of one of the three conclusions, if the corresponding parameter has any value in this subsegment. This model has been used in many applications in domain of image processing and medical data processing, as well as segmentation of medical video sequences.

At the stage of clustering, from the sub-segments, which can be described by a logical reasoning and a general conclusion, clusters were formed, but the reasonings were formalized in the form of production rules of IF <condition> THEN <conclusion> type. The condition is made of the characteristics of the sub-segments, which form the given cluster.

The production rules are among the most popular methods of knowledge presentation in medical informatics field.

Using the proposed principle of segmentation, "Spleen area", "Congestion index", "Splenoportal index", "PHI", "Por-

Table 1

Results of six imaging diagnostic criteria segmentation

Spleen aria	**x<57**	**57<=x<113**	**113<=x<206**	**206<=x**
Low*	66.67%	17.91%	0	0
Middle*	33.33%	52.24%	36.36%	0
High*	0	29.85%	63.64%	100%
Congestion index	**x<0.07**	**0.07<=x<0.11**	**0.11<=x<0.18**	**0.18<=x**
Low*	80.00%	29.79%	0	0
Middle*	20.00%	61.70%	38.89%	0
High*	0	8.51%	61.11%	100%
Splenoportal index	**x<29%**	**29%<=x<=60%**	**60%<x<=67%**	**67%<x**
Low*	100%	24.29%	0	0
Middle*	0	52.86%	35.00%	0
High*	0	22.86%	65.00%	100%
Portal vascular index	**9<=x**	**7<=x<9**	**x<7**	
Low*	28.57%	0	0	
Middle*	61.90%	29.41%	0	
High*	9.52%	70.59%	100%	
PHI	**x<1.5**	**1.5<=x<1.6**	**1.6<=x<2.7**	**2.7<=x**
Low*	100%	64.29%	0	0
Middle*	0	35.71%	68.42%	0
High*	0	0	31.58%	100%
Portosystemic collaterals' presence	**0**	**1**	**2**	**3**
Low*	62.50%	38.10%	10.53%	3.57%
Middle*	37.50%	47.62%	52.63%	39.29%
High*	0	14.29%	36.84%	57.14%

* Low - confidence level of conclusion: low severity of portal hemodynamics disorders.
Middle - confidence level of conclusion: middle severity of portal hemodynamics disorders.
High - confidence level of conclusion: high severity of portal hemodynamics disorders.

Table 2

Scoring for portal hemodynamics disorders severity in liver cirrhosis assessment by duplex ultrasound

Measure	1 point	2 points	3 points	4 points	5 points	6 points
Spline area		x<57	57<=x<113		113<=x<206	206<=x
Congestion index		x<0.07	0.07<=x<0.11		0.11<=x<0.18	0.18<=x
PHI	x<1.5	1.5<=x<1.6		1.6<=x<2.7		2.7<=x
Portal vascular index			9<=x		7<=x<9	x<7
Splenoportal index	x<29%		29%<=x<60%		60%<=x<67%	67%<x

tosystemic collaterals' presence" parameters were divided into four sub-segments, and "Portal vascular index" in 3. For each sub-segment the confidence level in one of those three conclusions was calculated (tab. 1).

Analyzing the obtained results, it was found that the parameter "Portosystemic collaterals' presence" was less informative to differentiate portal hemodynamics disorders severity in liver cirrhosis. As a result, the six parameter system has been reduced to five.

At the next stage there was realized clustering of portal hemodynamic disorders severity assessment domain based on results of five imaging diagnostic criteria segmentation. Cluster analysis (or clustering) is the task of grouping a set of patients with portal hemodynamics disorders in such a way that patients in the same group (called a cluster) are more similar to each other than to those in other groups. More similar in the sense of disorder severity description based on five imaging diagnostic criteria. Seven clusters were identified. Taking into consideration the logical reasoning of each cluster expressed in the production rules and their role in the overall assessment of portal hemodynamics severity disorders, a scoring system was developed and the way of its interpretation was proposed (tab. 2).

Portal hemodynamics disorders severity was classified in: low severity, middle severity and high severity (tab. 3).

Table 3

Scoring interpretation

Total points	Portal hemodynamics disorders severity	Confidence level
9-10	Low	More than 90%
11-12	Low to Middle	Up to 70%
13-16	Middle	Up to 68%
17-24	Middle to High	Up to 65%
25-30	High	More than 95%

Two ways of applying the obtained results in this research can be pointed out:

1. The scoring system can be used directly as a means of differential diagnosis of liver cirrhosis;

2. The decision rules in the form of productions, obtained during the clustering stage, represent for computer scientists a formalized knowledge that can be used to develop medical information systems;

The obtained scoring system and its way of interpretation were validated in actual clinical practice. This process demonstrated their efficacy and veracity. In addition, the possibility of their use in assessing the dynamics of liver cirrhosis was observed.

Conclusions

For a broader test the authors intend to use the obtained results to develop computer-aided tools (desktop, web and mobile versions) for the evaluation and classification of portal hemodynamics disorders severity.

At the moment, a condition for the utilization of the proposed approach is that all five parameters of the scoping system should indicate any deviations from the norm. The proposed methodology is foreseen to be used in future in cohorts of patients with some additional restrictions as: patients with one or more normal parameters, patients after splenectomy, etc.

References

1. Procopeț B, Tantau M, Bureau C. Are there any alternative methods to hepatic venous pressure gradient in portal hypertension assessment? *J Gastrointestin Liver Dis.* 2013;22(1):73-78.
2. Child CG, Turcotte JG. Surgery and portal hypertension. Child CG. The liver and portal hypertension. Philadelphia: Saunders, 1964;50-64.
3. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *British journal of surgery.* 1973;60(8):646-649.
4. Tambala C, Secrieru Iu, Puiu S. Evaluation of severity of portal hemodynamic disorders using segmentation analysis. Book of Abstracts of 27th Congress of European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) - EUROSON2015, Athens, Greece, November 6-8;102.
5. Țâmbală C, Țurcanu V, Dumbravă V-T, et al. Portal hemodinamics depending on the severity of hepatic cirrhosis. *Public health, economics and management in medicine*. 2015;4(61):82-85.
6. Țâmbală C. Dopplerographic haemodynamic predictive parameters for portal hypertension associated with hepatic cirrhosis. *Curierul medical.* 2015;58(4):20-24.
7. Cojocaru S, Gaindric C, Popcova O, et al. SonaRes Platform for Development of Medical Informatics Applications. In: Proceedings of the 3rd International Conference on Nanotechnologies and Biomedical Engineering ICNBME-2015, September 23-26, 2015, Chisinau. ISSN 1433-9277. Springer, IFMBE Proceedings, Volume 55. doi 10.1007/978-981-287-736-9.
8. Secrieru Iu. SonaRes methodology enhancement using knowledge discovery technique. In: *Proceedings IMCS-50* – The Third Conference of Mathematical Society of the Republic of Moldova. IMCS, Chisinau, Moldova, August 19-23. 2014;557-562.
9. Secrieru Iu, Cojocaru S, Gaindric C, et al. Classification of Early Stages of NAFLD Based on Dual Diagnostic Methods. *Computer Science Journal of Moldova*. 2015;23(3):376-385.

REVIEW ARTICLES

Spontaneous intracerebral supratentorial hemorrhage: general aspects and updates in surgical treatment

***E. Condrea[1], V. Timirgaz[1], N. Rotaru[3], S. Groppa[2]**

[1]Laboratory of Neurosurgery Anesthesia and Reanimation, Institute of Neurology and Neurosurgery
[2]Department of Neurology, Institute of Emergency Medicine
[3]Department of Radiology and Medical Imaging, Nicolae Testemitsanu State University of Medicine and Pharmacy
Chisinau, the Republic of Moldova

*Corresponding author: condrea.eugeniu@gmail.com. Received November 30, 2015; accepted February 05, 2016

Abstract

Background: Spontaneous intracerebral hemorrhage (SIH) accounts for 9 to 25% of all strokes and is associated with a high morbidity and mortality, with less than 40% of affected persons surviving 1 year. The condition commonly presents a sudden onset of focal neurological deficits with accompanying headache, nausea, vomiting, elevated blood pressure and altered consciousness. Medical treatment commonly includes airway support, blood pressure control, management of cerebral edema, symptomatic therapy such as anticonvulsive medication, anticoagulation reversal etc. Different surgical options such as open craniotomy, stereotactic aspiration, endoscopic evacuations with or without thrombolysis have also been considered. Most of these techniques have already been implemented successfully in the Republic of Moldova. According to the data of the Institute of Neurology and Neurosurgery and the Institute of Emergency Medicine for the period 2011-2014, just within these two institutions were performed 137 neurosurgical interventions, including 67 interventions involving minimally invasive techniques with local fibrilolysis and 70 interventions involving other minimally invasive surgery or conventional craniotomy. The obtained results are in concordance with those reported by other European institutions.

Conclusions: The continuous efforts to improve the outcome of SIH during the recent years have led to the development of a variety of minimally invasive techniques, most of which have already been adopted by the autochthonous surgeons. New randomized controlled trials are required to establish the suitability of these techniques for different clinical situations and SIH localizations.

Key words: spontaneous intracerebral hemorrhage, supratentorial hematoma.

Introduction

Definition. Intracranial hemorrhages can be classified by anatomical and etiological aspects. According to anatomical aspects, can be distinguished parenchymatous, subarachnoid, subdural, epidural, supratentorial and infratentorial hemorrhages. From etiological point of view, intracranial hemorrhages can be further categorized into primary or spontaneous and secondary hemorrhages [1,2]. Spontaneous intracerebral hemorrhage (SICH) represents blood effusion in cerebral parenchyma that is nontraumatic and without any known cause of hemorrhage (AVM, cerebral aneurysm or tumor). Spontaneous intracerebral hemorrhages (SICHs) are considered medical emergencies, commonly having a clinical course similar to an intracranial expansive process, with early neurological deterioration within the first few hours after onset [3.5]. Based on their location, supratentorial SICHs can be further divided into lobar or superficial (situated in cortical and subcortical areas of frontal, temporal, parietal and occipital lobes) and central or deep (localized in the areas of nucelus caudatis, globus pallidus, thalamus, internal capsule, white periventricular substance or cerebral ventricles), while infratentorial SICHs can involve the cerebellum, pons and the brain stem. About 1/3 of SICHs have lobar localizations, and about 2/3 of SICHs have bazal or infratentorial localizations [2,6,7]. Overall, supratentorial SICHs represent over 80% of all SICHs [8,9]. According to the results of STICH (Surgical Trial in Intracerebral Hemorrhage) trial, about 39-40% of supratentorial SICHs were lobar, 42% were deep (involving basal ganglia and thalamic nuclei), 17-19% had mixed locations and 1% could not be evaluated [10].

Epidemiology. Worldwide incidence varies between 10 and 40 cases per 100,000 population and increases with age [4, 11, 12]. The pathology affects a substantial proportion of the population in Europe and worldwide, representing 9-27% of all strokes [262]. Studies performed in the last decade indicate that SICH represents 10-15% of all strokes in Europe, USA and Australia, 20-30% of strokes in Asia [June 13-17], about 10% of strokes in high-income countries and 20% of strokes in middle and low-income countries [18, 19].

It is also known that intracerebral hematomas represent the third leading cause of death after cardiovascular diseases and cancers, accounting for 12.5 to 15% of overall mortality and being a major cause of disability. Reported mortality during the first month after SICHs varies between 30-59%, with an overall survival of less than 40% at 1 year and less than 20% at 10 years [13, 17, 20-23]. Among the survivors, disability reaches 70-80% [2, 3, 24], with only 10% of patients becoming functionally independent at 1 month and about 20% at 6 months [12, 17, 20, 25, 26].

Etiology, pathogenesis and pathophysiology. Predisposing factors for SICHs include modifiable risk factors (hypertension, diabetes, alcohol abuse, smoking, poor diet, obesity, anticoagulation therapy, previous stroke, illicit drugs

consumption, especially cocaine) and non-modifiable risk factors (male sex, age, ethnicity - African or Asian, genetic predisposition, brain amyloidosis, various coagulopathies). The main risk factors (male sex, age, hypertension, alcohol abuse, smoking, diabetes, poor diet, abdominal obesity and physical inactivity) account for over 80% of the overall risk of stroke worldwide [18, 27]. Association of additional risk factors, such as high serum level of certain apolipoproteins, increases the risk up to 90% [27]. Most authors agree that from all risk factors, the most important are hypertension and cerebral amyloid angiopathy [1, 2, 15, 17, 28, 29]. Thus, chronic hypertension is responsible for 50-70% of all SICHs [15, 17, 30]. The disease leads to small structural changes of the brain vessels, being associated with atherosclerosis, lipohialinosis and formation of micro aneurisms. A variety of risk factors can also lead to so-called *small brain vessel disease*, which is the underlying pathology in many cases of SICHs. The prevalence of cerebral small vessel disease in general population increases with age and also leads to progressive cognitive changes and vascular dementia [2, 6, 15, 18, 26, 29].

As the brain hematoma expands, it increases local pressure affecting the brain tissue and tearing adjacent vessels. Coagulation disorders and hypertension predispose to rebleeding in the early stages. The mass effect of the hematoma further increases intracranial pressure, causing significant damage to adjacent brain structures and also affecting distant regions by shifting the midline structures to the contralateral side and even resulting in various degrees of brain herniations. If the circulation of cerebrospinal fluid is disturbed, hydrocephalus occurs [18, 31, 32].

Pathophysiological changes of supratentorial SICH were studied in detail clinically and experimentally [29, 32, 33]. Mechanical compression of local microcirculation with subsequent release of vasoconstrictor substances from hematoma causes a marginal zone of ischemia called secondary or perilesional ischemia. Various terms such as "ischemic penumbra" or "tissue at risk" have been proposed to describe this altered functional brain area, but potentially recoverable [20, 29, 32-35]. Some authors suggest that perilesional hypoperfusion is rather a consequence of reduced metabolic demand than a true tissue ischemia [6, 14]. Various degrees of perilesional hypoperfusion with or without "spot" sign on CT angiography, have been reported in about 60% of patients with acute SICH [36]. That's why the reason for surgical treatment in SICHs is not only to eliminate the mass effect, but also to reduce the toxic effects of blood components for potential brain tissue recovery in the ischemic penumbra [29, 32, 37, 38].

Another pathogenic factor is related to the brain edema, which increases over several days, leading to mass effect and raised intracranial pressure, secondary neuronal damage and neurological deterioration. Disruption of the blood-brain barrier and serum protein leakage into extracellular space is followed by an increase in osmolarity and release of biologically active substances (arachidonic acid, histamine) with associated development of vasogenic edema (extracellular). Disruption of the energy metabolism of the cell membranes and cellular wall pumps leads to fluid shift into the cells and development of cytotoxic edema (intracellular). In the subsequent phase, the lysis of red blood cells with release of hemoglobin metabolites, inflammatory cytokines, matrix metalloproteinases, iron and thrombin triggers generation of free radicals with associated inflammatory, neurotoxic and apoptotic effects [15, 20, 29, 32, 33, 35]. Perilesional edema peaks at 72 hours and usually persists for 5 days, although it may persist for up to 2 weeks [2, 6, 20].

Re-bleeding, hematoma expansion and intraventricular eruption are major predictors of death in the acute phase of the SICHs or severe disabilities in survivors [4, 5, 14, 16, 39-43]. Intraventricular extension occurs in 30-45% of patients with SICHs, depending on the size and location of the bleeding [3, 17, 26, 30, 32, 41, 44]. The overall mortality in patients with intraventricular hemorrhage is 5 times higher than in patients with isolated SICHs [45]. Since the rigid shape of the skull limits the ability of volumetric expansion of its content, hematomas with a volume exceeding 150 ml inevitably lead to death [18]. Hematoma growth is also associated with increased mortality and poor functional outcomes, regardless of its initial volume or other associated factors.

Three definitions have been used to define the growth of SICHs: (1) any increase in size of SICH, (2) an increase of ≥ 33% or ≥ 12.5 ml and / or (3) interval radial increase in size over 1 mm confirmed at computed tomography (CT) at 24 hrs compared with the original CT [39, 46]. Identification of techniques for predicting the expansion of SICHs remains a priority of many research studies [21, 47]. Among the proposed methods for estimating the probability of hematoma growth can be mentioned determination of density and hematoma shape at CT scanning [18, 46] or the presence of the "spot" sign on CT angiography [18, 36, 47, 48]. According to the published results, heterogeneous density on CT independently predicts expansion of SICH, the irregular shape of hematoma being also associated with its expansion [48]. The presence of the "spot" sign on CT angiography represents another independent predictor of hematoma expansion, increased mortality and a poor prognosis [36, 47]. In addition, the "spot" sign allows patient selection for individualized therapeutic regimens such as administration of early hemostatic treatment (recombinant activated factor VII), more aggressive reduction of blood pressure and / or surgical interventions [36].

Staging of intraparenchimal hemorrhage. SICH is not a monophasic event and includes three distinct phases: (1) initial hemorrhage, (2) expansion of the hematoma and (3) perihematomal edema [14, 42]. Disease progression and subsequent results are influenced primarily by two factors: hematoma expansion and cerebral perihematomal edema. After the initial bleeding, hematoma reaches its maximum size in 15-20 minutes, even though occasionally the bleeding may continue for up to 6 or even 24 hours. Elucidating the cause of hematoma expansion (on-going bleeding or re-bleeding from one or more vessels) confirmed by CT is particularly useful for selecting the treatment strategy [6, 14].

Histologically can be distinguished 5 phases of intraparenchymal hematomas that are based on cellular changes during the process of degradation and absorption of blood

products. These phases are also distinguished at brain MRI as follows: hyperacute phase (from onset to 12 hours), acute phase (from 12 hours to 2 days), early subacute phase (from 2 to 7 days), late subacute phase (from 8 days to one month) and chronic phase (after one month) [49].

Clinical picture

Symptoms of SICHs can be divided into general and focal. The clinical manifestations may vary depending on hematoma location, size and eruption into the ventricular system [1, 4, 5, 12, 14, 30, 41]. The onset is usually sudden with headache, vomiting, seizures and / or development of focal neurological deficits. In the acute phase can be encountered alterations of consciousness (from sleepiness to coma), signs of meningeal irritation, motor deficits (hemiparesis, hemiplegia), dysmetria, cranial nerve palsy (especially involving oculomotor nerve), various autonomic dysfunctions, etc [4, 6, 12, 18, 30, 50]. Depending on the affected brain regions, the clinical presentation can range from minor neurological deficits to fatal herniation syndromes resulting from hematoma expansion, prominent mass effects and increased intracranial pressure [42]. Although the clinical picture alone is insufficient to reliably differentiate SICHs from ischemic strokes [14, 30, 50], it maintains its relevance for prompting imaging and laboratory investigations as well as for initiating a treatment plan, taking into account the fast dynamics of SICHs.

For obtaining a consensus among institutions, a better communication and a more accurate assessment of neurologic status and its dynamics, a number of neurological deficit scales and functional status scores have been adopted internationally.

Table 1

Glasgow Score(GCS)

Components	Grading	Points
Eye opening	Does not open eyes, even under pressure	1
	Opens eyes in response to painful stimuli	2
	Opens eyes on verbal command	3
	Opens eyes spontaneously	4
Motor responce	No response	1
	Extension to painful stimuli (decerebrate response)	2
	Abnormal flexion to painful stimuli (decorticate response)	3
	Flexion / Withdrawal to painful stimuli	4
	Localizes painful stimuli	5
	Obeys commands	6
Verbal responce	Makes no sounds	1
	Incomprehensible sounds	2
	Utters inappropriate words	3
	Confused, disoriented	4
	Oriented, converses normally	5

Among the most common can be listed: Glasgow Coma Scale (GCS) is the most common scoring system used to describe the level of consciousness in a person with brain injury. It is composed of three parameters (best eye opening, best motor response and best verbal response), the overall score varying between 3 and 15 (Table 1). A score of 13 or higher correlates with a mild brain injury, a score of 9 to 12 correlates with a moderate injury, and a score of 8 or less correlates with a severe brain injury. A diagnosis of coma corresponds to a

Table 2

ICH score and ICH-GS score [53]

Components	ICH-GS Score		ICH Score	
	Grading	Points	Grading	Points
Age (years)	< 45	1	< 80	0
	45 - 64	2	≥ 80	1
	> 65	3		
GCS (points)	13 - 15	1	13 - 15	0
	9 - 12	2	5 - 12	1
	3 - 8	3	3 - 4	2
ICH Localization	Supratentorial	1	Supratentorial	0
	Infratentorial	2	Infratentorial	1
IVH	Yes	1	Yes	0
	No	2	No	1
ICH Volume (ml)			<30	0
			≥30	1
Supratentorial ICH volume (ml)	< 40	1		
	40 - 70	2		
	> 70	3		
infratentorial ICH volume (ml)	< 10	1		
	10 - 20	2		
	> 20	3		

score below 7-8. The summation to provide an overall score for coma (from 3 to 15) results in some loss of information, but still proves valuable for a variety of purposes, including triage and epidemiological studies [45, 51].

ICH (intracerebral hemorrhage) **score**, original and modified, represents reliable grading scales for patients with intracerebral hemorrhage evaluated at presentation, allowing risk stratification and predicting the mortality in the first 30 days. The ICH scale uses such factors as age, volume of ICH, GCS score and presence of intraventricular hemorrhage (Table 2). Scale range is between 0 and 6 points. Higher ICH scores are associated with increasing mortality during the first month – all patients with a score 0 survive and all patients with a score greater than or equal to 5 die within 30 days [6, 42, 52, 53].

ICH-GS Score (intracerebral hemorrhage-grading scale) developed for SICHs, appears to possess greater sensitivity in predicting in-hospital mortality, mortality at 30 days and post-therapy functional results compared with the original ICH score (Table 2) [53].

FUNC score is another prediction tool for risk stratification and functional outcome at 90 days after stroke [42]. FUNC score ranges from 0 to 11 based on the volume of ICH, age, location of ICH, GCS and cognitive dysfunction (Table 3) [42]. For each patient with ICH, a particular FUNC score value corresponds to the percentage probability of attaining functional independence (Glasgow Outcome Score greater than or equal to 4) at 90 days. A higher score is associated with a greater likelihood of functional independence, defined as GOS ≥ 4 at 90 days. No patients with a FUNC score ≤ 4 reach functional independence and more than 80% of patients with FUNC score of 11 achieve functional independence at 90 days. However, only scores at the extreme ends appear to be clinically useful, while the average scores have a lower predictive value [42].

Table 3

FUNC Score [42]

Components	Grade	Points
ICH Volume (cm3)	< 30	4
	30 - 60	2
	> 60	0
Age (years)	< 70	2
	70 - 79	1
	≥ 80	0
ICH Localization	Lobar	2
	Deep	1
	Infratentorial	0
GCS (points)	≥ 9	2
	≤ 8	0
Pre-ICH cognitive impairment	No	1
	Yes	0
Total FUNC Score	0 - 11	

Rankin Scale is a commonly used scale for measuring the degree of disability or dependence in the daily activities in patients with stroke or other acute neurological disabilities. The scale was developed in 1957 and modified in 1988. The modified Rankin scale ranges between 0 and 6, running from perfect health without symptoms to death: 0 - without symptoms; 1 - no significant disability; able to carry out all usual activities, despite some symptoms; 2 - mild disabilities; able to look after own affairs without assistance, but unable to carry out all previous activities; 3 - moderate disabilities; requires some help, but able to walk unassisted; 4 - moderately severe disabilities; unable to walk without assistance or to care unassisted to own bodily needs; 5 - severely disabled, bedridden, incontinent and requiring constant care; 6 - dead [54, 55].

Barthel Index evaluates 10 basic activities of daily living, which include: (1) feeding, (2) bathing (3) grooming (washing face, combing hair, brushing teeth), (4) dressing (5) bowel control (6) bladder control, (7) the ability to use the toilet, (8) chair transfer, (9) ambulation (10) stair climbing. The total score ranges between 100 points (independent) and 0 points (completely dependent) [54, 56].

GOS score (Glasgow Outcome Score) is a scale for assessing the final state after an acute brain disease. Depending on their recovery, the patients are grouped into 5 categories: (1) good recovery with resumption of normal life despite minor deficits, (2) moderate disability, but relatively independent without needs for assistance in everyday life (employment is possible but may require special equipment), (3) severe disabilities – conscious, but dependent for daily support, (4) persistent vegetative state with prolonged periods of unresponsiveness or minimal responsiveness (5), deceased [45, 52, 54]. The correlation between ICH score and GOS score is negative and statistically significant [52].

Paraclinical diagnosis

Neuroimaging studies are vital to elucidate the diagnosis and etiology of SICHs [4, 6, 42, 57]. Brain imaging is the cornerstone for diagnosing SICHs because hemorrhagic and ischemic strokes can not be differentiated by clinical data alone [4, 6, 42, 57]. Neuroimaging studies are needed not only for diagnosis, but also provide valuable information related to the type of bleeding, its etiology and pathophysiology [4, 49, 57]. Neuroimaging studies include a compulsory brain CT scanning, an optional brain MRI followed by angiography of the cerebral vessels obtained by CT and / or MRI [4, 5, 18, 33, 58].

Brain CT is the investigation of choice for the diagnosis of SICHs, able to establish the diagnosis within minutes from the onset of symptoms and to provide additional details such as the bleeding size and localization. Non-contrast CT remains the "gold standard" for diagnosis, although a variety of new neuroimaging techniques can provide additional information related to pathophysiology of SICHs and their prognosis in individual patients [3, 5, 6, 30, 42]. Brain CT also enables rapid calculation of the volume of bleeding, which may be performed by two methods: the "ellipse" method based on routine CT images and the planimetric method using the neuronavigation station equipment [59]. CT angiography in hyperacute phase, followed by a post-contrast scan can also identify the "spot" sign – one or more hyperintense spots in

hematoma caused by the leak of contrast material into its cavity. Its presence is an independent predictor associated in 60% of cases with hematoma expansion and a reserved prognosis [4, 18, 35, 41, 47, 48]. Carotid angiography is performed when the cause of the bleeding remains equivocal or when a vascular malformation is suspected.

MRI identifies SICHs shortly after their onset [5, 6, 18, 42, 49], being also reliable for detecting chronic iron deposits related to previous bleedings [6, 18, 42, 49]. MRI is especially indicated when the clinical picture and cerebral CT exams cannot establish the final diagnosis or the etiology of bleeding [14, 18, 42, 49]. Initial MRI can be also performed as part of prognostic score protocols for predicting clinical outcomes in acute SICHs [18, 30]. Micro-hemorrhages detected by MRI can be occasionally useful in elucidating the pathophysiology and development of SICHs. Recent studies indicate that transcranial ultrasound has an excellent correlation with cerebral CT for evaluating the degree of bleeding in patients with hyperacute SICHs, therefore the modality can be also considered for early diagnosis and non-invasive monitoring of SICHs [60].

Due to the rapid advances in the field of medical imaging during the last decade and the absence of a standardized international protocol related to SICHs imaging [3, 18, 50], the imaging modalities and employed protocols for managing SICHs may vary considerably across different countries. In most institutions, CT is recommended as a standard imaging procedure for differentiating hemorrhagic from ischemic strokes. CT angiography is performed immediately in case of suspected aneurismal hemorrhages. In general, a younger age and a lobar location of SICH without pre-existing hypertension require a wider variety of diagnostic investigations beyond the initial cerebral CT [18, 61]. The relevance of other investigations such as MRI angiography may depend upon the clinical situation, the choice being also affected by local resources and recommended protocols by the national healthcare systems [18].

Management

While the search for a specific targeted therapy for SICHs continues, excellent medical care likely has a potent, direct impact on morbidity and mortality even now, before a specific therapy is found [3]. Current treatment is targeting a variety of components such as preventing hematoma expansion, reducing the mass effect, minimizing brain injuries and preventing secondary neurological and nosocomial complications [4, 29]. Hospital admission is mandatory, preferably in a specialized neurosurgical department. If such facilities are not available, admission to a Neurology department is also acceptable [18]. Before admission, the treatment is directed at providing basic airway and breathing support, blood pressure control and hemodynamic stabilization, lowering the intracranial pressure, monitoring vital signs etc. [3, 5, 6, 29, 41].

Medical treatment

Medical management is initiated immediately and continues in the intensive care unit, including cardio-respiratory and blood pressure control, reversal of coagulation defects, cerebral edema, intracranial hypertension and seizure management, addressing the risk factors and associated medical conditions etc [15, 17, 26 62]. Most studies show superior results for patients admitted into an intensive care unit, preferably of neurological or neurosurgical profile [5, 6, 18, 63]. Patients with a low level of awareness often require ventilatory support [29]. Although the treatment may vary depending on the patient's condition, it also addresses a number of general principles such as blood pressure control, management of coagulation deficiencies, management of cerebral edema and elevated intracranial pressure, neuroprotective therapy etc [4, 5, 35, 41, 63, 65].

Management of coagulation deficiencies. Congenital or acquired coagulation factor deficiencies worsen the prognosis for SICHs by increasing the rate of hematoma expansion as well as by affecting its subsequent resorption [4, 6, 41]. Patients at risk also include those taking oral anticoagulants and those with qualitative or quantitative platelet abnormalities. Recognition of the underlying coagulopathy allows developing a treatment strategy. For example, in patients with thrombocytopenia or a coagulation factor deficiency, administration of platelets or the appropriate deficient factor is indicated [2-4, 6, 41]. Acquired coagulopathy may be attributed to longstanding liver and/or renal disease, malignancy, or medication. For patients being treated with oral anticoagulants, the medications are immediately canceled and specific antidotes are administered to correct the international normalized ratio (INR) as rapidly as possible [4-6, 14, 41]. Infusions of vitamin K and fresh-frozen plasma (FFP) have usually been recommended for this purpose, but more recently, prothrombin complex concentrates (PCCs) and recombinant factor VIIa (rFVIIa) have emerged as potential therapies [3]. Concominant use of vitamin K with FFP, cryoprecipitate, or clotting factor concentrates can be also used to hasten reversal of oral anticoagulants. Even in patients without any coagulation deficiencies, administration of various hemostatic agents such as aminocaproic acid, tranexamic acid and recombinant activated factor VII has been proposed [5, 18, 63]. Although their routine usage in patients without coagulation deficiencies was associated with enhanced hemostasis and reductions in hematoma growth, the medication did not alter severe disability or mortality rates [14, 35, 41].

Management of hypertension. Arterial hypertension is associated with hematoma expansion and poor prognosis, although a clear causal effect has not been established [4, 14, 35, 41, 64]. Current guidelines suggest aggressive reduction of systolic blood pressure (BP) with intravenous infusion of vasoactive drugs (labetalol, esmolol and nicardipine) only if systolic BP is over 180 mm Hg and/or mean BP is over 130 mm Hg [3-5, 64]. Given the altered cerebral perfusion, the blood pressure reduction should be also gradual, most authors suggesting reducing systolic BP just below 160 mm Hg and/or mean BP just below 110 mm Hg as an initial step [3, 4, 64]. The Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) I Trial, a multi-center prospective study performed during 2004-2008 to determine the appropriate level of systolic

BP reduction with intravenous nicardipine infusion for 18 to 24 hours postictus in subjects with intracerebral hemorrhage who are present within 6 hours of symptom onset, showed that the treatment was well tolerated and reduced the risk of hematoma expansion, neurological deterioration and hospital mortality [6, 14, 35]. The results of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT) I randomized trial also suggested that early intensive blood pressure reduction to systolic values ≤ 140 mmHg initiated within 6 hours of symptom onset appeared to attenuate hematoma expansion in patients with intracerebral hemorrhage. In subgroup analyses, patients recruited within 3 hours and patients with an initial SBP ≥181 mm Hg appeared to have the greatest benefit with intensive blood pressure reduction [14, 35, 66]. The INTERACT-2 trial found that intensive blood pressure lowering in patients with intracerebral haemorrhage reduced the risk of major disability and improved the chances of recovery by as much as 20%, even though no changes in mortality rates were reported [14, 66, 67]. A variety of new studies are also underway. One such trial is the perioperative antihypertensive treatment in patients of spontaneous intracerebral hemorrhage (PATICH) trial, which aims to determine if the intensive preoperative BP reduction improves the overall prognosis and the postoperative outcome [68].

Cerebral edema and intracranial hypertension management. The Intracranial hypertension is an important cause of secondary brain injuries. Elevation of the head of the bed to about 30° promotes displacement of cerebrospinal fluid from the intracranial compartment to the spinal compartment. Medical management can also include sedation, analgesia, osmotherapy with either mannitol or hypertonic saline, controlled transient hyperventilation as well as drainage of cerebrospinal fluid depending on the degree of intracranial hypertension [3, 4, 41, 50, 64, 66]. Even though randomized clinical trials have failed to demonstrate a significant benefit of bolus therapy with mannitol on cerebral blood flow and mortality rates [5, 20, 35], monitoring of intracranial pressure is commonly associated with better functional results in patients with SICHs [23]. Intracranial pressure monitoring and its maintenance within 50-70 mm Hg is especially indicated in patients with a GCS score < 8 and/or evidence of brain herniation, significant intraventricular hemorrhage and hydrocephalus.

Anticonvulsant therapy. Seizures are reported in 4-8% of patients with SICHs, and are more prone to occur in lobar (superficial) hematomas: about 4.2% of cases occur in the first 24 hours and about 8.1% - within 1 month after the onset of SICHs [2, 4, 14]. Their presence is commonly associated with higher rates of complications, increased mortality, and poor functional outcomes in survivors [69]. Seizures in SICHs are usually treated with intravenous administration of lorazepam (0.05–0.10 mg/kg) followed by an intravenous loading dose of phenytoin or fosphenytoin (15–20 mg/kg), valproic acid (15–45 mg/kg), or phenobarbital (15–20 mg/kg). The anticonvulsant therapy can be discontinued if no seizures are noted for one month. Although, no randomized trials have addressed the efficacy of prophylactic antiepileptic medication in SICHs, the option may be considered for patients with lobar hematomas and higher risks for seizures [3, 20, 35, 41, 50, 69]. In addition, 24-hrs electroencephalography (EEG) monitoring should be considered for patients with reduced consciousness and depressed mental status out of proportion to the degree of brain injury [3, 5, 35, 41].

Deep venous thrombosis prophylaxis. Immobilized state and paresis predispose SICHs patients for deep vein thrombosis and pulmonary embolism. The reported incidence of symptomatic venous thromboembolism in SICHs varies between 0.5% - 13%, and that of pulmonary embolism between 0.7% - 5% [41]. Intermittent pneumatic compression devices and elastic stockings are indicated and should be placed on admission on all immobilized patients. Low doses of unfractionated heparin or low-molecular-weight heparins can be considered in patients with hemiplegia, 3-4 days after the onset of SICHs and after ensuring that the intracerebral bleeding stopped [2-5, 35, 50].

Glycemic control. Hyperglycemia has a deleterious effect on cerebral ischemia, being associated with increased mortality and reduced rates of early functional recovery [5, 14, 23, 70]. Even though studies performed in SICHs patients suggest that early glycemic control can improve the outcome [5, 26, 70], there is growing evidence that "enhanced" glycemic control (<2.8 mmol/l or <50 mg/dL) obtained by insulin infusions in patients with acute brain injury may be associated with significantly reduced concentrations of extracellular glucose in the brain [5, 14, 70]. Because of this, many clinicians are reluctant to lower serum glucose if the level is below 10.0 mmol/l (180 mg/dL) [14, 70]. At the moment the optimal management of hyperglycemia in SICHs and the target glucose levels remain to be clarified; however, hypoglycemia should be avoided [3].

Neuroprotection. The goal of neuroprotective agents (such as magnesium, minocycline, deferoxamine) is to favorably influence the cascade of biochemical events triggered by the intracerebral hemorrhage, subsequently leading to neuronal deterioration an cell death [35]. Various neuroprotective management strategies have been studied in SICHs [71]. Although the results suggest that neuroprotective agents may provide incremental improvements, new trials are required to further elucidate their effects and to define their clinical indications [71]. Hypothermia has also been studied among the neuroprotective strategies in patients with ischemic and hemorrhagic strokes. Thus, a pilot study of therapeutic hypothermia in patients with SICHs reported reduction in cerebral edema and perihematomal inflammation [5, 35]. Several other clinical studies, however, showed incremental or little benefits for patients with SICHs treated with NXY-059, mannitol, glycerol, and citicoline [5, 35, 66, 72].

Surgical treatment

Surgical management of SICHs may be required in many clinical situations such as intracranial hematomas greater than 3 cm, a structural vascular lesion or lobar hemorrhage in a young patient, increasing intracranial pressure with neurological deterioration, etc. A variety of procedures including

conventional open craniotomy, simple aspiration, ventriculostomy, endoscopic evacuation, stereotactic aspiration with local fibrinolysis or various combinations have been used for this purpose [20, 35]. However, the decision about whether and when to surgically remove the hematoma and the type of procedures to be used still remain controversial. Surgical evacuation of SICHs is aimed at reducing the mass effect, decreasing intracranial pressure, improving of regional blood flow, minimizing the release of blood degradation products, minimizing cerebral edema and secondary brain injury [5, 29, 64]. The interval from the initial onset of SICHs is commonly divided into 3 stages: ultra-early (less than 7 hours), early (from 7 to 24 h) and delayed (over 24 hours) [73]. Most studies indicate that early stage (7-24 hours) appears the optimal time for surgical interventions [73], while ultra-early brain surgery (within first 4 hours of symptom onset) is often associated with higher rates of rebleeding [73, 74]. The employed surgical techniques used in the evacuation of SICHs can be grouped into several categories such as evacuation by conventional craniotomy, evacuation by endoscopy, evacuation via stereotactic techniques and aspiration methods with local fibrinolysis [1, 3, 63, 75].

Conventional craniotomy involves removing a portion of the skull (a bone flap ranging from about 5x5cm to 10x10cm in size) and conducting open surgery to drain the hematoma and repair the ruptured blood vessel. This represents a major surgical procedure that is typically used when the hematoma is very large, or when it is compressing the brain stem or other centers that control vital functions. Hematoma cavity is cleared and a hemostatic sponge can be applied if needed. The cavity is also drained and the bone flap is fixed. In cases of severe cerebral edema or prolapsing cortex through the surgical wound, the bone flap can be temporarily preserved in the subcutaneous fat of the abdominal region (for later use to close the skull defect).

Evacuation via endoscopy involves drilling a small burr hole in the skull and draining the hematoma using an endoscope. It represents an advanced technique that allows simultaneous monitoring of intracranial pressure and using a variety of instruments for microsurgery such as an operating microscope, laser and ultrasound equipment for clot lysis and aspiration etc. A supraorbital approach through an eyebrow incision has been frequently used for this purpose, being originally described by Justin et al in 2012 [31]. The method is particularly useful for anterior basal ganglia hematomas that are usually elongated in shape, allowing an optimal trajectory along their longitudinal axis with a complete evacuation after a single pass of the endoscopic tube [31]. Other endoscopic approaches may involve using small burr holes on coronal suture for accessing anterior basal ganglia hemorrhages, or in the parietal-occipital region for accessing basal ganglia and thalamus. In superficial lobar SICHs, a small burr hole can be applied just above the hematoma in its closest proximity to the surface [31].

Stereotactic evacuation represents an advanced technique that uses a special stereotactic frame for immobilizing the patient's head. The technique allows a preliminary computer calculation of the puncture route and a greater degree of precision and accuracy than otherwise possible. Apart from aspirating the content of the hematoma, the method also allows ultrasound clot lysis or local administration of fibrinolytic agents (streptokinase, urokinase, recombinant APT etc) [3, 37].

Puncture and aspiration with local fibrinolysis uses CT for guidance and includes several steps: 1) applying a burr hole according to the automatically calculated puncture site and catheter trajectory based on CT data, 2) guiding the puncture cannula into hematoma cavity according to the calculated trajectory, 3) aspiration of the liquid part of hematoma and application of a special catheter in the hematoma cavity for subsequent infusion of thrombolytic agents to enhance clot drainage [63, 74, 76, 77]. Local fibrinolysis and aspiration of the remaining content is then carried out in the postoperative period. A major advantage of this technique is the possibility of being carried out within 20 minutes under local anesthesia in the emergency department relying on a routine brain CT scan [78]. In many institutions, a special navigation system that allows calculating the optimal puncture site and catheter trajectory based on CT data is integrated into the CT angiography scanner for convenience. The catheter can be also inserted under the fluoroscopic guidance and its placement is evaluated by a post-procedural CT scan [79].

Early studies have failed to demonstrate superior outcomes following conventional craniotomy in supratentorial SICHs compared with best medical therapy [5, 16, 80, 81]. This resulted in a more conservative attitude and application of tighter selection criteria for surgical interventions in SICHs [13]. The increasing requirements for convincing evidence in clinical decision making led to the initiation of STICH (Surgical Trial in Intracerebral Haemorrhage) trial, the largest prospective randomized study that was conducted in 83 centers across 27 countries. The study was initiated in 1995 and the final results were published in 2005, concluding that in cases where surgical intervention is not heavily favored by current clinical judgement, early clot evacuation does not offer clinical benefit over conservative management [6, 10, 66]. Thus, after 6 months of follow up, 26% of surgically treated patients versus 24% of patients treated with medication had a favorable outcome. The trial results affected the clinical decision making and surgical interventions were employed less frequent [82]. Noteworthy, however, is that in STICH trial less than 25% of surgeries were minimally invasive [5, 10, 66, 83, 84]. The subgroup analysis of the STICH trial also revealed that patients with lobar superficial hematomas (≤1 cm from the brain surface) without intraventricular hemorrhage who underwent surgery had a more favorable outcome, about 49% of them demonstrating positive results (representing an 8% absolute increase in good outcomes compared with similar subjects in the medical arm). This subgroup of patients was the target of the STICH II study, an international, parallel-group trial undertaken in 78 centers in 27 countries, comparing early surgical hematoma evacuation within 12 hrs of randomization plus medical treatment versus initial medical treatment alone (later evacuation was allowed if judged necessary) [3, 6, 84].

The results of STICH II trial confirmed that early surgery does not increase the mortality or disability at 6 months and might have a small but clinically relevant survival advantage for patients with superficial SICHs without intraventricular hemorrhage, the greatest benefits being obtained in patients with GCS between 9-12 [5, 66, 83, 84]. Other studies and meta-analyses also confirmed the benefits of surgical interventions for superficial SICHs compared to conservative management alone [10].

The continuous search to improve the outcomes of SICHs has lead to the development of minimally invasive techniques. During the last decade, a variety of techniques of minimally invasive surgery, including endoscopic neurosurgery and stereotactic aspiration have emerged and are widely used for treating supratentorial SICHs. Among the advantages of minimally invasive methods can be listed: 1) significantly lower invasiveness and the possibility of being applied earlier than the standard surgical treatment 2) reduced operation time, 3) the option of being performed under local anesthesia, and 4) reduced brain trauma, especially for deep lesions [50, 66]. Recent studies showed that clot reduction with minimally invasive surgery plays an important role in limiting brain edema, reducing cellular damage and neurological deficits after SICHs [40, 85]. A meta-analysis published in 2012, reported that patients with supratentorial SICHs may benefit more from minimally invasive surgery compared with other treatment options [86]. Candidates who can have the greatest benefit from minimally invasive procedures within the first 72 hours from the onset of symptoms are patients of both sexes, aged 30-80 years, with superficial hematomas, GCS ≥ 9, and a hematoma volume between 25-40 ml [86]. However, conventional craniotomy for hematoma evacuation maintains its actuality in patients with GCS between 4 - 8 at admission, those with large hematomas associated with cerebral edema or mass effect compressing the brain stem or centers that control vital functions etc [3, 87-89].

Stereotactic evacuation and the method of puncture and aspiration with local fibrinolysis added new values to the minimally invasive techniques by allowing clot lysis inside the hematoma (using ultrasound waves or irrigation with fibrinolytic agents). Recent studies actually report that the enthusiasm for endoscopic aspiration seems to be declining in the context of emerged options allowing local instillation of fibrinolytic agents in the hematoma cavity for clot thrombolysis (streptokinase, urokinase, rTPA [65, 90]. The rate of reported favorable results of SICHs treated with stereotactic aspiration varies between 20.3% and 55.6% [74, 81, 91]. The puncture does not cause significant brain damage and accelerates the recovery of cerebral function, avoiding the need for an open craniotomy or general anesthesia [37, 38]. An increasing number of studies have also shown that stereotactic aspiration and local thrombolysis are safe and effective techniques in reducing the volume of SICHs [37, 85, 92]. However, none of these studies provided conclusive evidence for the choice of a treatment method according to patient's clinical condition, hematoma location, neurological status and associated disorders [93, 94]. To answer these questions, a number of randomized clinical trials such as MISTICH or MISTIE have been started. The MISTICH (Minimally invasive surgery treatment for the Patients with spontaneous supratentorial intracerebral hemorrhage) study is a multi-center, prospective, randomized, assessor-blinded, parallel group, controlled clinical trial that began in 2012 and was designed to determine whether minimally invasive surgeries could improve the prognosis for patients with SICHs compared with craniotomy [95]. The MISTIE (Minimally Invasive Stereotactic Surgery plus recombinant tissue plasminogen activator for intracerebral hemorrhagic Evacuation) trial was designed to investigate the difference between surgical intervention plus rtPA and standard medical treatment for SICHs management [16, 80, 96, 97]. Preliminary results revealed that minimally-invasive surgery plus rtPA shows greater clot resolution than traditional medical management. As a result of this, a phase II (MISTIE II) trial was designed to determine the safety and efficacy of using minimally invasive surgeries combined with rt-PA administration. A variety of other studies exploring new approaches and new avenues to improve the outcome of minimally invasive surgical techniques are also underway.

Surgical techniques applied in the Republic of Moldova

Neurosurgical institutions in Moldova have accumulated valuable experience in the treatment of supratentorial SICHs, including minimally invasive techniques that are used worldwide. According to statistical data from the National Centre for Health Management, the incidence of intracerebral bleeding in Moldova comprised 677 cases in 2010, 632 cases in 2011 and 707 cases in 2012, with an average record of 672 cases annually. According to the latest publications, SICHs (primary bleedings into the brain parenchyma without a known cause) represent 66% of intracerebral bleedings [58], and supratentorial SICHs represent about 86.7% of all SICHs [8]. Thus, the annual incidence in the Republic of Moldova represents about 447 cases of SICHs, from which 388 are supratentorial.

According to institutional statistics reported by the Institute of Neurology and Neurosurgery and the Institute of Emergency Medicine, only in these two institutions, during 2011-2014 were performed 137 nerosurgical interventions for SICHs. From these, 67 interventions employed the puncture and aspiration technique with application of local fibrinolysis, and 70 interventions employed other minimally invasive techniques or conventional craniotomy. Of note is that almost 50% of surgical interventions were performed using the puncture and aspiration with application of local fibrinolysis, which is one of the most advanced methods for treating SICHs at the international level. Moreover, some details of the technique were further refined by our experts, who obtained two patented inventions in this area.

An example of supratentorial SICH treated using the puncture and aspiration method with application of local fibrinolysis is shown in fig. 1. The technique can be divided into 4 steps:

1. **Application of the burred hole**. The procedure was

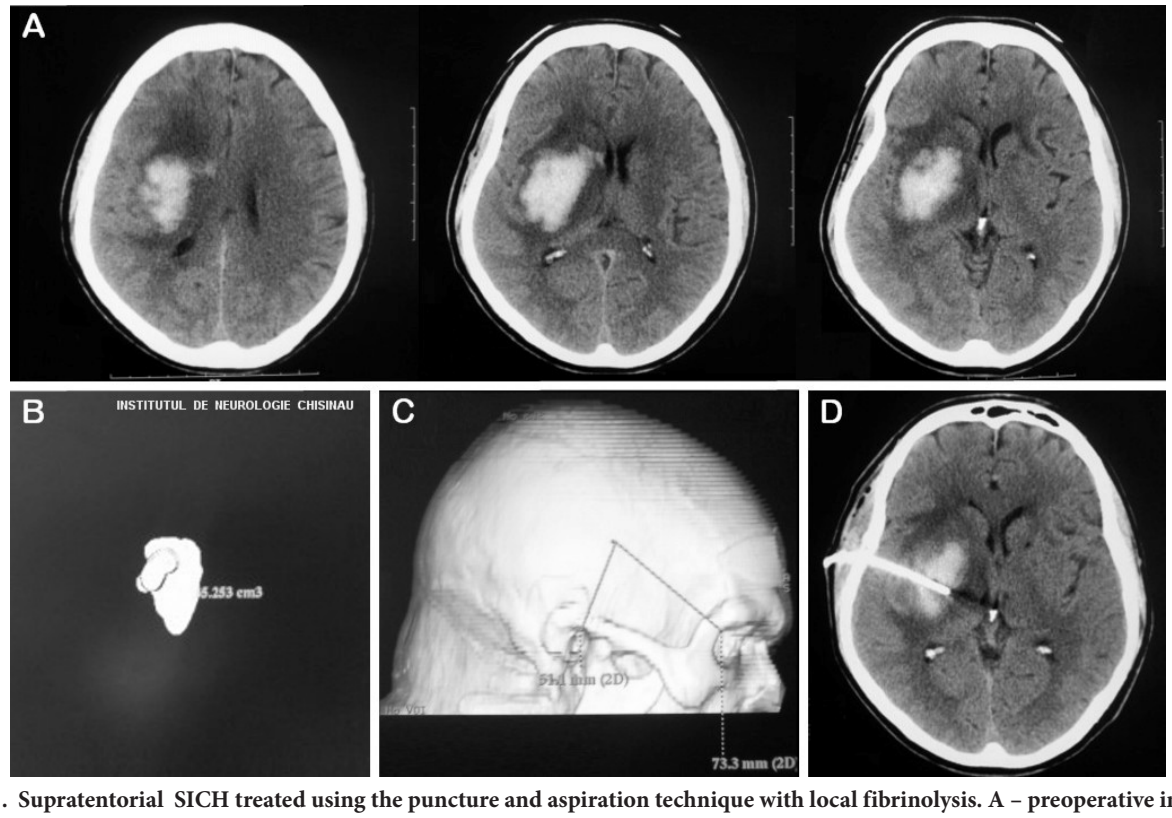


Fig. 1. Supratentorial SICH treated using the puncture and aspiration technique with local fibrinolysis. A – preoperative images showing an intracerebral hemorrhage into the right cerebral hemisphere, B – estimation of the volume of hematoma, C – 3D computer modelling allowing calculation of the puncture trajectory and its correlation with external anatomical structures, D – postoperative images confirming the position of the catheter and post-therapy changes.

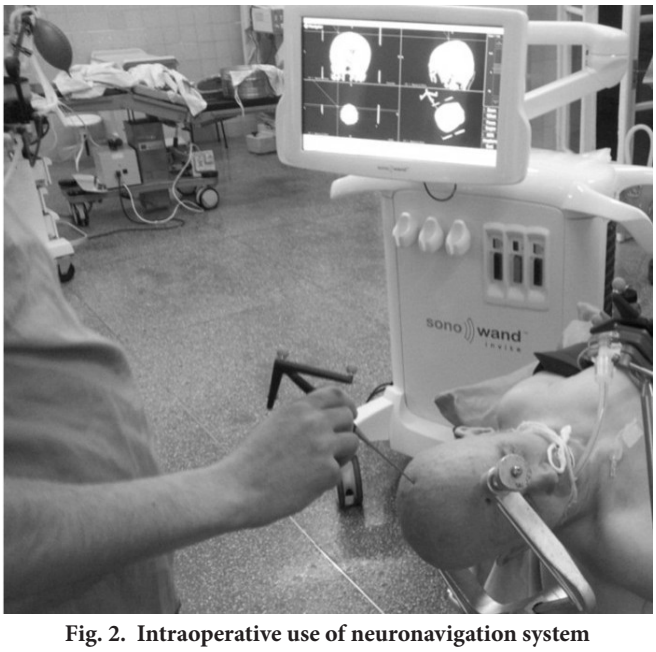


Fig. 2. Intraoperative use of neuronavigation system (SonoWand, USA) in the Institute of Neurology and Neurosurgery in Chisinau. The patient's head is stabilized with rigid pinning fixation (Mayfield frame).

performed using preoperative CT images, allowing 3D modelling of external anatomical landmarks (such as the external acoustic meatus and the lateral margin of the orbit). The calculations were subsequently applied intraoperatively for carrying out the procedure using a special device patented by our team (patented invention no. 824 of 11.06.2013).

2. Puncture and drainage of intracerebral hematoma. Standard radiopaque silicone catheters for external ventricular drainage can be also used for draining intracerebral hematomas. The catheters should have an internal diameter of 1.5 -2.5 mm, a 30 cm length, visible gradations at 5, 10 and 15 cm, as well as additional side perforations at the blunt end of the catheter to increase the irrigation surface with a fibrinolytic agent. In some cases, a special intraoperative neuronavigation system (SonoWand and Medtronic, USA, fig. 2) was also employed. The neuronavigation system provides a higher precision and allows a more accurate placement of the catheter, which proved particularly useful for accessing small SICHs (≤30 ml) located deeply within basal ganglia.

3. Aspiration of the liquid part of hematoma. In most cases, about 2-10 ml of the liquid content can be aspirated immediately after the puncture, depending on the evolution stage of hematoma. After aspirating the liquid content, the catheter is secured for subsequent fibrinolysis. An intraoperative image of an inserted catheter is displayed in fig. 3. As the hematoma decreases in size, the catheter may require repositioning. A special guided catheter was developed for this purpose in the Institute of Neurology and Neurosurgery in Chisinau (patent invention no. 795 of 01.16.2014). The end of the catheter can change its direction at any angle, allowing an easy re-positioning without the need for a surgical intervention.

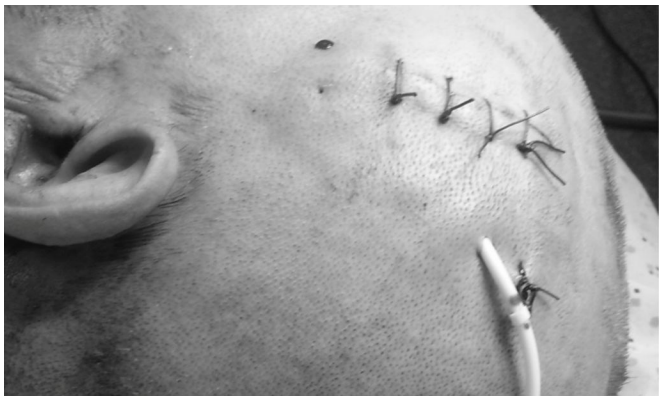


Fig. 3. An inserted catheter applied for external drainage of an intracerebral hemorrhage. Following the aspiration of the liqid part of hematoma, the catheter was secured. A fibrinolytic agent is then injected through the catether in the hematoma cavity for local fibrinolysis of the remaining blood clots.

4. Performing local fibrinolysis. A second-generation fibrinolytic agent – recombinant prourokinase (Hemaza) was administered for this purpose (5,000 IU every 6-10 hours). The number of procedures varied from 3 to 6 depending on the size of residual hematoma, with an average duration of 48 hours. The decision to stop the fibrinolysis and remove the catheter was based on the follow-up CT scans.

The obtained results showed many advantages of this technique such as: a lower rate and a reduced period of tracheal intubation, a lower rate of local postoperative complications, a reduced length of hospital stay, a lower overall mortality, a more frequent initiation of an early rehabilitation program with relatively better functional outcomes. The results are in agreement with those reported by many leading institutions at the European and international level. It should be noted that other treatment methods maintain their actuality depending on the type of hematoma and a variety of other factors, including the bleeding size and location as well as the patient's clinical condition and associated pathology. The experience gained in the Institute of Neurology and Neurosurgery allowed the development of a formal protocol for managing patients with suspected supratentorial SICHs that can be applied in neurological and neurosurgical units throughout the country (fig. 4).

Conclusions and recommendations

1. All patients with symptoms suspicious for SICH require a complex assessment, regardless of hematoma stage.
2. Consulting a neurologist or a neurosurgeon is mandatory for detailed evaluation and for establishing an early treatment strategy.
3. Immediate admission of patients with SICHs in specialized ICU departments or Stroke units increases the chances for survival and for a better recovery of neurological deficits.
4. After discharge from specialized institutions, patients with SICHs require periodic assessments at 1, 3, 6 and 12-month intervals for detailed evaluation of their functional status, interval response to therapy and for preventing recurrences by controlling risk factors and associated diseases.

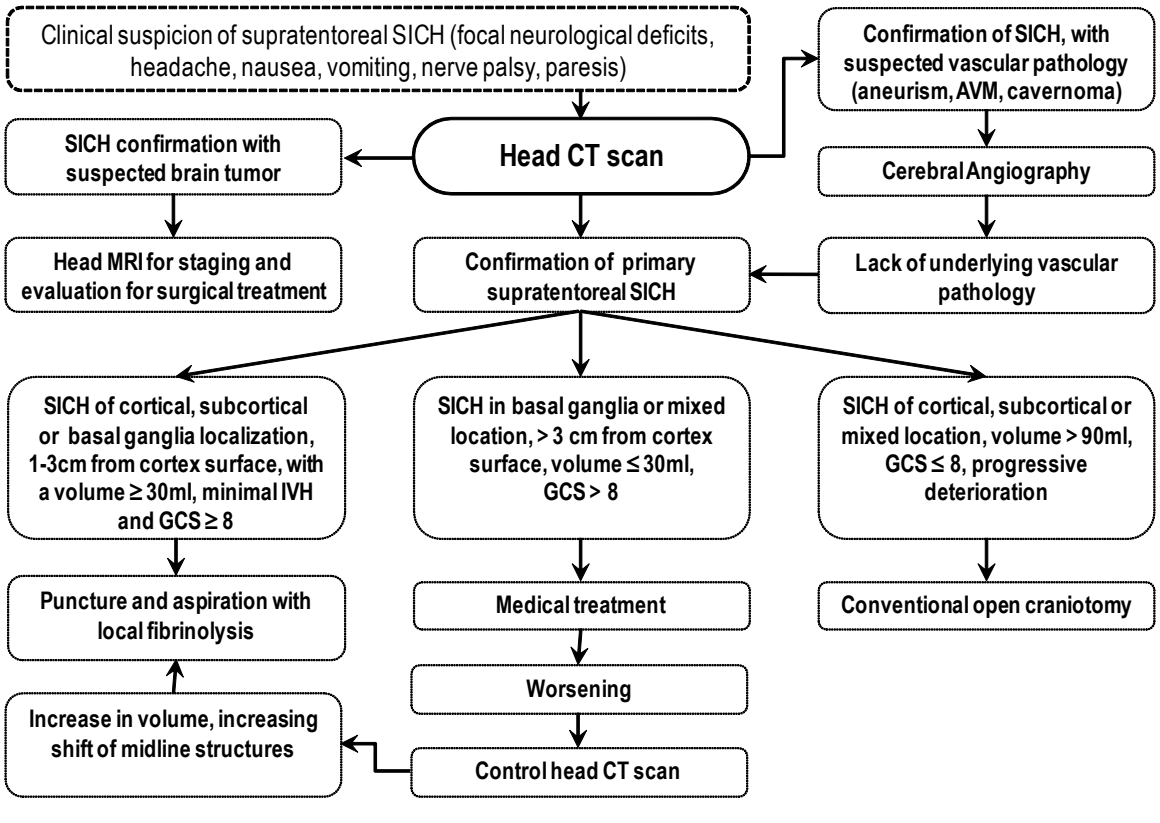


Fig. 4. Developed protocol for managing patients with suspected supratentorial SICHs.

References

1. Reichart R, Frank S. Intracerebral Hemorrhage, Indication for Surgical Treatment and Surgical Techniques. Open. *Crit. Care. Med. J.* 2011;4(1):68-71.
2. Aguilar MI, Freeman WD. Spontaneous intracerebral hemorrhage. *Semin. Neurol.* 2010;30(5):555-564.
3. Morgenstern L, Hemphill J, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2010;41(9):2108-29.
4. Beslac-BumbasIrevic L, Paden V, Jovanovic D, et al. Spontaneous intracerebral hemorrhage. *Period. Biol*. 2012;114(3):337-45.
5. Hemphill JC, Greenberg SM, Anderson CS, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2015;46(7):2032-60.
6. Aguilar MI, Brott TG. Update in intracerebral hemorrhage. *Neurohospitalist*. 2011;1(3):148-159.
7. Sacco S, Marini C, Toni D, et al. Incidence and 10-year survival of intracerebral hemorrhage in a population-based registry. *Stroke*. 2009;40(2):394-399.
8. Zurasky J, Aiyagari V, Zazulia A, et al. Early mortality following spontaneous intracerebral hemorrhage. *Neurology*. 2005;64(4):725-727.
9. Perez-Nunez A, Lagares A, Pascual B, et al. Surgical treatment for spontaneous intracerebral haemorrhage. Part I: supratentorial haematomas. *Neurocirugia (Astur)*. 2008;19(1):12-24.
10. Mendelow AD, Gregson BA, Fernandes HM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomized trial. *Lancet*. 2005;365(9457):387-397.
11. Chan CL, Ting HW, Huang HT. The incidence, hospital expenditure, and, 30 day and 1 year mortality rates of spontaneous intracerebral hemorrhage in Taiwan. *J. Clin. Neurosci*. 2014;21(1):91-94.
12. Domingues R, Rossi C, Cordonnier C. Diagnostic evaluation for nontraumatic intracerebral hemorrhage. *Neurol. Clin*. 2015;33(2):315-328.
13. Kelly ML, Sulmasy DP, Weil RJ. Spontaneous intracerebral hemorrhage and the challenge of surgical decision making: a review. *Neurosurg. Focus*. 2013;34(5). article E1.
14. Elliott J, Smith M. The acute management of intracerebral hemorrhage: a clinical review. *Anesth. Analg*. 2010;110(5):1419-27.
15. Provencio JJ, Da Silva IR, Manno EM. Intracerebral hemorrhage: new challenges and steps forward. *Neurosurg. Clin. N. Am*. 2013;24(3):349-359.
16. Dey M, Stadnik A, Awad I. Spontaneous intracerebral and intraventricular hemorrhage: advances in minimally invasive surgery and thrombolytic evacuation, and lessons learned in recent trials. *Neurosurgery*. 2014;74(suppl. 1):142-150.
17. Adeoye O, Broderick J. Advances in the management of intracerebral hemorrhage. *Nat. Rev. Neurol*. 2010;6(11):593-601.
18. Steiner T, Petersson J, Al-Shahi Salman R, et al. European research priorities for intracerebral haemorrhage. *Cerebrovasc. Dis*. 2011;32(5):409-419.
19. Feigin VL, Lawes CM, Bennett DA, et al. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet. Neurol*. 2009;8(4):355-369.
20. Thanvi B, Sprigg N, Munshi S. Advances in spontaneous intracerebral haemorrhage. *Int. J. Clin. Pract*. 2012;66(6):556-564.
21. Zis P, Leivadeas P, Michas D, et al. Predicting 30-day case fatality of primary inoperable intracerebral hemorrhage based on findings at the emergency department. *J. Stroke. Cerebrovasc. Dis*. 2014;23(7):1928-33.
22. Abraham M, Romano L, Latini F, et al. Supratentorial correlation of age and haematoma volume in patients with spontaneous intracerebral hemorrhage. *Neurol. Arg*. 2014;6(1):23-28.
23. Ferrete-Araujo A, Egea-Guerrero J, Vilches-Arenas A, et al. Predictors of mortality and poor functional outcome in severe spontaneous intracerebral hemorrhage: A prospective observational study. *Med. Intensiva*. 2015;39(7):422-432.
24. Sampron N, Mendia A, Azkarate B, et al. Early mortality in spontaneous supratentorial intracerebral haemorrhage. *Neurocirugia (Astur)*. 2010;21(2):93-98.
25. Broderick J, Adams H, Barsan W, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke*. 1999;30(4):905-915.
26. Caceres JA, Goldstein JN. Intracranial hemorrhage. *Emerg. Med. Clin. North. Am*. 2012;30(3):771-794.
27. O'Donnell M, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*. 2010;376(9735):112-123.
28. Zhang Y, Wang X, Schultz C, et al. Postoperative outcome of cerebral amyloid angiopathy-related lobar intracerebral hemorrhage: case series and systematic review. *Neurosurgery*. 2012;70(1):125-130.
29. Zazulia AR. Intracerebral Hemorrhage, Primary. Encyclop. *Neurol. Sci*. 2014;2:734-741.
30. Dubourg J., Messerer M. State of the art in managing nontraumatic intracerebral hemorrhage. *Neurosurg. Focus*. 2011;30(6). article E22.
31. Dye JA, Dusick JR, Lee DJ, et al. Frontal bur hole through an eyebrow incision for image-guided endoscopic evacuation of spontaneous intracerebral hemorrhage. *J. Neurosurg*. 2012;117(4):767-773.
32. Xi G, Strahle J, Hua Y, et al. Progress in translational research on intracerebral hemorrhage: is there an end in sight? *Prog. Neurobiol*. 2014;115:45-63.
33. Martínez-Domeño A, Martí-Fàbregas J. Hemorragia cerebral. *Medicine*. 2015;11(71):4242-51.
34. Rivera L, Nekoovaght-Tak S, Saylor D, et al. Successful Management of Reversible Cerebral Vasoconstriction Syndrome-Induced Intracerebral Hemorrhage with Minimally Invasive Surgery Plus Recombinant Tissue-Type Plasminogen Activator. *J. Neurol. Stroke*. 2014;1(5). article 00030.
35. Blacker D, Musuka T. Management of intracerebral hemorrhage in 2020. *Future. Neurol*. 2011;6(6):745-756.
36. Hou XY, Gao PY. Perihematomal perfusion typing and spot sign of acute intracerebral hemorrhage with multimode computed tomography: a preliminary study. *Chin. Med. Sci. J*. 2014;29(3):139-143.
37. Wang JW, Li JP, Song YL, et al. Stereotactic aspiration versus craniotomy for primary intracerebral hemorrhage: a meta-analysis of randomized controlled trials. *PLoS One*. 2014;9(9). article e107614.
38. Zhou H, Zhang Y, Liu L, et al. Minimally invasive stereotactic puncture and thrombolysis therapy improves long-term outcome after acute intracerebral hemorrhage. *J. Neurol*. 2011;258(4):661-669.
39. Dowlatshahi D, Demchuk A, Flaherty M, et al. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. *Neurology*. 2011;76(14):1238-44.
40. LoPresti M, Bruce S, Camacho E, et al. Hematoma volume as the major determinant of outcomes after intracerebral hemorrhage. *J. Neurol. Sci*. 2014;345(1-2):3-7.
41. Chan S, Hemphill J. Critical care management of intracerebral hemorrhage. *Crit. Care. Clin*. 2014;30(4):699-717.
42. Magistris F, Bazak S, Martin J. Intracerebral Hemorrhage: Pathophysiology, Diagnosis and Management. *Clin. Rev*. 2013;10(1):15-22.
43. Li Y, Zhang H, Wang X, et al. Neuroendoscopic surgery versus external ventricular drainage alone or with intraventricular fibrinolysis for intraventricular hemorrhage secondary to spontaneous supratentorial hemorrhage: a systematic review and meta-analysis. *PLoS One*. 2013;8(11). article e80599.
44. Cutting S, Castro C, Lee V, et al. Impaired renal function is not associated with increased volume of intracerebral hemorrhage. J. Stroke. *Cerebrovasc. Dis*. 2014;23(1):86-90.
45. Jennett B. Development of Glasgow Coma and Outcome Scales. *Nepal. J. Neurosci*. 2005;2:24-28.
46. Barras C, Tress B, Christensen S, et al. Density and shape as CT predictors of intracerebral hemorrhage growth. *Stroke*. 2009;40(4):1325-31.
47. Du F, Jiang R, Gu M, et al. The accuracy of spot sign in predicting hematoma expansion after intracerebral hemorrhage: a systematic review and meta-analysis. *PLoS One*. 2014;9(12). article e115777.
48. Park SY, Kong MH, Kim JH, et al. Role of 'Spot Sign' on CT Angiography to Predict Hematoma Expansion in Spontaneous Intracerebral Hemorrhage. *J. Korean. Neurosurg. Soc*. 2010;48(5):399-405.
49. Kidwell C, Wintermark M. Imaging of intracranial haemorrhage. *Lancet. Neurol*. 2008;7(3):256-267.
50. Broderick J, Connolly S, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association, Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. *Stroke*. 2007;38(6):2001-23.

51. Wijdicks EF. Clinical scales for comatose patients: the Glasgow Coma Scale in historical context and the new FOUR Score. *Rev. Neurol. Dis.* 2006;3(3):109-117.
52. Rashid H, Amin R, Rahman A, et al. Correlation between intracerebral hemorrhage score and surgical outcome of spontaneous intracerebral hemorrhage. Bangladesh. *Med. Res. Counc. Bull.* 2013;39(1):1-5.
53. Ruiz-Sandoval J, Chiquete E, Romero-Vargas S, et al. Grading scale for prediction of outcome in primary intracerebral hemorrhages. *Stroke*. 2007;38(5):1641-44.
54. Kasner SE. Clinical interpretation and use of stroke scales. *Lancet. Neurol.* 2006;5(7):603-612.
55. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19(5):604-607.
56. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *State. Med. J.* 1965;14:61-65.
57. Aguiar GB. Neurosurgical handling of spontaneous intracerebral hemorrhage - a review. *Rev. Chil. Neurocirugía*. 2013;39:38-44.
58. Constantinescu A, Dănăilă L. Hematomul intracerebral spontan. Ghid de diagnostic şi tratament. [Spontaneous intracerebral hematoma. Guide for diagnosis and treatment]. http://www.usmf.md/Infomedica/documente/Alre%20resurse/Ghiduri%20 medicale/ hematom_ic_spontan.pdf sau http://l.academicdirect.org/Medicine/Informatics /Evidence-Based/Guidelines/display/?gno=4 (citat 14.02.2014).
59. Maeda A, Aguiar L, Martins C, et al. Hematoma volumes of spontaneous intracerebral hemorrhage: the ellipse (ABC/2) method yielded volumes smaller than those measured using the planimetric method. *Arq. Neuropsiquiatr*. 2013;71(8):540-544.
60. Perez ES, Delgado-Mederos R, Rubiera M, et al. Transcranial duplex sonography for monitoring hyperacute intracerebral hemorrhage. *Stroke*. 2009;40:987-990.
61. Cordonnier C, Klijn C, van Beijnum J, et al. Radiological investigation of spontaneous intracerebral hemorrhage: systematic review and trinational survey. *Stroke*. 2010;41(4):685-690.
62. Aguiar GB. Neurosurgical handling of spontaneous intracerebral hemorrhage - a review. *Rev. Chil. Neurocirugia*. 2013;39(1):38-44.
63. Delcourt C, Anderson C. Acute intracerebral haemorrhage: grounds for optimism in management. *J. Clin. Neurosci*. 2012;19(12):1622-26.
64. Teleanu DM, Constantinescu AI. Management of spontaneous intracerebral hemorrhage – a review. *Roman. J. Neurol*. 2014;13(1):12-16.
65. Naval NS, Nyquist PA, Carhuapoma JR. Advances in the management of spontaneous intracerebral hemorrhage. *Crit. Care. Clin*. 2006;22(4):607-617.
66. Gomes J, Manno E. New developments in the treatment of intracerebral hemorrhage. *Neurol. Clin*. 2013;31(3):721-735.
67. Anderson C, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N. Engl. J. Med*. 2013;368(25):2355-65.
68. Zheng J, Lin S, Li H, et al. Perioperative antihypertensive treatment in patients of spontaneous intracerebral hemorrhage (PATICH): a clinical trial protocol. Contemp. *Clin. Trials*. 2014;39(1):9-13.
69. Li Z, Zhao X, Wang Y, et al. Association between seizures and outcomes among intracerebral hemorrhage patients: the China National Stroke Registry. *J. Stroke. Cerebrovasc. Dis*. 2015;24(2):455-464.
70. Tapia-Pérez J, Gehring S, Zilke R, et al. Effect of increased glucose levels on short-term outcome in hypertensive spontaneous intracerebral hemorrhage. *Clin. Neurol. Neurosurg*. 2014;118:37-43.
71. Kellner CP, Connolly ES. Neuroprotective strategies for intracerebral hemorrhage: trials and translation. *Stroke*. 2010;41(10):99-102.
72. Lyden P, Shuaib A, Lees K, et al. Safety and tolerability of NXY-059 for acute intracerebral hemorrhage: the CHANT Trial. *Stroke*. 2007;38(8):2262-69.
73. Wang Y, Wu J, Mao Y, et al. The optimal time-window for surgical treatment of spontaneous intracerebral hemorrhage: result of prospective randomized controlled trial of 500 cases. *Acta. Neurochir.* 2008;105:141-145.
74. Chen X, Chen W, Ma A, et al. Frameless stereotactic aspiration and subsequent fibrinolytic therapy for the treatment of spontaneous intracerebral haemorrhage. *Br. J. Neurosurg*. 2011;25(3):369-375.
75. Newell D, Shah M, Wilcox R, et al. Minimally invasive evacuation of spontaneous intracerebral hemorrhage using sonothrombolysis. *J. Neurosurg*. 2011;115(3):592-601.
76. Li G, Qin X, Pen G, et al. Effect of minimally invasive aspiration in treatment of massive intracerebral hemorrhage. Acta. Neurochir. 2011;111:381-382.
77. Wang T, Guan Y, Du J, et al. Factors affecting the evacuation rate of intracerebral hemorrhage in basal ganglia treated by minimally invasive craniopuncture. *Clin. Neurol. Neurosurg*. 2015;134:104-109.
78. Xiao B, Wu F, Zhang H, et al. A randomized study of urgent computed tomography-based hematoma puncture and aspiration in the emergency department and subsequent evacuation using craniectomy versus craniectomy only. *J. Neurosurg*. 2012;117(3):566-573.
79. Yang Z, Hong B, Jia Z, et al. Treatment of supratentorial spontaneous intracerebral hemorrhage using image-guided minimally invasive surgery: Initial experiences of a flat detector CT-based puncture planning and navigation system in the angiographic suite. *AJNR Am. J. Neuroradiol*. 2014;35911):2170-75.
80. Auer L, Deinsberger W, Niederkorn K, et al. Endoscopic surgery versus medical treatment for spontaneous intracerebral hematoma: a randomized study. *J. Neurosurg*. 1989;70(4):530-535.
81. Zuccarello M, Brott T, Derex L, et al. Early surgical treatment for supratentorial intracerebral hemorrhage: a randomized feasibility study. *Stroke*. 1999;30(9):1833-39.
82. Kirkman M, Mahattanakul W, Gregson B, et al. The effect of the results of the STICH trial on the management of spontaneous supratentorial intracerebral haemorrhage in Newcastle. *Br. J. Neurosurg*. 2008;22(6):739-746.
83. Steiner T, Al-Shahi Salman R, Beer R, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *World Stroke Organizat*. 2014;9(7):840-855.
84. Potts MB, Riina HA. Refining the role for evacuation of spontaneous intracerebral hematomas: results of STICH II. *World. Neurosurg*. 2014;82(5):549-550.
85. Teernstra O, Evers S, Lodder J, et al. Stereotactic treatment of intracerebral hematoma by means of a plasminogen activator: a multicenter randomized controlled trial. *Stroke*. 2003;34(4):968-974.
86. Zhou X, Chen J, Li Q, et al. Minimally invasive surgery for spontaneous supratentorial intracerebral hemorrhage: a meta-analysis of randomized controlled trials. *Stroke*. 2012;43(11):2923-30.
87. Yang CD, Chen YW, Wu HC. Meta-analysis of randomized studies of surgery for supratentorial intracerebral hemorrhage. *Formosan. J. Surg*. 2014;47:90-98.
88. Heuts SG, Bruce SS, Zacharia BE, et al. Decompressive hemicraniectomy without clot evacuation in dominant-sided intracerebral hemorrhage with ICP crisis. *Neurosurg. Focus*. 2013;34(5). article E4.
89. Fung C, Murek M, Z'Graggen W, et al. Decompressive hemicraniectomy in patients with supratentorial intracerebral hemorrhage. *Stroke*. 2012;43(12):3207-11.
90. Chang YH, Hwang SK. Frameless stereotactic aspiration for spontaneous intracerebral hemorrhage and subsequent fibrinolysis using urokinase. *J. Cerebrovasc. Endovasc. Neurosurg*. 2014;16(1):5-10.
91. Montes JM, Wong JH, Fayad PB, et al. Stereotactic computed tomographic-guided aspiration and thrombolysis of intracerebral hematoma: protocol and preliminary experience. *Stroke*. 2000;31(4):834-840.
92. Sun H, Liu H, Li D, et al. An effective treatment for cerebral hemorrhage: minimally invasive craniopuncture combined with urokinase infusion therapy. *Neurol. Res*. 2010;32(4):371-377.
93. Prasad K, Mendelow A, Gregson B. Surgery for primary supratentorial intracerebral haemorrhage. *Cochrane. Database. Syst. Rev*. 2009;1. CD000200.
94. Anik I, Secer H, Anik Y, et al. Meta-analyses of intracerebral hematoma treatment. *Turk. Neurosurg*. 2011;21(1):6-14.
95. Zheng J, Li H, Guo R, et al. Minimally invasive surgery treatment for the patients with spontaneous supratentorial intracerebral hemorrhage (MISTICH): protocol of a multi-center randomized controlled trial. *BMC Neurol*. 2014;14. article 206.
96. Mould W, Carhuapoma J, Muschelli J, et al. Minimally invasive surgery plus recombinant tissue-type plasminogen activator for intracerebral hemorrhage evacuation decreases perihematomal edema. *Stroke*. 2013;44(3):627-634.
97. Monteith S, Kassell N, Goren O, et al. Transcranial MR-guided focused ultrasound sonothrombolysis in the treatment of intracerebral hemorrhage. *Neurosurg. Focus*. 2013;34(5). article E14.

Percutaneous biopsy in oncological pathology of the spinal column

T. Rusu

Department of Spinal Neurosurgery, Institute of Neurology and Neurosurgery, Chisinau, the Republic of Moldova
Corresponding author: tatianarussu@mail.ru. Received December 28, 2015; accepted February 05, 2016

Abstract

Background: Among oncological patients there is a group of patients with outcomes hard to predict because of few possibilities to diagnose, even though there are a lot of procedures, some of them being very painful. Absence of a diagnose lowers the chances of healing even before treatment starts, fact that makes patients refuse specific therapy. Often, these patients are referred to different medical centers during the short life that they have left. We are talking about patients in whom the clinical signs are metastasis; meanwhile the primary tumor doesn't have any manifestations at all. Percutaneous biopsy of the spinal column is a minimal invasive and rapid technique that obtains tissue samples from the vertebral body, intradiscal regions and paravertebral regions. Despite progress of computed tomography and magnetic resonance imaging technologies, basic diagnosis of different pathologies of the spinal column remains difficult. In most of the cases, a tissue sample is needed to settle a clear diagnosis. Percutaneous biopsy is preferred over the open biopsy because of the low costs, morbidity and mortality. The aim of this article is to review and to highlight in details the efficiency of percutaneous biopsy, by pointing out its influence on the treatment and decisions in such branches like surgery, chemotherapy, radiotherapy depending on the morphological nature of the lesions.

Conclusions: Percutaneous biopsy of the spinal column is the elective procedure in definitive diagnosis of pathological lesions.
Key words: percutaneous biopsy, metastasis, tumour, spine.

Introduction

Among oncological patients there is a group of patients with outcomes hard to predict because of few possibilities to diagnose, even though there are a lot of procedures, some of them being very painful. Absence of a diagnose lowers the chances of healing even before treatment starts, fact that makes patients refuse specific therapy. Often, these patients are referred to different medical centers during the short life that they have left. We are talking about patients in whom the clinical signs are metastasis; meanwhile the primary tumor doesn't have any manifestations at all [1].

Studies made on patients with metastasis without a known primary tumor, show that, until now, there is no optimal algorithm for diagnosing patients with metastasis with unknown primary tumor, an adequate determination of different methods of diagnosis and evaluation of metastasis does not exist [1].

Studies of autopsies with bone metastasis have 27% incidence in patients with carcinomas, 47-85% of whom die of breast cancer, 33-85% – of prostate cancer and 32-60% – of lung cancer. Bone metastasis may be the first clinical manifestation in almost 20% of patients with systemic cancer [57].

Global incidence of bone metastasis in patients with all kinds of cancer is about 70%. After lungs and liver, bones are on the 3rd place of metastasis. Out of all metastasis of the spinal column, 3% are primary unknown, and 75% derive from secondary tumors. About 30% of patients with cancer have metastasis at the moment of diagnose [63].

Metastases appear in a way that does not follow the laws of typical dissemination of tumors with known localization [1]. D. A. Casciato [25] compared the group of patients with metastasis with unknown primary tumor (later the primary tumor was found), with the group of patients with unknown source of the primary tumor and discovered the following particularities: patients with lung cancer had bone metastasis in 30-50% of the cases, and patients that had metastasis with an unknown focus (which later was found in the lungs), had bone metastasis only in 5% of the cases. In a similar way, bone metastases were found in 5-10% of patients with pancreatic cancer, and patients with metastasis with an unknown focus (which was later found in the pancreas) represented 30% of the cases. Metastases in the lungs and liver are found in 15% of patients with prostate cancer; meanwhile patients with metastasis with unknown focus (later discovered in the prostate), represent 50% of the cases of lung and liver metastasis. Atypical dissemination of tumors prevents essentially the process of identification of the primary focus, which in most of the cases complicates the localization's prognosis (according to the identified metastasis) [25].

It was established that during a thorough examination, that includes all methods of diagnosis, the primary focus could be identified in only 7.1% of the patients [43, 66]. Costs of examination of such a patient in USA are about 18.000 USD. The mean life expectancy of these patients does not exceed 8.1 months [62, 68].

Choosing a correct treatment tactics for spinal metastasis is difficult and depends on many factors, primary the life expectancy and the balance between the surgery risks against the risk of quality of life improvement. Prognosis was designed to help the clinician to decide the optimal tactics, but until now, we are against the version of choosing the best option, that in most of the cases is based on the subjective experience of the surgeon as well [22]. Generally, it is admitted that a surgery is indicated when a patient has a life expectancy more than 3 months [53].

Out of all oncologic patients without apparent clinical metastasis, only 50% can be cured with loco-regional treatments (surgery, radio-surgery), and according to recent data, about 60% of patients have microscopic metastasis at the moment of diagnosis. Metastases are responsible for almost 90% of deaths from cancer. About 5-30% of patients with metastasis in the spinal column have neurological symptoms. Metastasis

represents the fundamental process that differentiates the benign and malignant tumors, that transforms an organ cancer in a disease of the entire body, systemic disease [22, 52], and these patients become patients of a multi-modal branch [12, 31, 58, 59, 146]. Prognosis for patients with metastasis in the spinal column is the most important factor in choosing the correct tactics of treatment [16, 26].

The key to success in deciding the tactics of treatment of tumors of the spinal column is the histological type of the tumor. Tissue biopsy represents the basis of oncology.

Biopsy can be of three types:

- Percutaneous (transpedicular, transfacetar, lateral approaches);
- Open incision (when a larger quantity of tissue is required);
- Excisional.

Before imagistic guidance techniques of spinal column biopsy were developed, open biopsy procedure was necessary for definitive diagnosis. The advantage of open biopsy was double: the first was direct visualization, big and multiple tissue samples can be obtained for histological examination; and the second was the possibility of spine surgical decompression and / or column stabilization.

Percutaneous biopsy of the spinal column was firstly described by Minge in 1934 and then by Robertson and Ball in 1935 [56]. Though, their procedure did not use imagistic guidance. Siffert and Arkin [60] used posterior-lateral approach for spinal biopsy with radiographic guidance. Biopsy with imagistic guidance was reported in literature in 1949 with conventional radiography, followed by fluoroscopy in 1969, computed tomography (CT) in 1981, magnetic resonance imaging (MRI) in 1986, and CT fluoroscopy in 1996 [56]. At the beginning, open biopsies were performed, but percutaneous biopsy proved to be a more rapid, cost effective method with less complications [2, 3, 6, 17, 54].

There are 5 major indications for percutaneous biopsy of spinal lesions:

1. In order to identify an unknown lesion before a treatment plan is established;
2. Lesion that does not respond to empirical conventional treatment;
3. Infection that does not respond to 6-week treatment;
4. Fracture from compression on an unknown focus;
5. Intensification or persistence of pain in a patient with history of Paget disease [46].

Additional indications are:

- Metastasis confirmation in case of known primary focus;
- Diagnosis of primary bone lesion;
- Specific of nonspecific infection, with antibiotic sensibility;
- Determination of chemotherapy efficiency;
- Multiple myeloma cytological diagnosis;
- Benign lesion confirmation (osteoporosis, renal dystrophy);
- Diagnosis confirmation through histology and immunehistochemical methods in cases of FFD tumors;
- Symptomatic synovial cysts.

The major indication of this method is the correct choice of subsequent management of oncological patients, important in case of multimodal treatment's tactic change in this category of patients [4].

Among the first indications for biopsy are the lithic or blastic lesions, soft expansive process in the spinal column in patients with oncological history [5, 6, 61].

The second place after metastasis are discitis, with adequate planning of management of the symptomatic treatment, surgical radicalness, prevention of infection progress to sepsis, of local progression of the infection in cases of metallic implants [6, 7, 8], followed by pathological fractures, aspiration of symptomatic synovial cyst, etc [6, 9, 10].

Relative contraindications are:

- Hemorrhagic diathesis, coagulopathies, thrombocytopenia (50.000);
- Infection, including infection at the level of projection of the biopsy, including adjacent infection of the affected vertebrae;
- Non-accessible localization, for example C1 arch, the tooth of C2, bone fusion;
- Uncritical patient, with the need of general anesthesia;
- Pregnancy;
- Allergy to medications required for the procedure;
- Patients with medullar compressions at the level of interest [10, 11].

An absolute contraindication for percutaneous biopsy is coagulopathy. Nevertheless, even this condition, if correctly managed in advance, can be sufficiently corrected in order to permit the surgeon to make the procedure. If a vascular tumor, such as renal metastasis, is suspected, angiography should be taken into consideration in preliminary diagnostics.

Imagistic methods of intra-operatory guidance are:

Ultrasonography. Offers real time monitoring, it is rapid, cheap, avoids radiation and offers the possibility to visualize the tip of the needle during the entire procedure. It is often used in diagnostics of parenchymal organs such as: liver, thyroid gland, pancreas, lungs, prostate, breast. Its applicability at the level of spinal column resumes to superficial lesions of cervical spine [12, 13].

Fluoroscopy. The first fluoroscopic procedure was made in 1949, followed by single plan, bi-plan and C-arm fluoroscopy [14, 15].

Studies about fluoroscopic guidance and CT uncover the advantages and disadvantages of each procedure [46, 54, 56, 65].

Computed tomography (CT) has been used more than 20 years. It is a standard for many institutions. CT offers an exact trajectory planning, avoids lung passage at the thoracic level or other vital organs, it also offers to delimitate solid, necrotic, sclerotic lesions and exact depth. The disadvantage is the duration of the procedure and the dose of radiation for the patients and medical staff, and cost as well [18, 19].

CT fluoroscopy was described for the first time in 1994 [19, 21], it combines the advantages of conventional fluoroscopy with real-time visualization of six concomitant images. CTF is useful for visualization of retro-peritoneal organs that

are prone to physiological movements. One of the major concerns about CTF is the great dose of radiation. Conventional fluoroscopy doses are measured in centigrays per minute of exposure, meanwhile, the doses of CTF are measured in centigrays per second of exposure [19, 21].

Magnetic resonance imaging is a unique method, but with many economical disadvantages, described in literature being 15% more expensive than other methods [23, 24]. First of all, the procedure is expensive, the instruments must be made of titanium, the duration of the procedure is increased, also patients must not have contraindications for this type of procedure [23].

Before the procedure, patients must be fully examined clinically and paraclinically as for a surgical intervention: complaints, history, oncological history, and contact with contagious diseases. If the patient takes aspirin or other NSAI drugs, they must be suspended 3 days prior the procedure, with renewal after the procedure; in case of infection suspect, suspention of antibiotics 48h prior the procedure, special attention is paid to anesthetics drugs [25, 27, 29].

The procedure is made in the operating room, under sterile conditions, or in an angiographic laboratory, with a specialized table, that allows C-arm rotations for rapid anterior and profile images. The positioning of the patient on the table depends on the affected region, for superior cervical region with trans-oral and oropharyngeal approach the position is dorsal, in the rest of the cases, the position is ventral. Indications for posterolateral or transpedicular approach depend on the localization of the lesion. If the lesion is located primarily in the intervertebral space, or in cases of infectious diseases, posterolateral approach is to be used. This approach is mandatory in cases of lesions in the inferior part of the vertebral body. However, if the lesion is situated in the posterior part of the vertebral body, or if the pedicle is implied, transpedicular method is very efficient for biopsy [55, 64]. In cases of lesions of the entire vertebral body, transpedicular approach is usually preferred [10. 36, 45, 50, 54].

Skin is treated in a standard way, 3 times, with antiseptics. The marking of the entrance point is made with the C-arm (necessary angle inclusive, which can be estimated based on CT). Skin incision is about 2-3mm, with local anesthesia made with 1% lidocaine infiltration through the pedicle. Under fluoroscopic guidance advancing through the pedicle is made in case of transpedicular approach, or lateralized in case of costotransverse approach. Biopsy material is taken from several superficial and profound regions, soft paravertebral tissue inclusive, if required, aspirational liquid is taken for cytologic, bacteriologic exam [30].

Taken material is being taken for necessary examinations: histological, cytological, immune histological or bacteriological if required. Schematically surgical approaches (fig. 1).

Histology is the tissue examination sampled from the patient. Cyto-pathology is the cell study obtained from the tissue by means of fine needle biopsy. Benign and malignant tumors have two basic components:

1. Neoplastic and proliferative cells – their parenchyma;
2. Supporting stroma made of connective tissue and blood vessels.

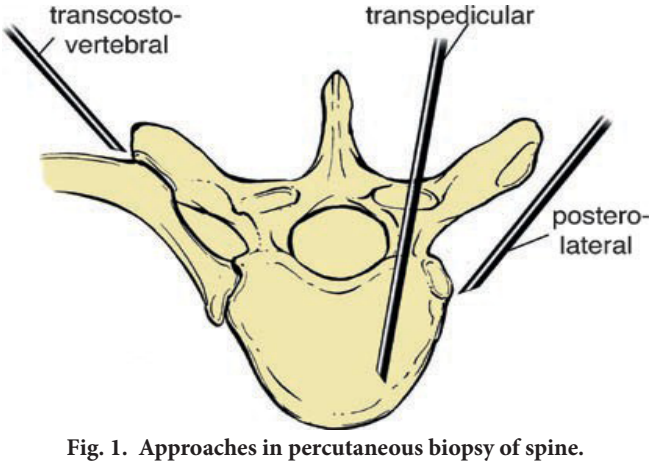


Fig. 1. Approaches in percutaneous biopsy of spine.

The parenchyma is the proliferative compartment of tumors and as a result determines the pathological compartment, tumoral growth and evolution that critically depends on its stroma [52].

Hyperplasia represents the physiological excessive proliferation of cells (pregnancy, breast-feeding, physical effort), compensatory proliferation (wounds, bone fractures, healing processes) and pathological (if the excess goes beyond the physical capacities). Tumoral growth doesn't obey any of these rules, neoplastic modifications can occur in hyperplastic tissues.

Dysplasia is a size, shape and cell organization disturbance in a tissue, as a result of growth and differentiation disruption caused by irritative factors, inflammation and hormonal factors/

Dysplasia is abnormal, but does not equal to malignancy [52].

Differentiation is about the functional and morphological features neoplastic cells resemble the normal cells; the absence of differentiation is called anaplasia [52].

Absence of differentiation or anaplasia is marked by a number of morphological modifications:

- Pleomorphic;
- Altered nuclear;
- Mitosis [28, 52].

There are national guidelines and standard protocols for pathological analysis of the majority of tumors. A vast number of staining can be made besides the standard staining with hematoxylin-eosine. Important progress of the techniques made it possible to offer results in an hour or one day. Immune histochemistry and molecular pathology are used in order to classify tumors [52].

The goal of immune histochemistry is to detect cellular or tissue-specific antigens by means of marked antibodies that can be visualized through microscopy of fluorescence. Immune histochemistry is very important in stabilizing the differentiation line in poorly differentiated tumors. The majority of pathologists use an approach based on steps. On the first step, they use generic markers that contain cytokeratins (for epithelial differentiation), melanocytic markers, CD 45 (leucocyte common marker, for hematopoietic differentiation) and vimentine (for mesenchymal differentiation). On the

second step, attention is paid to specific antibodies selected based on previous results [52].

Advantages of cytopathology:

- Small tissue lesions;
- Lesions that are not accessible for large biopsy;
- Patients' comfort;
- Rapid diagnosis.

Disadvantages of cytopathology:

- Limited possibility of detailed classification;
- Not capable to differentiate cancer.

Criteria that confirm diagnosis or at least suspect the diagnosis are:

1. Morphology of the cancer cell is different (size, shape) compared to the normal cell.
2. The nucleus of the cancer cell is bigger and is hyperchromatic than the normal cell, nuclei-cytoplasm ratio is bigger, nucleoluses are larger.
3. The number of cells in mitosis is greater in cancer cells, more than 20 mitosis per 1000 cells (1 in 1000 cells).
4. Abnormal mitosis, "giant cells", with polymorph features or multiple nuclei.
5. Normal tissue invasion of a neoplasm with high possibilities of metastasis [20].

Some authors claim that biopsy tissue with intra-operatory cytology had 96.9% sensibility, 100% specificity, 100% positive predictive value, negative predictive value of 87.5% well-correlated with the histological examination with 95.7% precision. The mean needed for result declaration was 8.9 +/- 1.7 minutes [38].

Complications in case of percutaneous biopsy of the spinal column are estimated to be less than 1% [31, 32].

Complications associated with percutaneous biopsy of the spinal column are:

1. Active bleeding;
2. Hematoma;
3. Vascular lesion;
4. Dural or radicular lesions (of the spine or nerves) with transitory or permanent neurological deficit.
5. Pneumothorax;
6. Infection, meningitis inclusive.

Most of the complications occur in the thoracic part of the spinal column: pleura / lung lesions, lesions of main vessels [33, 34], pneumothorax, radicular or medullar lesions with transitory neurologic deficit. Allergic reactions, even anaphylactic shock, are possible [35]. Post-procedure pain usually recedes after 24h. Hemorrhagic and infectious complications occur rarely.

Percutaneous biopsy of the spinal column is a well-known, efficient, rapid and less invasive technique that obtains tissue samples from the vertebral body, intradiscal regions and paravertebral regions [6, 10, 21, 24, 30, 36]. Despite progresses of CT and MRI technologies, basic diagnosis of different pathologies of the spinal column remains difficult. In most of the cases, a tissue sample is needed to settle a clear diagnosis. Percutaneous biopsy is preferred over the open biopsy because of the low costs, morbidity and mortality [6].

Efficiency of percutaneous biopsy in the management of spinal lesions was largely evaluated [10, 67]. The risk implied in percutaneous biopsy was estimated differently: 0% [44]. 2.2% [55], 7.6% [10] and 26% [29]. The most frequent complications reported were pulmonary, neurological and infectious complications. Precision of vertebral biopsy with posterolateral approach ranged between 50% and 90% [10, 29, 44, 45, 55, 67]. Other authors claim that the precision rate of percutaneous biopsy is 87-95%, and complications' rate is 0.2% [54].

Biopsy results which affect subsequent clinical management of the patient and will influence the treatment and decisions in such branches as surgery, chemotherapy, radiotherapy, antibiotic therapy depending on the morphological nature of the lesions.

Patients' survival with metastasis in the spinal column according to the morphology of the primary focus of the tumor (tab. 1).

Table 1

Patients' survival with metastasis in the spinal column

Type of cancer	Mean survival	5 years %	Mentions
Breast cancer	1-2 months	13%	
Prostate cancer	1-2 months	17%	
Lung cancer	3 months	2%	
Multiple mieloma	2-3 years		
Colo-rectal cancer	13 months		
Cervical cancer			The majority die in 18 months
Kidney cancer	1 year	30% if there is a single bone tumor	

Precision of percutaneous biopsy with different imagistic guidance methods is estimated in literature to be 88-100% [1, 37, 39, 40].

Positive prediction value of this procedure is 82%, negative prediction value is 100% [41]. Precision rate is higher in cases of metastasis or recurrent sarcoma, being 94% [41, 42, 44, 45, 47]. Capacity of culturing in cases of infection is low, ranging from 46% to 91% [48, 49, 50].

Conclusions

Percutaneous biopsy of the spinal column is a safe procedure, efficient and cost effective. It is the elective procedure in definitive diagnosis of pathological lesions of the spinal column.

References

1. Mereuță Ion. Tumorile maligne secundare cu focare primare necunoscute [Secondary malign tumors with unknown origin]. Chisinau, 2012;130.
2. Abbruzzese JL, et al. The biology of unknown primary tumors. *Semin. Oncolog.* 1993;20:238.
3. Abbruzzese JL, Abbruzzese MC, Hess KR, et al. Unknown primary carcinoma: natural history and prognostic factors in 657 consecutive patients. *J clin Oncolog.* 1994;12(6):1272-80.
4. Abrahm JL, Banfly MB, Harris MB. Spinal cord compression in patients with advanced metastatic cancer:„all I care about is walking and living my life„. *JAMA*. 2008;299:937-946.

5. Appel NB, Gilula LA. "Bull's-eye" modification for transpedicular biopsy and vertebroplasty. *Am J Roentgenol*. 2001;177:1387-9.
6. Ashizawa R, Ohtsuka K, Kamimura M. Percutaneous transpedicular biopsy of thoracic and lumbar vertebrae - method and diagnostic validity. *Surg Neurol*. 1999;52:545-51.
7. Avva R, Vanhemert RL, Barlogie B, et al. CT-guided biopsy of focal lesions in patients with multiple myeloma may reveal new and more aggressive cytogenetic abnormalities. *Am J Neuroradiol.* 2001;22:781-5.
8. Ball RP. Needle (aspiration) biopsy. *J Tenn Med Assoc*. 1934;27:203-6.
9. Bartels RH, Van Der Linclm YM, Van dr Groaf WT. Spinal extradural metastasis:review of current treatment options. *CA Cancer J Clin*. 2008;58:245-59.
10. Bender CE, Berquist TH, Wold LE. Imaging-assisted percutaneous biopsy of the thoracic spine. *Mayo Clin Proc*. 1986;61:942-950
11. Biopsy of the thoracic spine. *Mayo Clin Proc*. 1986;61:942-950.
12. Bradley W, Jacobs MD, et al. Evaluation and treatement of spinal metastasis: an overview. *Neurosurg. Focus*. 2001;11(6).
13. Buyukbebeci O, Karakurum G, Tutar E, et al. Biopsy of vertebral tumour metastasis for diagnosing unknown primaries. *J Orthop Surg*. 2010;18(3):361-3.
14. Carbone M, Barbanti M, Brodano G. Viral carcinogenesis. In Chang AE et al. Oncology – an evidence-based approach. New York: Springer, 2006;214-232.
15. Chew FS, Kline MJ. Diagnostic yield of CT-guided percutaneous aspiration procedures in suspected spontaneous infectious diskitis. *Radiology*. 2001;218:211-4.
16. Choi D, Crockard A, Bunger C, et al. Review of metastatic spine tumour classification and indications for surgery : the consensus statement of the Global Spine Tumour Study Group. *Eur Spine J*. 2010;19:215-222.
17. Chong-Suh Lee, Chul-Hee Jung. Metastatic Spinal Tumor. *Asian Spine J*. 2012;6(1):71-87
18. Coleman RE. Metastatic bone disease: clinical feature, pathophysiology and treatment strategies. *Cancer Treatment Rev*. 2001;27:165-76.
19. Czervionke LF, Fenton DS. Percutaneous spine biopsy. In: Fenton DS, Czervionke LF, editors. Image-guided spine intervention. Philadelphia: Saunders, 2003;141-87.
20. Daniel K, Steven Resnick, Garfin R. Vertebroplasty and Kyphoplasty, 2005;8.
21. Dave BR, Nanda A, Anandjiwala JV. Transpedicular percutaneous biopsy of vertebral body lesions: a series of 71 cases. *Spinal Cord*. 2009;47:384-9.
22. Choi D, Crockard A, Bunger C, et al. Review of metastatic spine tumour classification and indications for surgery: the consensus statement of the Global Spine Tumour Study Group. *Eur Spine J*. 2010;19(2):215-222.
23. Davis TM. Spinal biopsy techniques. In: Mcgraw JK, editor. Interventional radiology of the spine. Totowa: NJ: Humana Press Inc, 2004;181-96.
24. De Lucas EM, Mandly AG, Gutierrez A, et al. CT-guided fine-needle aspiration in vertebral osteomyelitis: true usefulness of a common practice. *Clin Rheumatol*. 2009;28:315-20.
25. Dennis A, Casciato DA, Barry B. Manual of clinical Oncology. Spiral-bound January 15, 1995, 3th edition.
26. Derek GJu, Yurter Al, et al. Diagnosis and surgical management of breast cancer metastatic to the spine. *WJCO*. 2014;5(3):263-271.
27. Dupuy DE, Rosenberg AE, Punyaratabandhu T. Accuracy of CT-guided needle biopsy of musculoskeletal neoplasms. *Am J Roentgenol*. 1998;171:759-62.
28. Frederick L Greene, David L. Cancer Staging handbook, 6th edition. New York: Springer-Verlag, 2002;1-26.
29. Fyfe I, Henry APJ, Mulholland RC. Closed vertebral biopsy. *J Bone Joint Surg*. 1983;65:140-143.
30. Garces J, Hidalgo G. Lateral Access for CT-guided percutaneous biopsy of the lumbar spine. *AJR*. 2000;174:425-26.
31. Gasbarrini A, Beisse R, Fisher C, et al. Spine metastasis. *Int J Surg Oncol*. 2011;375097.
32. Gerszten PC, Welch WC. Current surgical management of metastatic spinal disease. *Oncology*. 2000;14:1013-24.
33. Ghelman B. Biopsies of the musculoskeletal system. *Radiol Clin North Am*. 1998;36:567-80.
34. Gupta RK, Cheung YK, Al Ansari AG, et al. Diagnostic value of image-guided needle aspiration cytology in the assessment of vertebral and intervertebral lesions. *Diagn Cytopathol*. 2002;27:191-6.
35. Hadjipavlou AG, Kontakis GM, Gaitanis JN, et al. Effectiveness and pitfalls of percutaneous transpedicle biopsy of the spine. *Clin Orthop*. 2003;411:54-60.
36. Işik HS, Çagli S, Zileli M. Percutaneous Biopsy of the Spine: Analysis of 84 Cases. *Journal of Neurological Sciences (Turkish)*. 2012;29(2):258-265
37. Hecht S. Etiology of cancer: Tabaco. In: De Vita, Lawrence T.S., Rosenberg S.A., De Pinho R.A., Weinberg RA (eds): De Vita, Hellman, and Rosenberg's Cancer principles and practice of oncology 8th edition, Wolter Kluwer. Philadelphia: Lippincott Williams and Wilkins, 2008;147-244.
38. Naresh-Babu J, Neelima G, Reshma-Begum S.K. Increasing the specimen adequacy of transpedicular vertebral body biopsies. Role of intraoperative scrape cytology, January 27, 2014.
39. Jelinek JS, Kransdorf MJ, Gray R, et al. Percutaneous transpedicular biopsy of vertebral body lesions. *Spine*. 1996;21:2035-40.
40. Kang M, Gupta S, Khandelwal N, et al. CT-guided fine-needle aspiration biopsy of spinal lesions. *Acta Radiol*. 1999;40:474-8.
41. Kattapuram SV, Rosenthal DI. Percutaneous biopsy of skeletal lesions. *Am J Roentgenol.* 1991;157:935-42.
42. Klimo PJr, Schmidt MH. Surgical management of spinal metastasis. *Oncologist*. 2004;9:188-196.
43. Kollmann D, Hoetzenecker K, Prosch H, et al, Removal of a large cement embolus from the right pulmonary artery 4 years after kyphoplasty:consideration of thrombogenicity. *J Thorac. Cardiovasc. Surg*. 2012;143:122-124.
44. Laredo JD, Bard M. Thoracic spine: percutaneous trephine biopsy. *Radiology* 1986;160:485-489
45. Pierot L, Boulin A. Percutaneous Biopsy of the Thoracic and Lumbar Spine: Transpedicular Approach under Fluoroscopic Guidance. *AJNR Am J Neuroradiol*. 1999;20:23-25.
46. Lee CS, Jung CH. Metastatic spinal tumor. *Asian Spine J*. 2012;6(1):71-87
47. Leffler SG, Chew FS. CT-guided percutaneous biopsy of sclerotic bone lesions; diagnostic yield and accuracy. *Am J Roentgenol*. 1999;172:1389-92.
48. Lis E, Bilsky MH, Pisinski L, et al. Percutaneous CT-guided biopsy of osseous lesion of the spine in patients with known or suspected malignancy. *Am J Neuroradiol*. 1994;25:1583-8.
49. Logan PM, Connell DG, O'Connell JX, et al. Image-guided percutaneous biopsy of musculoskeletal tumors: an algorithm for selection of specific biopsy techniques. *Am J Roentgenol*. 1986;166:137-41.
50. Loredo JD, Bard M. Thoracic spine: Percutaneous trephine biopsy. *Radiology*. 1986;160:485-89.
51. Mackillop WJ, Dixon P, O·Sullivan B. The role of cancer staging in evidence-based medicine. In: Pollock R.E.(ed) UICC- Manual of clinical Oncology. 8th edition. New York: Willey-Liss, 2008:215-223.
52. Nagy V. Principii de oncologie generală. Cluj-Napoca, 2007;37-47.
53. National collaborating Centre for Cancer 2008. Metastatic spinal cord compression. Diagnosis and management of adults at risk of and with metastatic spinal cord compression. Nice Guidelines CG 75, TJ International Ltd, Cardiff, UK.
54. Pierot L, Boulin A. Percutaneous biopsy of the thoracic and lumbar spine: transpedicular approach under fluoroscopic guidance. *Am J Neuroradiol*. 1999;20:23-5.
55. Renfrew DL, Whitten CG, Wiese JA, et al. CT- guided percutaneous transpedicular biopsy of the spine. *Radiology*. 1999;180:574-576.
56. Robertson RC, Ball RP. Destructive spine lesions: diagnosis by needle biopsy. *J Bone Joint Surg (AM)*. 1935;57:749-58.
57. Schiff D, O·Neill BP, Suman VJ. Spinal epidural metastasis as the initial manifestation of malignancy: clinical features and diagnosis approach. *Neuroradiology*. 1997;49:452-56.
58. Sciubba DM., Gakaslan ZL. Diagnosis and management of metastatic spine disease. *Surg. Oncolog*. 2006;15:141-151.
59. Sciubba DM, Petteys RJ, Dekutoski MB, et al. Diagnosis and management of metastatic spine disease. *J Neurosurgery Spine*. 2010;13:94-108.
60. Siffert RS, Arkin AM. Trephine bone biopsy with special reference to the lumbar vertebral bodies. *J Bone joint Surg (AM)*. 1949;31:146-9.

61. Smith RA, Cokkinides V, Eyre HJ. Cancer screening in the United States, 2007: a review of current guidelines, practices, and prospects. *CA Cancer J Clin*. 2007;57:90-104.
62. Smith RA, Cokkinides V, Eyre HJ. Cancer screening in the United States, 2007: a review of current guidelines, practices, and prospects. *CA Cancer J Clin*. 2007;57:90-104.
63. Stylianidou S, Tzitzikas I, Chatzigiannaki A, et al. The current role of radiotherapy is vertebral hemangiomas without neurological signs. A case report and a review of literature. *Aristotle University Medical Journal*. 2013;40(1).
64. Sucu HK, Bezircioğlu H, Çiçek C, et al. Computerized tomography-guided percutaneous transforaminodiscal biopsy sampling of vertebral body lesions. *J Neurosurg*. 2003;99:51-5.
65. Tehranzadeh J, Browning CA. Percutaneous needle biopsy of the spine. *Acta Radiolog*. 2007;48(8):860-8.
66. Tourtienr JP, Cottez S. Images in clinical medicine. Pulmonary cement embolism after vertebroplasty. *J. Med.* 2012;366:258.
67. Babu VN, Titus VTK, Chittaranjan S, et al. Computed tomographically guided biopsy of the spine. *Spine*. 1994;19:2436-42
68. Zozulya YZ. Spinal cord and vertebral tumors. 2012. ISBN 978-966-460-016-0:400.00

ANNIVERSARIES

These enlightened by the strong sign of Capricorn days, our colleague, university professor and head of the Cardiology unit of the Department of Internal Medicine, Valeriu Revenco, reaches a beautiful age of 60 years. This age is generally considered the age of achievements and accomplishments, when the person who reaches it begins to sum up all the important and long-lasting things he has succeeded in life so far. It gives us the happy occasion to evoke a few pages from the celebrated person's prodigious life, a prominent personality, who has been serving to cardiology honorably for over 37 years, being daily involved in both care and treatment activities of hundreds, perhaps even thousands of patients as well as in the education process of several generations of doctors.

Mr. Valeriu Revenco was born on January 16, 1956 in Soroca town, the Republic of Moldova, in a family of farmers, worthy and hardworking persons, as are all people from northern Moldova characterized. In 1973 he graduated successfully from the famous School No 1 in his hometown. These days the professor recalls with love and tenderness the teachers who taught him to love work and literature, to think and act freely. It was during those distant years of school, around the lordly towering Soroca fortress, that he believes, the moral and cognitive foundations that formed the basis of his subsequent professional formation have been built.

In 1979 he graduated with honors from the State Institute of Medicine in Chisinau. He was enrolled in cardiology specialty clinical internship during the same year, within the Cardiology All-Union Scientific Center in Moscow.

During the 1981-1984 period he continued his postgraduate studies working on his doctorate. In 1984 our dear colleague successfully presented his doctorate thesis, and in 1992, finished his second doctorate, obtaining a PhD in Medicine.

1984 was the year when Valeriu Revenco started his multilateral activity in Nicolae Testemitsanu State University of Medicine and Pharmacy with a rising career – from the assistant (1984-1992) to the university professor (1993), and the head of Cardiology Department (1998 to present).

In addition, Professor Valeriu Revenco carries out an extensive research work, being today the author of over two hundred scientific works, among which

his monograph on clinical cardiology and functional diagnosis stands out particularly.

Having reached this level of professional experience, Professor Valeriu Revenco believes that in order to maintain yourself in a permanent working condition, you need to respect certain rules and principles of life. At the basis of any integral professional activity and a completed life lies the sense of responsibility, honesty, proper hierarchy of priorities, and openness towards everything new and advanced in the professional field. He consistently applies these principles in the guiding activity of his nine dissertations and one PhD thesis in medicine. During these years, he performed two international scientific projects: "Lipid and glucose metabolism in patients with insulin resistance" (2006-2007) and "Pathophysiological mechanisms of insulin resistance and coronary flow disorders in patients with metabolic syndrome" (2008-2009), as well as the institutional scientific project "Development of the concept of primary and secondary prevention of metabolic syndrome based on evaluation of ethiopathogenic mechanisms of the clinical picture and sympatholytic drugs action" (2011-2014).

Over more than a third of a century period of activity at the Department of Cardiology, Mr. Valeriu Revenco has proved to be a skilled and competent professor. Many generations of doctors, residents and fellows consider him a teacher and guide, attending his lectures and addressing for practical advice, based on his extensive experience as a physician, teacher and scientific researcher. Professor Valeriu Revenco is truly considered one of the most valued and talented cardiologists in the Republic of Moldova. Being an "old-school" doctor, he possesses at the same time a wide and consequently open attitude towards everything new in the domain of cardiology. During his activity, he found a way to apply his practice – gained knowledge, by being for a long time the chief of the 5th department in the Clinic of The Institute of Cardiology, taking care of patients day and night, reanimating and saving a large number of lives.

It is known that medicine has been and still is a special profession. This fact has long been acknowledged by renowned scientists, writers and other adherents of human intelligence. Being a true intellectual he not only loves and cares for the chosen profession but also has a strong calling for beauty, having a special attraction towards music, painting, literature and history.

To this date, his activity comprises an especially wide spectrum. Beyond the direct professional mission, he has held for many years the function of Chairman of the Attestation Committee of cardiologists and functional diagnostics doctors, he is a member of the University Senate, Scientific Council and Administrative Committee of Nicolae Testemitsanu State University of Medicine and Pharmacy. From 1992 until now, he has been the Dean of The Residency and Fellowship Faculty, faculty which besides the pertaining departments has about 1700 residents and fellow doctors.

On this beautiful anniversary occasion, allow us to offer you, Professor Valeriu Revenco, the most special congratulations and best wishes. We wish you and your close ones only success and joy, spiritual peace and new professional achievements. We also wish you good health and strong heart that will beat warmly and generously for many years to come and save other people's hearts!

Liviu Grib, MD, PhD, Professor
From colleagues of the Department of Cardiology
Nicolae Testemitsanu State University of Medicine and Pharmacy
Chisinau, the Republic of Moldova

GUIDE FOR AUTHORS

The authors are strongly requested to visit our web site www.curierulmedical.org, and follow the directions of the Publication Ethics and Publication Malpractice Statement.

The articles are accepted for publication in English. All articles are double-blind peer reviewed by two independent experts.

The articles must be sent electronically by the authors, responsible for the correspondence, with a cover letter written to the Editor-in-Chief Boris Topor, MD, PhD, Professor. The letter should contain a statement, saying that the manuscript has been seen and approved by all the authors and the article has not been previously published.

The authors are responsible for the content of the articles. The papers describing a research, involving animal or human subjects, should state in the cover letter that the rules of working with animals have been observed and the official consent has been obtained from the patients, and it has been approved by the designated board of the institution involved. The potential conflict of interests should be acknowledged by all the authors and editorial reviewers. If such a conflict is recognized, the reviewer is excluded from the review process and another reviewer is assigned.

All papers must be executed in the following manner:

1. The manuscripts should be typed in format A4, 1.5-spaced, with 2.0 cm margins, printing type 12 Times New Roman, in Microsoft Word.

2. The title page should include the first and last names of all the authors, their academic degrees, the name of the department and institution from which the paper has arrived, the phone number and e-mail address of the corresponding author.

3. The abstract should be written on the title page in English and be limited trom 220 to 240 words. The abstract should end with 3 to 6 key words.

4. The text of clinical or experimental articles (has to be less than 16 pages long) should consist of an Introduction, Material and Methods, Results, Discussion, Conclusions and be followed by no more than 40 References. The **review articles** must not exceed 25 pages and contain no more than 100 references.

5. The tables and figures must be typed, consecutively numbered and followed by an explanatory text. The figures that have to emphasize a comparison or details are published in colour. If coloured figures are to be placed, the author must pay an additional fee of €100 per page (1-8 figures on a page).

6. The references are to be listed in order of their appearance in the text, and the appropriate numbers are to be inserted in the text [in square brackets] in proper places. The references must comply with the general format outlined in the Uniform Requirements for the Manuscripts Submitted to Biomedical Journals developed by the International Committee of Medical Journal Editors (www.icmje.org), chapter IV.A.9. The references in the Cyrillic script should be transliterated into Latin script as follows: А–A, Б–B, В–V, Г–G, Д–D, Е–E, Ё–E, Ж–ZH, З–Z, И–I, Й–Y, К–K, Л–L, М–M, Н–N, О–O, П–P, Р–R, С–S, Т–T, У–U, Ф–F, Х–KH, Ц–TS, Ч–CH, Ш–SH, Щ–SCH, Ы–Y, Э–E, Ю–YU, Я–YA, Ь and Ъ are omitted. Immediately after the transliteration the translation of the title in English [in the square brackets] should follow. For example: Ivanov IV, Sidorov VM, Kozlov NF. Transplantatsiya organov i tkaney [Transplantation of organs and tissues]. Vestnik Khirurgii [Messenger of Surgery]. 2010; 26(6):45-49.

GHID PENTRU AUTORI

Redacția recomandă insistent autorilor să viziteze pagina web a revistei Curierul Medical www.curierulmedical.org pentru a face cunoștință cu cerințele și respectarea ulterioară a „Regulamentului despre etica editorială".

Sunt acceptate spre publicare articole în limba engleză. Toate articolele sunt îndreptate pentru recenzare la 2 experți independenți.

Articolele se expediază prin poșta electronică, în adresa redactorului-șef Boris Topor, dr. h., profesor, cu o scrisoare de însoțire din partea autorului, responsabil pentru corespondență. Scrisoarea va confirma faptul că toți autorii sunt de acord cu conținutul articolului și că articolul dat nu a fost publicat anterior.

Pentru conținutul articolelor sunt responsabili autorii. Dacă în articol sunt prezentate date despre rezultatele cercetărilor efectuate pe oameni sau animale, este necesar ca în scrisoarea de însoțire să se indice, că au fost respectate regulile de rigoare în privința experiențelor efectuate pe animale sau a fost obținut acordul pacienților și permisiunea administrației instituției. În caz de apariție a conflictului de interese, despre aceasta vor fi informați toți autorii și colegiul de redacție al revistei. Dacă conflictul se confirmă, persoanele cointeresate se exclud din procesul de evaluare a articolului și se numește un nou expert.

Articolele trebuie să respecte următoarea structură:

1. Articolele se imprimă în formatul A4, Times New Roman 12, în Microsoft Word la intervalul 1,5, cu câmpurile de 2 cm.

2. Foaia de titlu conține prenumele și numele autorilor, titlul și gradul științific, instituția, numărul de telefon și adresa electronică a autorului corespondent.

3. Rezumatul în limba engleză (220-240 cuvinte) se expune consecutiv pe foaia de titlu, inclusiv cuvintecheie, de la 3 până la 6. În rezumat este obligat să fie expus scopul cercetării (dacă nu este clar din titlu), metodologia studiului, rezultatele obținute și concluziile.

4. Textul articolelor clinice, experimentale (până la 15 pagini) cuprinde: Introducere; Material și metode; Rezultate obținute; Discuții; Concluzii și Bibliografie până la 40 de referințe. Altă structură se acceptă, dacă aceasta corespunde conținutului materialului. **Articolele de sinteză** nu vor depăși 25 de pagini și bibliografia până la 100 de surse.

5. Tabelele și figurile trebuie să fie enumerate și însoțite de legendă. Figurile care necesită contrastare sau evidențierea detaliilor sunt executate color. Figurile color se publică din sursele autorului – 100 €, 1-8 figuri pe pagină.

6. Referințele, în conformitate cu cerințele Comitetului Internațional al Editorilor Revistelor Biomedicale (www.icmje.org, capitolul IV.A.9), se expun în ordinea apariției în text. În lista referințelor titlul articolului, se traduce în limba engleză, poziționându-se în paranteze pătrate. Referințele bibliografice prezentate în grafie chirilică sunt transliterate în grafie latină, utilizând următoarele semne grafice: А–A, Б–B, В–V, Г–G, Д–D, Е–E, Ё–E, Ж–ZH, З–Z, И–I, Й–Y, К–K, Л–L, М–M, Н–N, О–O, П–P, Р–R, С–S, Т–T, У–U, Ф–F, Х–KH, Ц–TS, Ч–CH, Ш–SH, Щ–SCH, Ы–Y, Э–E, Ю–YU, Я–YA; Ь și Ъ se omit. Imediat după transliterare, în paranteze pătrate, se prezintă traducerea titlului articolului în limba engleză. De exemplu: Ivanov IV, Sidorov VM, Kozlov NF. Transplantatsiya organov i tkaney [Transplantation of organs and tissues]. Vestnik Khirurgii [Messenger of Surgery]. 2010; 26(6):45-49.

ГИД ДЛЯ АВТОРОВ

Редакция настоятельно рекомендует авторам посетить электронную страницу журнала Curierul Medical www.curierulmedical.org для ознакомления с требованиями и последующего соблюдения «Положения об издательской этике».

К публикации принимаются статьи на английском языке. Все статьи направляются на рецензию двум независимым экспертам.

Статью подают на имя главного редактора, д. м. н., профессора Б. М. Топор, в электронной форме, с сопроводительным письмом от имени автора, ответственного за переписку. Письмо должно содержать подтверждение, что все авторы согласны с содержанием статьи и она нигде ранее не публиковалась.

Ответственность за содержание статьи несут авторы. Если в статье приводятся результаты исследований, проведенных на животных или пациентах, в сопроводительном письме следует указать, что соблюдались правила работы с животными, было получено согласие пациентов и разрешение администрации учреждения. В случае возникновения конфликта интересов об этом извещаются все авторы и редакционный совет журнала. Если конфликт подтверждается, заинтересованные лица исключаются из процесса рассмотрения статьи, и назначается другой эксперт.

Все статьи должны быть оформлены следующим образом:

1. Статью печатают в формате А4, с интервалом 1,5, с полями в 2,0 см, шрифтом 12 Times New Roman, Microsoft Word.

2. Титульный лист включает в себя фамилию, имя и отчество авторов, ученые степени и звания авторов, название учреждения, из которого поступает работа, а также номер телефона и электронный адрес автора, ответственного за переписку.

3. Реферат (220-240 слов) на английском языке должен быть напечатан на титульном листе. За рефератом приводят ключевые слова – от 3 до 6. Текст реферата должен содержать обоснование исследования (если оно не отражено в названии), материал и методы, результаты и выводы. При составлении реферата необходимо использовать активный, а не пассивный залог.

4. Статья клинического и экспериментального характера (до 15 страниц) должна содержать следующие разделы: введение, материал и методы, результаты, обсуждение, выводы и библиография (не более 40 источников). Иной порядок изложения допустим, если он соответствует содержанию. **Обзорная статья** может содержать до 25 страниц и включать не более 100 ссылок на литературу.

5. Таблицы и рисунки нумеруют и сопровождают пояснениями. Рисунки, которые требуют выделения контраста или деталей по цвету, печатаются в цвете. Цветные рисунки оплачивают авторы: 100 € – от 1 до 8 рисунков на странице.

6. Список литературы необходимо печатать в порядке появления ссылок в тексте и в соответствии с едиными требованиями Международного Комитета Издателей Медицинских Журналов (www.icmje.org, глава IV.A.9). Библиографические ссылки на кириллице транслитерируют на латиницу следующим образом: А–A, Б–B, В–V, Г–G, Д–D, Е–E, Ё–E, Ж–ZH, З–Z, И–I, Й–Y, К–K, Л–L, М–M, Н–N, О–O, П–P, Р–R, С–S, Т–T, У–U, Ф–F, Х–KH, Ц–TS, Ч–CH, Ш–SH, Щ–SCH, Ы–Y, Э–E, Ю–YU, Я–YA, Ь и Ъ опускают. Сразу же после транслитерации приводят в квадратных скобках перевод на английском языке. Например: Ivanov IV, Sidorov VM, Kozlov NF. Transplantatsiya organov i tkaney [Transplantation of organs and tissues]. Vestnik Khirurgii [Messenger of Surgery]. 2010; 26(6):45-49.

Address of the Journal Office
192, Stefan cel Mare Avenue
Chisinau, MD-2004
Republic of Moldova

Telephone: +37322244751
Fax: +37322295384
www.curierulmedical.org
editor@curierulmedical.org
secretary@curierulmedical.org

Adresa redacției
Bd. Ștefan cel Mare, 192
Chișinău, MD-2004
Republica Moldova

Telefon: +37322244751
Fax: +37322295384
www.curierulmedical.org
editor@curierulmedical.org
secretary@curierulmedical.org

Адрес редакции
Пр. Штефан чел Маре, 192
Кишинёв, MD-2004
Республика Молдова

Телефон: +37322244751
Факс: +37322295384
www.curierulmedical.org
editor@curierulmedical.org
secretary@curierulmedical.org