



## Original article

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## THE NATURAL HISTORY OF MUSCULAR VENTRICULAR SEPTAL DEFECTS

### SUMMARY

Ventricular septal defect (VSD) is the most frequently diagnosed congenital heart defect. The prognosis is usually good as it has spontaneous closure evolution, especially small muscular VSDs. The aim of this study was to determine the natural history of isolated muscular VSDs including frequency of spontaneous closure in relation to location in the muscular septum and age at the time of closure.

Doppler color flow mapping studies were performed to define ventricular septal defect anatomy, location and evolution. Of approximately 19,500 live births in the region during last 6 years, VSD was identified as isolated congenital heart lesion in 87 infants (incidence 5.8 per 1,000 live births). Forty-six infants (53%) had a muscular VSD. Thirty of 46 were followed up for a minimum of 1 year.

Spontaneous closure occurred in 17 of 30 cases (56.7%). The time of spontaneous closure ranged from 1 to 42 months and it was most commonly recorded during the first 6 months after birth. In the 6th month, 1st year and 18th month, spontaneous closure occurred in 11 (36.7%), 14 (46.7%) and 16 (53.3%) cases, respectively. It was registered in all cases except one within the first 18 months; the other defect closed in the 42nd month. It was remarkable that spontaneous closure was seen in 15 of 21 cases (71.4%) with apical VSD and 2 of 7 cases (28.6%) with trabecular VSD.

In conclusion, the frequency of spontaneous closure is very high in the first 6 months, especially within the first four years of life. Because of the high closure rate of muscular VSDs especially apical ones, it is recommendable to detect them early using color flow imaging and follow up patients up to spontaneous closure.

**Key words:** muscular ventricular septal defects, rate of spontaneous closure, color flow imaging

### INTRODUCTION

Ventricular septal defect (VSD) is the most common congenital cardiac anomaly encountered after bicuspid aortic valve. Isolated VSD occurs in approximately 2-6 of every 1000 live births (1.5-3.5 per 1000 term infants and 4.5-7 per 1000 premature infants) (1) and constitutes over 20% of all

congenital heart diseases. VSDs are slightly more common in females; 44% occur in males, and 56% occur in females. An area of residence may influence the prevalence of known VSDs. For example, a small muscular VSD is more likely to be defined in urban locations possibly because of greater access to sophisticated health care.

Since 1979, real-time 2-dimensional echo-

cardiography has dramatically improved the non-invasive anatomical assessment of VSD. Cross-sectional echocardiography coupled with Doppler echocardiography and color flow imaging can be used to determine the size and location of virtually all VSDs. (2, 3). In muscular septal defect, all views that image the ventricular septum must be employed. Color Doppler echocardiography is critical to determine small asymptomatic defects(4).

The evolution of the VSD has been the focus of several studies. The natural history has a wide spectrum, ranging from spontaneous closure to congestive cardiac failure and death in early infancy. Spontaneous closure of VSD especially in the first years of life is a well-known phenomenon and it occurs in about one third of all cases. Closure is most frequently observed in muscular defects (80%), particularly apical, followed by perimembranous defects (35-40%)(2).

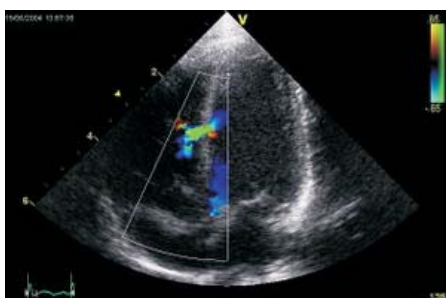
We followed up all patients with a muscular VSD, diagnosed over 6 years, to determine the frequency of spontaneous closure in relation to location in the muscular septum and age at time of closure.

### MATERIAL AND METHODS

Of approximately 19.500 live births in the region under study (Nis and the surroundings) during last 6 years, VSD was identified as isolated congenital heart lesion in 87 infants using color flow Doppler echocardiographic examination (incidence 5.8 per 1,000 live births). Forty-six (53%) had a muscular VSD. Thirty of 46 were followed up for a minimum 1 year.

Echocardiographic examination was performed using available echocardiographic equipment (Hewlett Packard Image Point). Two dimensional, CW Doppler and color flow Doppler echocardiographic images were obtained at the standard parasternal long-axis view, classic and modified short-axis views and apical, subcostal four-chamber views. (Figure 1)

Figure 1. Color flow signals crossing the interventricular septum at the middle portion of the right ventricle show the presence of a small muscular ventricular septal defect on an apical four-chamber view.



When color imaging showed interventricular shunting, the diagnosis was confirmed by continuous and/or pulsed Doppler analysis, which indicated the timing and direction of the flow transversing the interventricular septum.

The muscular defects were categorized as apical, trabecular, or outlet, according to the classification of Gatzoulis et al (5). Defect sizes were measured in two-dimensional image or as the maximum thickness of color jet at the level of interventricular septum. VSDs were seemed large if the defects were as large as or greater than the aortic orifice, and small if only seen in some parts of the cardiac cycle or not seen at all but identified on color flow mapping. All other defects were classified as moderate.

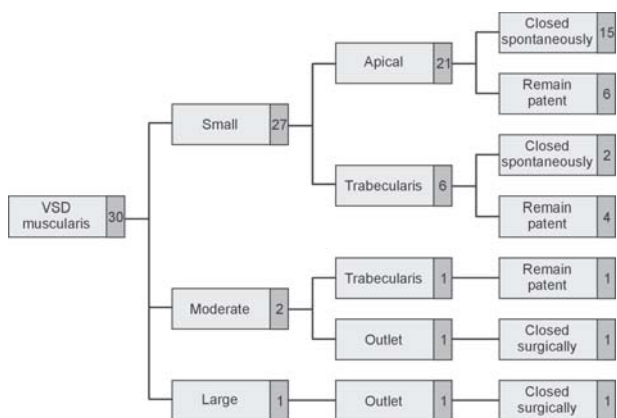
The patients were follow-up in intervals of 1, 3, and 6 months and 1 year. All received prophylaxis for infective endocarditis.

### RESULTS

The ages of 30 cases who were followed-up for at least 6 years ranged from 1 day to 5 years old (mean  $5.23 \pm 7.03$  months) at the time of initial examination. Eighteen of 30 cases (60%) were diagnosed in the neonatal period. In 7 cases, initial echocardiographic examination was performed between the 1<sup>st</sup> and 6<sup>th</sup> month, in 3 cases between the 6<sup>th</sup> and 12<sup>th</sup> month, and only in 2 patients it was after the 12<sup>th</sup> month. Sixteen of them were female and 14 male (F/M=1.1). Patients were followed up to a minimum of 1 year of age and a maximum of 5 years.

Figure 2 summarizes the natural history of the VSDs.

Figure 2. The natural history of the 30 ventricular septal defects (VSDs) studied



Twenty seven VSDs were small, 21 of which were apical and 6 trabecular; two were moderate, one of which was outlet and one trabecular; and one was a large outlet VSD. Two outlet VSDs required surgical

closure including one moderate and one large. Of 28 patients managed non-surgically, 17 muscular defects spontaneously closed: 15 were apical and 2 were trabecular. Of 11 muscular VSDs that did not require surgical closure and remain open, 6 are apical and 5 are trabecular.

Spontaneous closure occurred in 17 of 30 cases (56.7%). The time of spontaneous closure ranged from 1 to 42 months and it was most commonly recorded during the first 6 months after birth. In the 6<sup>th</sup> month, 1<sup>st</sup> year and 18<sup>th</sup> month, spontaneous closure occurred in 11 (36.7%), 14 (46.7%) and 16 (53.3%) cases, respectively. This was seen in all cases except 1 within first 18 months; the other defect closed in the 42<sup>nd</sup> month. (Table 1)

Table 1. Time of Spontaneous Closure During Follow-up Period

Time of the spontaneous closure (months)	Number of patients	Ratio (%)	Cumulative ratio (%)
≤ 1	1	5.9	5.9
1 - ≤3	4	23.5	29.4
3 - ≤6	6	35.3	64.7
6 - ≤12	3	17.7	82.4
12 - ≤18	2	11.7	94.1
18 - ≤42	1	5.9	100.0
Total	17	100.0	-

It was remarkable that spontaneous closure was seen in 15 of 21 cases (71.4%) with apical VSD and 2 of 7 cases (28.6%) with trabecular VSD.

There was no record of infective endocarditis in any patient.

## DISCUSSION

A spontaneous closure is the most exciting aspect of the natural history of ventricular septal defect. All data in the literature point to its frequency. However, this frequency varies greatly from one study to another, depending on the population, age studied, follow-up period and the percentage of different types of VSD. In previous clinical studies, the rate of spontaneous closure of muscular VSD has been reported to be between 24% and 96%. These rates are quite different, but as a common result, most of the small defects close within few months after birth<sup>1(2,6)</sup>.

Some investigators suggested that small defects are not a malformation and that early spontaneous closure of these defects is a normal developmental process<sup>(7)</sup>.

Our results were partly predictable as we expected the increased spontaneous closure rate of muscular defect, especially apical. There are a few clinical reports related to the rate of closure for muscular VSDs and influence of location on spontaneous closure VSD. Ramaciotti et al. (8) reported that the rate of closure for muscular VSDs and apical muscular VSDs was 24% and 23%, respectively. They emphasized that spontaneous closure of muscular VSDs was most commonly seen in the first 18 months of life. They also observed that the natural history of single muscular VSD is not influenced by location in the muscular septum.

Du et al. (7) screened full-term neonates with color flow Doppler imaging for muscular VSDs. The rate of closure at the end of the first year was 84.8%, but only one-fourth of defects were located in the apical region. They found that defects localized in the apical region and defects >4 mm in size remain patent more than VSDs located elsewhere.

Hiraishi et al (4) found a very high frequency for isolated VSDs when term neonates were routinely investigated using echocardiography. Most of the defects were small and muscular and 76% had closed by the age of 1, but 45% were apical muscular VSDs.

Turner et al. (6) confirmed that the position of a ventricular septal defect is extremely relevant to its natural history. The spontaneous closure rate for muscular defects was significantly greater than in perimembranous defects. Shirali (2) and colleagues studied 156 cases whose mean age was 28 months and also found a significantly higher spontaneous closure rate for muscular defects.

Our findings are very similar to those reported by Turner et al.<sup>2</sup> and Atalay et al. (9). In Atalay's study, a very high frequency of spontaneous closure of apical muscular VSDs was found. Spontaneous closure was seen in 24 of 42 cases (57.1%) between 1 and 36 months of age, and it was most commonly recorded during the first 6 months of life. Sapin et al. (10) found very high closure rate (75%) for apical VSDs, too.

Spontaneous closure becomes less likely during adolescence and adult life. In the study by Gabriel et al (11), spontaneous closure occurred in 6% of patients.

## CONCLUSION

A high chance of spontaneous closure is one of the major reasons why small VSDs are followed conservatively. However, diagnosing even a small VSD is important because of the risk of infective endocarditis. It is necessary to follow up patients to determine the spontaneous closure, especially within

the first years of life. Reported closure rates vary with size and location of VSD, age at presentation and patient population. Small VSDs have a >50% chance of spontaneous closure by four years of age.

Because of the high closure rate of muscular VSDs, especially apical, and the absence of serious clinical signs, parental anxiety should be minimized.

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## PRIRODNA ISTORIJA MUSKULARNIH VENTRIKULARNIH SEPTALNIH DEFEKATA

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### SAŽETAK

Ventrikularni septalni defekt (VSD) najčešća je urođena srčana mana. Prognoza je u najvećem broju slučajeva dobra, posebno ako se radi o malim muskularnim defektima, imajući u vidu njihovu sklonost ka spontanom zatvaranju. Cilj ovoga rada bio je da utvrdi prirodnu evoluciju izolovanih muskularnih VSD-a, odnosno frekvencu spontanog zatvaranja u zavisnosti od njihove lokacije u muskularnom septumu, kao i od uzrasta bolesnika.

Anatomija, lokacija i evolucija defekata praćena je korišćenjem Color Doppler tehnike. Za proteklih 6 godina, od približno 19500 živorođene dece u Nišu i okolini, VSD kao izolovana srčana mana nađena je u 87-oro (incidenca 5.8%). Njih 46-oro (53%) imalo je muskularnu lokalizaciju defekta. Tridesetoro dece, od njih 46, kontinuirano je praćeno najmanje po godinu dana.

U 17 od 30-oro dece došlo je do spontanog zatvaranja VSD-a (56.7%). Vreme spontanog zatvaranja kretalo se u intervalu od 1 meseca do 42 meseca po rođenju, pri čemu se najveći broj njih desio u prvih 6 meseci. Na kraju 6. meseca bilo ih je 11 (36.7%), na kraju 1. godine 14 (46.7%), a na kraju 18. meseca ukupno 16-oro dece (53.3%) sa spontano zatvorenim VSD-om. Dakle, samo kod jednog deteta zatvaranje defekta registrovano je posle 18. meseca, tj. u 42. mesecu života. Treba istaći da je čak u 15 od 17 (71.4%) defekt bio lociran u apikalnom delu muskularnog septuma, dok je samo 2 od 17 (28.6%) imalo trabekularni VSD.

Može se zaključiti da se najveći broj spontanih zatvaranja odvija u prvih 6 meseci života, odnosno do 4. godine. Pri tome se najčešće zatvaraju apikalni muskularni VSD-i, te ih treba na vreme otkrivati i kontinuirano pratiti do njihovog zatvaranja.

**Ključne reči:** muskularni ventrikularni septalni defekti, spontano zatvaranje, Color Doppler







## Original article

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## THE SIGNIFICANCE OF COLOR DOPPLER SONOGRAPHY IN SELECTION OF PATIENTS FOR CAROTID ENDARTERECTOMY

## SUMMARY

Sonography is the most widespread diagnostic procedure in obstructive disease of the arteries supplying the brain. The combined non-invasive information on morphology and function makes color Doppler sonography the procedure of choice in screening and follow-up of carotid artery disease. The aim of this study was to establish the significance of color Doppler sonography in selection of patients for carotid endarterectomy. Sonographic examinations of carotid arteries were performed in 5124 patients. The series consisted of all the patients with symptoms of carotid disease as well as asymptomatic patients with some risk factor. The examination was done on conventional ultrasound machines and linear 7,5 MHz transducers with color Doppler imaging. Ultrasound examinations aimed at establishing the presence and locus of the plaque, length of involved segment, degree of stenosis, plaque structure and plaque surface configuration. Stenosis degree determination was computer-assisted using two morphological and one hemodynamical methods of stenosis grading. In some cases, ultrasound findings were compared to DSA findings, and all ultrasound findings were compared to intraoperative ones. Out of the total number of examinees, 0.9% patients were selected based on surgically significant stenosis (over 75%). In cases in which angiography of the carotid bed was performed too, ultrasound findings correlated well with angiography. Ultrasound findings correlated well with intraoperative findings, too. The significance of color Doppler sonography in patient selection for carotid endarterectomy lies in the possibility of direct visualization of plaque morphology, determination of its properties, and the composition of configuration of its surface, which cannot be measured with other diagnostic procedures. Moreover, it is possible to measure the length of stenosis-involved segment, to determine precisely the grade of stenosis and to get an insight into hemodynamic disorders.

*Key words:* carotid endarterectomy, stenosis, color Doppler sonography

## INTRODUCTION

Stroke is one of the leading causes of death in industrialized countries (1,2). Approximately one-third of acute cases have a fatal outcome. In many patients, survival means prolonged and often irreversible disability. The paralysis following a

brain attack frequently leads to complete dependence on nursing care and permanent speech disorders that impair the stroke victim's ability to communicate.

Sonography is the most widespread diagnostic procedure in obstructive disease of the arteries supplying the brain. The combined non-invasive information on morphology and function

makes sonography the procedure of choice in screening and follow-up of carotid artery disease. Over the past years, numerous multicentric studies have investigated the merits of surgical interventions to repair carotid stenosis (e.g. ECST, NASCET, ACAS) (3, 4, 5, 6).

De Bakey was the first to successfully perform carotid endarterectomy back in 1953; Eastcott et al. performed it and were the first to publish the results in 1954. At the Clinic of Surgery, Clinical Centre Nis, the first carotid endarterectomy with eversion technique was performed in 2003.

Aim of the study was to establish the significance of color Doppler sonography in patient selection for carotid endarterectomy.

### MATERIAL AND METHODS

In the period from January 2003 to December 2005 at the Institute of Radiology in Nis, sonographic examinations of carotid arteries were performed in 5124 patients. The series consisted of all the patients with symptoms of carotid disease (TIA, RIND, complete brain stroke) as well as asymptomatic patients with some risk factors. Out of the total number of examinees, 49 (0.9%) patients were selected based on surgically significant stenosis (over 75%) and referred to the Council for Carotid Endarterectomy where the team of doctors (radiologist, neurologist, vascular surgeon) decided on further diagnostic and surgical proceedings. The examinations were performed on conventional sonographic machines with linear probes of 7.5 MHz with color Doppler imaging and longitudinal, transversal and oblique sections.

Sonographic examination aimed at establishing the presence of plaque, position of plaque related to bifurcation, length of involved segment, degree of stenosis, plaque composition, plaque surface configuration, and at establishing hemodynamic blood flow changes based on graphical flow curve. Diagnosis of stenosis by color Doppler sonography is generally based on a recognizable reduction of the perfused lumen and the flow disturbances described. Visualization in longitudinal and transversal planes can help locate the stenosis and provide a description of its length and geometry. Stenosis degree determination was computer-assisted using two morphological and one hemodynamical method of stenosis grading. In some cases, ultrasound findings were compared to DSA findings, and all ultrasound findings were compared to intraoperative findings.

### RESULTS

Most common, position of atherosclerotic plaques was at the bifurcation of common carotid artery and the initial portion of internal carotid artery (ICA) in 36 patients (73%). In 13 patients (27%), stenosis was present in ICA in its proximal segment at 8-25 mm distance from the source. The length of stenosis-involved segment ranged from 4 mm to 15 mm. Only one female patient had short concentric stenosis of 4 mm, which was difficult to measure and determine its degree.

Out of the total number of patients, 28 (57.1%) had stenosis of one ICA of over 75%, 12 (24.5%) patients had stenosis of both ICAs, with at least 75% stenosis in one or both of them, while 9 (18.4%) cases had 75% stenosis of one and occlusion of the other ICA. In most of them, calculation of the diameter and area of stenosis degree were utilized. (Figure 1 and 2)

Figure 1. Calculation of the local-diameter degree of stenosis

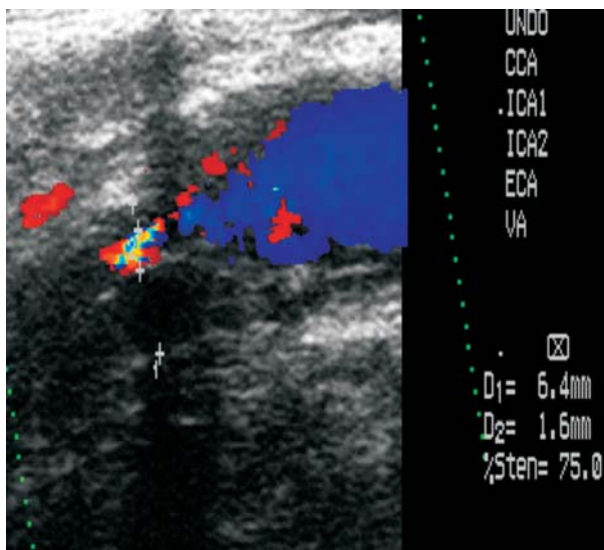
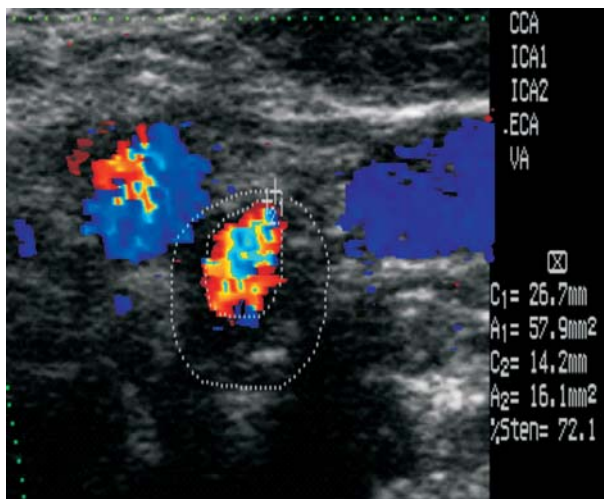


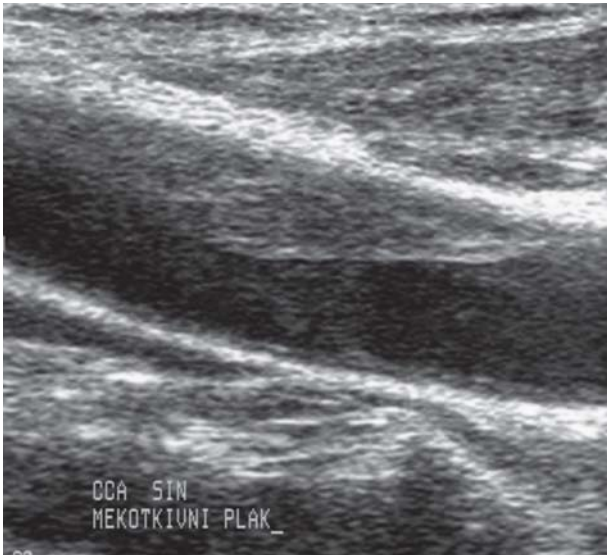
Figure 2. Calculation of the local-area degree of stenosis





Most of the plaques were soft tissue ones (lipid, fibrolipid) present in 25 (51%) patients. (Figure 3)

Figure 3. Eccentric soft lipid plaque in the common carotid artery



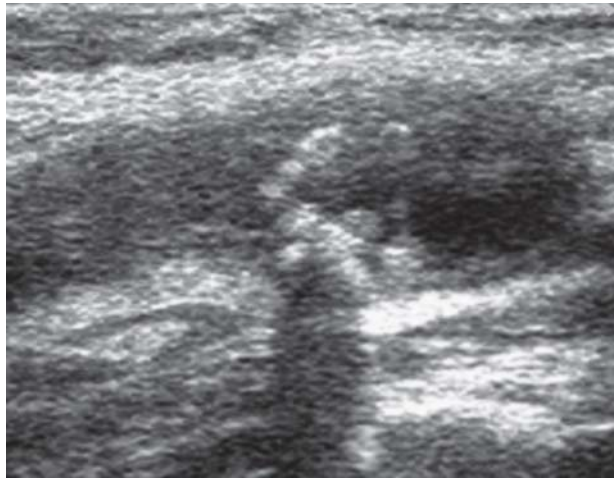
They were hypoechoic on sonography and, therefore, sometimes hard to identify in B-mode due to their blood-like characteristics. When preserved, intimal layer related to the lumen was visualized as linear echogenic structure. Hemorrhages within the plaque also had hypoechoic features. In one patient, in addition to high-percent ICA, stenosis caused by lipid plaque, soft tissue plaque were found in CCA, too. After lipid ones, most common were mixed-type plaques: calcified and with soft tissue component (fibrous or lipid) in 17 (34,7%) patients. (Figure 4)

Figure 4. Mixed plaque in the internal carotid artery



There were also entirely calcified plaques in 7 (14,3%) patients. (Figure 5)

Figure 5. Calcified plaque in the carotid bulb



Very echogenic plaques with calcifications produced acoustic shadowing. Calcifications prevented the demonstration of artery wall, and sometimes, it was difficult to determine the degree of stenosis.

Configuration of plaque surface is especially important for preoperative evaluation of the patients with lesions of the arteries supplying the brain. Ulceration of intraluminal plaque surface was found in 3 patients (6.1%), out of which one had high-percent stenosis, and two of them moderate stenosis of 50%. When there is intimal injury or ulceration, plaque surface is irregular, with occasional crater-like cavities. The significance of the plaques with irregular or crater-like surface or ulceration is reflected through the fact that the surface is thrombogenic. The thrombi create drop off the surface and produce distal embolism. The problem of identification of ulcerated plaque is practically far more important if there is moderate or low level stenosis. Ulcerated plaque with less than 60% carotid artery stenosis in symptomatic patients is more prone to ischemic complication, so that two patients required carotid endarterectomy.

In 12 patients in which angiography of carotid basin was performed, ultrasonographic findings correlated with angiography (in position of plaque related to bifurcation, length of involved segment, degree of stenosis, plaque surface configuration). All ultrasound findings correlated well with intraoperative findings, too. No false negative or false positive findings were found.

## DISCUSSION

Four-fifths of all ischemic events are heralded by arteriosclerosis. The large majority of pathological changes affect the extracranial arteries that supply the brain and are especially prevalent at the carotid bifurcation. Over the past years, numerous

multicentric studies have investigated the merits of surgical interventions to repair carotid stenosis (e.g. ECST, NASCET, ACAS) (3, 4, 5, 6). All studies have proposed limits defining the respective degree of stenosis above which a clinically favourable outcome of surgery can be expected. When specific inclusion criteria were applied, both symptomatic and asymptomatic patients benefited from surgical therapy. Two randomized studies (NASCET, ECST) on the efficacy of carotid thrombendarterectomy (TEA) in symptomatic patients (3, 4, 5, 6, 7) showed that patients with high-grade carotid artery stenosis, defined as a diameter reduction of between at least 70-80%, who were treated with surgery, achieved a greater benefit than the group undergoing conservative treatment. Even asymptomatic patients with carotid stenosis of at least 60% diameter reduction can benefit from carotid surgery. The ACAS study (7, 8) showed that surgery initially led to a significant risk reduction (absolute 5.8%, relative 55%). However, more recent meta-analyses indicate that carotid TEA reduces the absolute risk in asymptomatic patients by only 2%, approximately (4). While stent-supported percutaneous transluminal angioplasty (PTA) of the carotid artery has gained importance in recent years (9), the 5 and 10-year long-term results have not yet been verified in randomized studies. On the other hand, short and mid-term results for carotid stenting are acceptable (10).

The extracranial distribution of most vascular lesions makes them accessible to detection by ultrasound imaging. The examination aims at determining the nature, site, and extent of vascular lesions. Many of the abovementioned therapeutic studies in the past were followed by a great number of diagnostic studies comparing the results of ultrasound and invasive angiographic procedures, since all the data from large multicentric studies had been based solely on the angiographic estimation of degree of stenosis (11-17).

Most commonly, disturbances of cerebral blood flow are caused by the arteriosclerotic narrowing of the vessel lumen due to stenoses or occlusions. Overlapping of risk profiles occurs between cerebrovascular-ischemic and myocardial-ischemic diseases (18). Although it is possible for arteriosclerotic lesions of the arteries supplying the brain to develop anywhere, extracranial lesions particularly favour the carotid bifurcation. Even moderate luminal constrictions can induce hemodynamic changes (e.g., increase in flow velocity, poststenotic vorticity), but, stenosis is not hemodynamically relevant unless the residual lumen is so small that it causes a reduction in flow volume. In general, this is assumed when the cross-sectional area is reduced by 75% or more (19). Here, the degree of

stenosis correlates with stroke incidence (20). Critical appraisals are currently looking at how strictly risk assessment in carotid stenoses should focus on the degree of stenosis (21). It is assumed that the majority of ischemic cerebral lesions are caused by embolism arising from extracranial carotid stenoses. The clinical impact of stenosis, e.g., in the carotid region, only becomes apparent once all compensation mechanisms have failed, e.g., when additional stenoses impair the contralateral or intracerebral circulation (22). Over time, progressive arteriosclerosis, intraplaque haemorrhage, or local thrombosis can turn a hemodynamically insignificant stenosis into a flow-reducing stenosis or a complete occlusion.

Some examples of rare causes of arterial lumen constrictions with consecutive cerebral ischemia are various forms of arteritis, moyamoya disease, spontaneous and traumatic dissections, radiation exposure, fibromuscular dysplasia, and tumour-induced vascular compression and infiltration.

Detection of carotid stenoses and occlusions by color Doppler sonography relies chiefly on the combination of B-mode (gray-scale) and color-encoded flow imaging because of the good visualization these vessels offer. The major advantage of the procedure is that the B-mode image defines the outer boundary of the vessel wall and lumen-reducing material, while the color image demonstrates the associated flow pattern. The Doppler spectral analysis is not only used to confirm and quantify findings, but is additionally helpful when vascular segments are not unequivocally distinguishable in the color-coded image.

Although most stenoses are demonstrated at the origin of the internal carotid artery, many arteriosclerotic lesions involve the carotid bulb and the origin of the external carotid artery, thereby producing bifurcation stenoses.

The most subtle arteriosclerotic vascular lesion is the circumscribed plaque with a smooth surface that blends innocuously into the healthy vessel wall. Such early changes can be observed in the posterior part of the carotid bulb (23) and are hallmarked by slight wall thickening and the absence of normal flow reversal near the wall.

Higher degrees of luminal narrowing produce the typical flow disturbances, such as intrastenotic velocity increase, poststenotic flow separation and reversal, poststenotic disturbed flow and turbulence (24). Diagnosis of stenosis by color Doppler ultrasound is generally based on a recognizable reduction of the perfused lumen and the flow disturbances described. Visualization in longitudinal and transverse planes can help locate the stenosis and provide a description of its length and geometry. These images also allow a rough estimation of the

extent of luminal constriction similar to the subjective interpretation of angiograms.

There are four morphologically based (1-4, relying on the color image) and four hemodynamically based (5-8, relying on the Doppler spectra) methods for grading stenoses of the internal carotid artery (ICA):

1. Calculate the percentage of cross-sectional area reduction, i.e., the ratio of the perfused lumen area to outer contours (so-called local-area degree of stenosis).

2. Calculate the percentage of local diameter reduction, i.e., ratio of perfused lumen diameter to the outer contours (so-called local-diameter degree of stenosis).

3. Calculate the percentage of distal diameter reduction, i.e., the ratio of the diameter of the perfused intrastenotic lumen to the poststenotic diameter (so-called distal-diameter degree of stenosis).

4. Calculate the percentage of proximal-diameter reduction, i.e., ratio of the diameter of the perfused intrastenotic lumen to the prestenotic diameter the common carotid artery (so-called proximal-diameter degree of stenosis).

5. Obtain an absolute measurement of the internal carotid peak systolic frequency (ICPSF).

6. Obtain an absolute measurement of the internal carotid peak systolic velocity (ICPSV).

7. Obtain an absolute measurement of the internal carotid end-diastolic velocity (ICEDV).

8. Calculate the ratio of intrastenotic internal carotid peak systolic velocity to the prestenotic common carotid peak systolic velocity (ICPSV / CCPSV).

The literature abounds with reports and studies of indices, parameters, and grading methods, suggesting that there is not a single method available that allows precise quantification of the degree of stenosis. This can be explained by the fact that large clinical studies have worked on defining exclusively angiographic limits, although angiography only determines the diameter of the perfused vessel in several projections. It would take a combination of grading methods 2, 3, or 4 just to produce a duplex ultrasound correlation; however, because the stenosis area is sometimes partly obscured, hemodynamic measurement (methods 5-8) has become established in the literature. Naturally, correlating hemodynamic and geometric measures are subjected to limitations. That is why every centre must correlate their duplex ultrasound and angiographic results to establish its own internal thresholds as a basis for indication for the surgical therapy of carotid stenoses (13,14,16). In this study, calculation of the diameter and area of stenosis degree were utilized, and ratio of intrastenotic

internal carotid peak systolic velocity to the prestenotic common carotid peak systolic velocity (ICPSV/CCPSV) was calculated.

If the degree of stenosis cannot be established, selective catheter angiography is indicated (15).

A rough classification of the degree of stenosis is usually sufficient for clinical purposes.

Table 1. Hemodynamic quantification of carotid stenoses calculated from the ratio of maximal systolic velocity in internal carotid artery (ICA; intrastenotic) to common carotid artery (CCA)

Degree of stenosis in the ICA (diameter reduction as defined by NASCET;%)	Maximum systolic velocity ICA to CCA (ICPSV/CCPSV)
> 50	> 1,8
> 60	> 2,6
> 70	> 2,8
> 80	> 3,7
> 90	> 5

Comparisons of angiography and Doppler ultrasound (13) reveal that a ratio of <1.5-1.8 (internal carotid peak systolic velocity/peak systolic velocity in the prebulbar segment of the common carotid artery; ICPSV/CCPSV) is equivalent to an internal carotid artery stenosis of less than 50% diameter reduction (diagnostic accuracy of around 90%). An index >1.8 defines stenoses with a >50% diameter reduction. An index >2.6 implies a diameter reduction >60%, and an index >2.8 indicates a stenosis >70% diameter reduction (according to NASCET criteria, respectively). If the index exceeds 3.7, a stenosis of the internal carotid artery with a greater than 80% diameter reduction can be assumed. An index greater than 5 occurs in stenoses >90%. (Table 1). When these limits are applied, a high sensitivity of over 90% and thereby also a high negative predictive value can be expected.

The literature reports good results when absolute intrastenotic velocities were used (12, 13, 17). For example, an accuracy of over 90% in detecting >60% carotid stenoses was registered for the combination of limits >260 cm/s peak systolic velocity and end-diastolic velocity >70 cm/s (17).

A special case of high-grade internal carotid stenosis involves lesions that are so large that they reduce the flow down to a trickle. Such lesions might exhibit none of the typical intrastenotic or poststenotic flow abnormalities and can mimic an occlusion when the poststenotic flow velocity is below the sensitivity range usually selected for the instrument. If color-encoded flow signals are not detected in the internal carotid artery, the instrument sensitivity should be raised by switching the pulse



repetition frequency (PRF) and the filter frequency to the lowest settings and turning up the color sensitivity as high as possible. Duplex ultrasound just as always allows reliable differentiation of a very high-grade stenosis (>98% diameter reduction) from an occlusion (25). In such cases, velocity indices cannot be used. If there is still minimum residual flow in the internal carotid artery (few intraluminal color pixels), the examiner must favour more the color image than in velocity measurements.

Total vascular occlusion is characterized by the absence of a flow signal in the vessel lumen which is usually obliterated by hypoechoic thrombotic material. Especially in recent occlusions, a patent vascular stump of a few millimeters in length can frequently be demonstrated, as in an angiogram. Even in long-standing occlusions, it is usually possible to demonstrate a considerable length of the occluded lumen with ultrasound. In very old occlusions, this poses difficulty due to the scar contraction of the vessel. In such cases, diagnosis is aided by evidence of calcifications. It is very important to differentiate clearly between the occluded and the residual perfused vessel. The spectral features of the external carotid artery can be altered by an occlusion of the internal carotid artery. Here, reliable identification of the external carotid artery is only possible by demonstrating the branching vessels or by temporal tapping.

In addition to their hemodynamic effects caused by reduction of blood flow, stenoses of the carotid artery can also be a source of embolism. Even low-grade stenoses might lead to recurrent embolisms because of their surface properties or geometry. Subintimal hemorrhages in arteriosclerotic plaques can create defects (ulcerated plaque) and cause arteriosclerotic material to be mobilized (26). Local platelet aggregations tend to develop on irregular plaque surfaces, plaque ulcerations and in areas of poststenotic vorticity (flow reversal) with reduced flow rates. In this study it was determined that by using color Doppler sonography, 3 (6,1%) patients had ulcerated plaques.

A statistical correlation exists between plaque morphology and the likelihood of symptoms (27), but not the extent of the symptoms. The current literature is not very clear about the extent to which plaque assessment should be included in therapeutic decision making.

Principally, plaque ulcers posing as crater-shaped defects are detectable with B-sonography. However, the sensitivity is unsatisfactory (33% and 58% for ulcers smaller or larger than 2 mm) (28). There is no consensus as to whether the diagnosis of plaque defects is more accurate with color Doppler sonography or whether there is any obvious clinical correlation between ulcer size, ulcer localization and

tendency to embolisms. To date, no useful prospective studies have investigated if a clinically relevant connection exists between specific flow patterns detectable by color Doppler sonography and the risk of cerebral embolism. None of the ultrasound procedures can be expected to provide direct proof of embolism-endangered thrombi, since even thromboembolisms in the millimeter or micrometer range can have significant clinical consequences. Here, transcranial Doppler sonography is the method of choice.

The standard in carotid imaging, by which all non-invasive procedures are judged, is still the selective intra-arterial angiography. All major clinical studies of the recent past have applied angiographic criteria for diagnostic decision making. The main problem with catheter-based angiography is its invasiveness with an angiography-related stroke incidence of 0.4-1.2% in a high-risk population (29). One major advantage of angiography is that it provides a continuous and thereby markedly better reproducible visualization of the vessels. As with all ultrasound methods, the result of the sonographic examination strongly depends on the diligence and experience of the examiner. Severe impairment of renal function precluding the safe use of contrast agents, as well as heparin intolerance and haemorrhagic diathesis could exclude arteriography as a principle mode of carotid artery investigation. Furthermore, these conditions are clinical contraindications for carotid artery stenting. Also, severely tortuous aortic arch and arch vessels, or severe tortuosity and angulations of the carotid artery are anatomical contraindication for stenting. Having these in mind, color Doppler sonography examination, in absence of carotid artery stenting thoughts, is the principle investigation tool for carotid artery disease evaluation. Improvements of CT and MR angiography in centres where they are available further diminish necessity for carotid artery arteriography.

Based on the studies comparing color Doppler sonography and angiography, the ultrasound method has a sensitivity of 91-95% and a specificity of 86-97% in the detection and quantification of abnormalities of the carotid artery. In stenosis grading, color Doppler sonography and intra-arterial DSA have shown agreement in at least 90% of the cases when the described signs of stenosis were used (12,13,14,17). Color Doppler sonography is suitable for primary screening of patients with suspected carotid obstructive disease. Presently, many centres base the indication for carotid endarterectomy solely on color Doppler sonography (30).

Recently, numerous studies have been conducted on the value of magnetic resonance angiography (MRA) of supra-aortal arteries. The results

available (31) suggest that contrast-enhanced MRA will establish itself as a logical supplement to color Doppler sonography in the diagnosis of carotid artery lesions. Color Doppler imaging will be the primary procedure, with MRA being reserved for selected indications.

## CONCLUSION

Advancement of non-invasive diagnosis has radically changed the approach to the diseases which cause brain ischemia. These diseases are being identified earlier and before the appearance of first clinical symptoms. Therefore, the opportunity for preventative conservative and surgical management has been offered. Color Doppler sonography enables simultaneous visualisation of vascular lesions in gray scale (plaque, stenosis, occlusion) and associated flow disturbances with color-coded imaging and spectral analysis. This method has made possible direct plaque visualisation, determination of

its properties (composition and surface configuration) which other diagnostic procedures cannot provide. Besides, it is possible to measure the length of stenosis-involved segment and precisely determine the percent of stenosis.

In a large number of cases sonographic diagnosis is a method of choice and often the only approach required to diagnose the lesions in brain-supplying arteries. In most of the patients, diagnosis can be made precisely, enabling informed treatment decisions. In a small number of patients, additional proceedings are needed (such as MRI, intraarterial DSA). The method is invaluable in view of detection of surgically significant stenoses in patients without clinical symptoms (in 4 cases), so the screening of high risk subjects is a possible future opportunity.

It should be mentioned that quality depends on the experience of the examiner and that high standards should be set regarding the education and training of imaging specialists.

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## ZNAČAJ KOLOR DOPLER SONOGRAFIJE U SELEKCIJI PACIJENATA ZA KAROTIDNU ENDARTEREKTOMIJU

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### SAŽETAK

Ultrazvuk je najraširenija dijagnostička procedura kod opstruktivnih bolesti arterija koje prokrvljuju mozak. Kombinovane neinvazivne informacije o morfologiji i funkciji čine kolor Doppler ultrazvuk procedurom izbora u skrivanju i praćenju bolesti karotidnih arterija. Cilj ove studije je da ustanovi značaj kolor Doppler ultrazvuka u odabiru pacijenata za karotidnu endarterektomiju. Ultrazvučni pregled karotidnih arterija izveden je na 5124 pacijenta. Ovu seriju činili su svi pacijenti sa simptomima karotidne bolesti, kao i oni sa nekim od faktora rizika. Pregledi su izvođeni na konvencionalnim ultrazvučnim aparatima i linearnim 7,5 MHz sondama sa kolor Doppler imidžingom. Ultrazvučni pregledi imali su za cilj ustanovljavanje prisustva i mesta plaka, dužine zahvaćenog segmenta, stepena stenozе, strukture plaka i površinske konfiguracije plaka. Određivanje stepena stenozе bilo je kompjutersko korišćenjem dve morfološke i jedne hemodinamičke metode gradiranja stenozе. U nekim slučajevima su ultrazvučni nalazi upoređivani sa nalazima DSA, a svi ultrazvučni nalazi upoređivani su sa intraoperativnim. Od ukupnog broja ispitanika, 0.9% je izabrano na osnovu hirurški značajne stenozе (preko 75%). U slučajevima u kojima je izvedena i angiografija karotidnog korita, ultrazvučni nalazi bili su u korelaciji sa angiografijom. Ultrazvučni nalazi bili su u korelaciji sa intraoperativnim nalazima. Značaj kolor Doppler ultrazvuka u odabiru pacijenata za karotidnu endarterektomiju leži u mogućnosti direktne vizuelizacije morfologije plaka, u određivanju njegovih karakteristika, konfiguracije njegove površine, što se ne može uraditi drugim dijagnostičkim procedurama. Uz to, moguće je izmeriti dužinu stenozom zahvaćenog segmenta, precizno odrediti gradus stenozе i steći uvid u hemodinamičke poremećaje.

**Ključne reči:** karotidna endarterektomija, stenozа, kolor Doppler sonografija



## Original article

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## APPLICATION OF ATC/DDD METHODOLOGY TO COMPARE A ANTIBIOTIC UTILIZATION DURING A TWO-MONTH PERIOD IN TWO UNIVERSITY HOSPITAL SURGICAL DEPARTMENTS

## SUMMARY

The aim of the study was to analyze the overall drug consumption, compare antibiotic utilization in particular, and evaluate whether sound principles of surgical prophylaxis were applied at the Urology Clinics of two hospitals.

The study was carried out at the Urology Clinics of the Department of Surgery, Clinical Center in Nis and Institute of Surgery, University Teaching Hospital in Novi Sad, Serbia. Antimicrobial consumption was calculated during a two-month period as the number of Defined Daily Doses (DDDs) per 100 bed days (BD) for all antiinfectives for systemic use, i.e. group J of the Anatomical Therapeutic Chemical (ATC) classification and for classes of this group. This method allows us to determine drug consumption irrespective of the period of time over which consumption is monitored.

Antibiotics were the most frequently prescribed drug group at the Urology Clinic in Nis amounting to 263.54 DDD/100 BD (43.05% of total drug consumption). Co-trimoxazole (204.35 DDD/100 BD), quinolones (29.81 DDD/100 BD) and aminoglycosides (18.88 DDD/100 BD) were mostly prescribed. In Novi Sad, antibiotic utilisation amounted to 224.85 DDD/100 BD. Similarly, co-trimoxazole was most frequently prescribed (129.03 DDD/100 BD), followed by cephalosporins (43,54 DDD/100 BD) and aminoglycosides (20.5 DDD/100 BD).

In most instances, the chosen antibiotics for surgical prophylaxis were in accordance with international guidelines. However, an overuse was noted extending to the postoperative period. We believe that indications for antimicrobial use still need critical evaluation and that irrational use should be discouraged.

**Key words:** antibiotic utilization, surgical prophylaxis, Anatomical Therapeutic Chemical classification, Defined Daily Doses

## INTRODUCTION

Drug utilization studies can provide useful information to improve the appropriate and effective use of pharmaceuticals in populations. Many such studies have monitored antibiotic prescribing patterns in the surgical practice.

Serious morbidity and mortality are associated with postoperative wound infections. They have an enormous impact on patients' quality of life and contribute substantially to the financial cost of patient care. The use of perioperative antibiotics has

become an essential component of the standard of care in virtually all surgical procedures and has resulted in a reduced risk of postoperative infection when sound and appropriate principles of prophylaxis are applied (1).

In order to measure drug use, it is important to have both a classification system and a unit of measurement. Such a classification system is the Anatomical Therapeutic Chemical (ATC) classification. To deal with the objections against traditional units of measurement, a technical unit of measurement called the Defined Daily Dose (DDD)

to be used in drug utilization studies was developed by the WHO (2, 3). The average number of DDDs per bed-day (BD) is used in hospital studies. A "bed-day" is defined as the number of patients in the hospital or each ward per day and is calculated by multiplying the number of admissions by the average length of stay. This is a useful rate of expression for comparisons made between hospitals (4, 5, 6). Typically, the days of admission and discharge are counted as a single bed-day (7).

Scientific literature widely documents the current overuse of antibiotics, but often does not address the issue of the judicious use of antibiotics. Multiple analyses of prescribing patterns consistently reveal inappropriate prescribing of antibiotics, even when the clinician is aware of appropriate antibiotic use.

The purpose of our study was to analyze antibiotic prescribing trends among urologists for antimicrobial prophylaxis following urologic procedures, make a quantitative analysis of overall drug, especially antibiotic utilization at two urology clinics, and to evaluate whether sound principles of surgical prophylaxis were applied.

#### MATERIAL AND METHODS

The study was carried out at the Urology Clinics of Department of Surgery at the Clinical Center in Nis, and the Institute of Surgery, University Teaching Hospital in Novi Sad, Serbia.

We carried out a prospective study during a three-month period based on data obtained from case records of surgical patients admitted to the aforementioned clinics who received antibiotics either for prophylaxis or treatment. Also, data was obtained from the surgical departments' pharmacies which supplied the above mentioned clinics with the necessary drugs, including antibiotics. Information obtained included drug names, strengths and quantity (e.g. number of tablets) dispensed. Drugs were recorded by trade names. Each drug was then given its chemical name and a code according to the ATC classification. This classification comprises 5 levels. The first level is the anatomical group (e.g. antiinfectives for systemic use), the second is the therapeutic group (antibiotics for systemic use), the

third is a therapeutic subgroup (beta lactam antibiotics), the fourth gives the chemical form (broad-spectrum penicillins), and the fifth the chemical subgroup (e.g. ampicillin). For this study all five levels were used.

Even though total drug consumption was calculated, special attention was given to antibiotic utilization. Antimicrobial consumption was determined in terms of defined daily doses (DDD) per 100 bed days (BD) for all antiinfectives for systemic use, i.e. group J of the ATC classification and for classes and subclasses of this group. This method allows drug utilization to be analyzed irrespective of the period during which the study is carried over.

DDDs were calculated according to the 2004 ATC classification, while data on BDs was obtained from the surgical department's administrative services.

Statistical analysis was performed using a Student's t-test for comparison of means and Chi2 test to examine the association of qualitative variables.

#### RESULTS AND DISCUSSION

Recent studies have shown large differences in the use of antibacterial agents among European countries (8). These differences warrant closer analysis of antibiotic usage so as to identify the reasons for their overuse and find out measures that might rationalize this utilization (9). One could wonder how far drug consumption may vary across country or practice settings. Therefore, this study set out to analyze the consumption of medicines at two urology clinics in two Serbian cities with a special accent on antibiotic utilization.

Total drug consumption at the Urology Clinic in Nis amounted to 612.19 DDD/100 BD, where antiinfectives for systemic use (group J) constituted the most utilized group with 263.54 DDD/100 BD or 43.05% of overall drug utilization (Table 1), followed by drugs for blood and blood-forming organs (203.52 DDD/100 BD or 33.24%), central nervous system drugs (42.14 DDD/100 BD or 6.88%) and drugs for alimentary tract and metabolism (38.86 DDD/100 BD or 6.35%).

Table 1. Total drug consumption according to ATC classification and number of bed days (BD) at the Urology Clinic in Nis for the period from November 22, 2004 to December 31, 2004

ATC classification level	Main Group	DDD/100 BD	%
A	Alimentary tract and metabolism	38.86	6.35
B	Blood and blood forming organs	203.52	33.24
C	Cardiovascular system	23.20	3.79
D	Dermatologicals	0.38	0.06
H	Systemic hormonal preparations	14.31	2.34
J	Antiinfectives for systemic use	263.54	43.05
M	Musculo-skeletal system	19.59	3.2
N	Nervous system	42.14	6.88
R	Respiratory system	1.22	0.20
V	Various	5.43	0.89
TOTAL		612.19	100
BD=1840			

In Novi Sad, total drug utilization at the Urology Clinic amounted to 727.03 DDD/100 BD. The most utilized group were drugs for blood and blood-forming organs (318.34 DDD/100 BD or 43.79% of total drug consumption). Antiinfectives for systemic use were at the second place (224.85

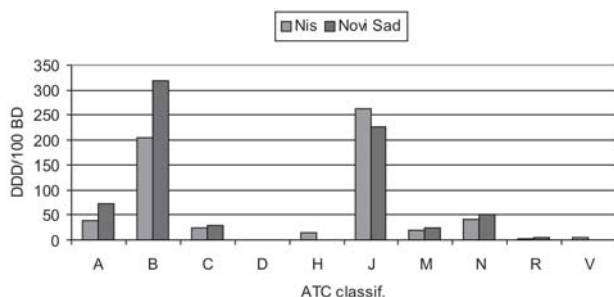
DDD/100 BD or 30.93%), followed by drugs for the alimentary tract and metabolism (72.01 DDD/100 BD or 9.9%), central nervous system drugs (51.58 DDD/100 BD or 7.09%), while utilization of other drug groups was neglectable (Table 2).

Table 2. Total drug consumption according to ATC classification and number of bed days (BD) at the Urology Clinic in Novi Sad for the period October 8, 2004 November 17, 2004

ATC classification level	Main Group	DDD/100 BD	%
A	Alimentary tract and metabolism	72.01	9.90
B	Blood and blood forming organs	318.34	43.79
C	Cardiovascular system	30.35	4.17
D	Dermatologicals	0.68	0.09
H	Systemic hormonal preparations	0.50	0.07
J	Antiinfectives for systemic use	224.85	30.93
M	Musculo-skeletal system	24.86	3.42
N	Nervous system	51.58	70.9
R	Respiratory system	3.86	0.53
TOTAL		727.03	100
BD=1333			

There was no statistically significant difference in total drug utilization at the Urology Clinics in Nis and Novi Sad ( $p < 0.05$ ). Also, there was no significant difference in antibiotic utilization (Figure 1).

Figure 1. Total drug consumption according to ATC classification at the Urology Clinics in Nis and Novi Sad expressed in DDD/100 BD



A three-month analysis of drug consumption in 2005 at the Department of Surgery Urology ward,

Clinical Centre in Montenegro reveals a lower overall drug utilization (5019.5 DDD/1000 BD) and a statistically significant difference in antibiotic consumption (672.2 DDD/1000 BD or 14.2% of total drug utilization;  $p < 0.001$ ) compared to Nis and Novi Sad (10).

Trends in antibiotic prescribing in Grampian hospitals, Scotland, have been monitored prospectively for 11 years from 1986. There was an overall increase of 16.9% in DDDs between 1992/3 and 96/7 to 424.0 DDDs/1000 BD (393.4 for antibacterials) (11). However, our findings show a much higher antibiotic utilization in our country compared to others with an assumed high drug consumption (eg. above mentioned Scotland).

Antiinfectives for systemic use were the most utilized drug group at the Urology Clinic in Nis, while they took second place in Novi Sad accounting for one-third of overall drug consumption. A qualitative and quantitative analysis of this utilization is shown in Tables 3-4, while Figure 2 displays the most commonly prescribed antibiotics by our urologists.

Table 3. Consumption of drugs in group J (antiinfectives for systemic use) at the Urology Clinic in Nis for the period November 22, 2004 to December 31, 2004

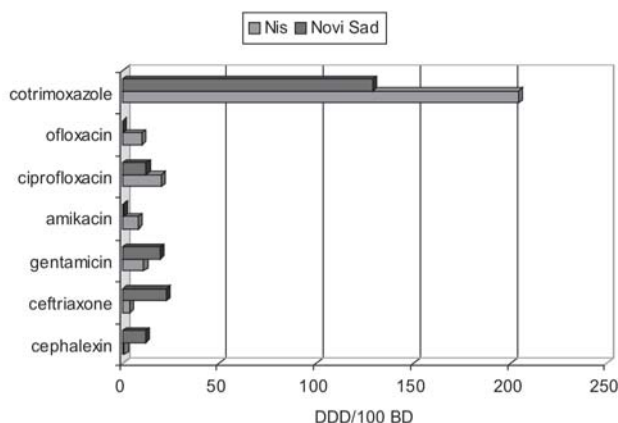
J		DDD/100 BD	%
J01DA	cephalosporins	7.85	2.98
J01DH	carbapenems	0.42	0.16
J01EE	cotrimoxazole	204.35	77.54
J01FA	macrolides	0.42	0.16
J01FF	linkozamines	0.88	0.33
J01G	aminoglycosides	18.88	7.16
J01MA	quinolones	29.81	11.31
J01XD	imidazoles	0.89	0.34
J05	antivirals	0.07	0.03
TOTAL:		263.54	100



Table 4. Consumption of drugs in group J (antiinfectives for systemic use) at the Urology Clinic in Novi Sad for the period October 8, 2004 to November 17, 2004.

J		DDD/100 BD	%
J01DA	tetracyclines	5.25	2.34
J01CA	broad spectrum penicillins	6.53	2.91
J01CE	Beta-lactamase-sensitive penicillins	0.08	0.03
J01DA	cephalosporins	43.54	19.37
J01DH	carbapenems	1.86	0.83
J01EE	cotrimoxazole	129.03	57.39
J01FF	linkozamines	0.26	0.12
J01G	aminoglycosides	20.50	9.12
J01MA	quinolones	12.17	5.41
J01XD	imidazoles	4.80	2.14
	other	0.80	0.36
TOTAL:		224.85	100

Figure 2. The most commonly used antibiotics following urologic procedures in Nis and Novi Sad expressed in DDD/100 BD



Cotrimoxazole was the most utilized anti-infective for systemic use at both clinics (subclass J01EE) with 204.35 DDD/100 BD or 77.54% of total antibiotic consumption in Nis and 129.03 DDD/100 BD (57.39% of total antimicrobial utilization) in Novi Sad. This practice should be recommended since it is in accordance with guidelines based on evidence obtained from clinical trials and from cohort studies. According to the recommendations given by the American Society of Health-System Pharmacists (ASHP) and guidelines from the Hospital Infection Control Practices Advisory Committee (HICPAC), if oral antimicrobials are used, a single dose of trimethoprim with sulfamethoxazole or lomefloxacin is recommended two hours before carrying out urologic procedures (12). In the postoperative period, cotrimoxazole is the drug of first choice in treating uncomplicated urinary tract infections. Since gram-negative enteric bacteria are the usual causative organisms, whereby *Escherichia coli* has been isolated in 90% cases of urinary tract infections (UTI), cotrimoxazole should be administered only if less than 20% of local *E. coli*

species are resistant to this antibiotic. If the percentage of resistant organisms is higher, a quinolone, oral cephalosporin, amoxicillin or nitrofurantoin should be administered (13, 14).

Quinolones were at the second place in Nis with 29.81 DDD/100 BD or 11.31%. Amongst the quinolones, ciprofloxacin was the most frequently prescribed drug (20.03 DDD/100 BD or 7.6%), while ofloxacin was prescribed half as much (9.78 DDD/100 BD or 3.71%). It is recommended that patients without demonstrated sterile urine, who have preoperative catheters in place, who are undergoing transrectal prostatic biopsy, or who are undergoing surgeries involving prosthetic material receive antibiotics to prevent contamination with enteric gram-negative bacilli and enterococci. The choice of prophylaxis is ciprofloxacin. In cases of prostatectomy where the predominant infecting microorganisms are coliforms, ciprofloxacin or gentamicin are the recommended agents (12). Thereby, quinolones are the drugs of choice in treating complicated UTIs.

In Novi Sad, cephalosporins were at second place with 43.54 DDD/100 BD or 19.37%. Amongst the cephalosporins, ceftriaxone, a third-generation cephalosporin, was most frequently administered (22.66 DDD/100 BD). Ceftriaxone obviously has some theoretical advantages for prophylaxis over I and II generation cephalosporins including stability against degradation by  $\beta$ -lactamase, broader spectrum coverage against gram-negative organisms, and extended serum half-life allowing once-daily administration (15, 16). Second place among the cephalosporins belonged to cephalixin (11.93 DDD/100 BD), a first generation cephalosporin, followed by cefotaxime (7.08 DDD/100 BD). Cefuroxime, a second-generation cephalosporin was used sparingly (1.21 DDD/100 BD or 0.54%). Other authors recommend cefazolin intravenously as acceptable prophylaxis in urologic surgery (17).



During our study we did not register the use of cefazolin in Novi Sad, but we did in Nis. However, in Nis, the use of cefazolin was negligible (1,27 DDD or 0,48% of total antibiotic use) as was the use of cefuroxime (0,93 DDD/100 BD or 0,35%). Similarly to Novi Sad, urologists in Nis prescribed ceftriaxone (3,64 DDD/100 BD or 1,38%) more readily than I generation cephalosporins which are recommended for prophylaxis in surgery based on the results of various studies. This underuse of I and II generation cephalosporins by our urologists can be attributed to their prescribing habits as well as to the unavailability of the above mentioned drugs.

Third place, in both clinics, belonged to the aminoglycosides (Nis:18.88 DDD/100 BD or 7.16%; Novi Sad: 20.5 DDD/100 BD or 9.12%). Gentamicin was prescribed more frequently (Nis: 10.94 DDD/100 BD; Novi Sad:19.34 DDD/100 BD) than amikacin (Nis: 7.93 DDD/100 BD; Novi Sad: 0.64 DDD/100 BD).

Other classes of antiinfectives were prescribed less frequently, such as cephalosporines in Nis (7.85 DDD/100 BD or 2.98%), imidazoles, linkozamines, carbapenems, macrolides and antivirals.

Many studies demonstrate that considering the low risk of serious infection after urologic surgery, antimicrobial prophylaxis should be considered only in patients at high risk of postoperative bacteriuria (patients who require prolonged catheterization and those with a positive urine culture) or in hospitals with high infection rates. Low-risk patients do not appear to benefit from the use of perioperative antimicrobials (12, 18).

We are pleased to notice that in most instances our urologists' prescribing habits were in accordance with the above stated guidelines, however, we must criticize the prolongation of antibiotic administration in the postoperative period which contributed to high drug utilization and consequently added to the rising cost of patient care. Antibiotic use is chaotic in our surgical practice. As such, our surgeons often mistake prophylaxis for treatment which consequently leads to drug overuse.

To illustrate this, if we take a look at quinolone use, these drugs constituted 6% of the total of antibiotics used in a University Hospital in

Nijmegen, The Netherlands (3). When this is compared to the 11.31% at the Urology Clinic in Nis, this warrants measures to rationalize the prescription of these drugs.

Analysis of antibiotic consumption in hospital care in Hungary in 2001, revealed that penicillins were the most frequently prescribed drugs (49%), followed by cephalosporins (12,7%), quinolones constituted 7% while aminoglycoside 3,9% of total antibiotic utilisation. The use of other antimicrobials was negligible.

The overuse of antibiotics at the urology clinics in our study can be attributed to prolonged administration extending the 24 hour period in cases where treatment was not indicated, i.e. continuation of antimicrobial prophylaxis postoperatively is not recommended (12). In cases where treatment is indicated postoperatively (established UTIs), optimal duration of therapy is 3 days (relapse is rare) to 7 days (less adverse reactions and minimal expenses).

## CONCLUSION

At the urology clinics of the departments of surgery in our study, the surgeons' prescribing habit was the main factor that directly influenced prescribing, since guidelines, formulary or an antibiotic policy did not exist. Overall antibiotic utilization was influenced by the availability of an agent through purchasing, dispensing, procurements, pricing, etc.

Even though in most cases antibiotic choice was in accordance with guidelines of leading medical centers and results of various studies, there was still unwarranted and overuse of prophylactic agents with increased costs to the hospital. Various methods should be developed to help curb undesirable antibiotic prescription. This can be accomplished by the development of national and local guidelines (based on international guidelines) for antimicrobial prophylaxis followed by lectures to medical and nursing staff. Also, a useful measure could be the introduction of an antibiotic policy due to rising costs and inappropriate use of antimicrobial drugs.

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## PRIMENA ATC/DDD METODOLOGIJE PRI UPOREĐIVANJU UPOTREBE ANTIBIOTIKA U TOKU DVOMESEČNOG PERIODA U DVEMA HIRURŠKIM BOLNICAMA

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### SAŽETAK

Farmakoterapijska praksa formira se pod uticajem faktora koji deluju na stvaranje propisivačkih navika pojedinih lekara. Poznavanje farmakoterapijske tradicije na nekom području omogućava sprovođenje edukativnih programa racionalne farmakoterapije.

Cilj našeg rada bio je da analiziramo i uporedimo upotrebu lekova, posebno antibiotika, na Klinikama za urologiju u Nišu i Novom Sadu kako bi procenili da li su sprovedeni principi hirurške profilakse bili u skladu sa međunarodnim smernicama.

U ovom radu ispitivanje je izvršeno na odeljenjima za urologiju Hirurških klinika u Nišu i Novom Sadu. U analizi upotrebe antiinfektivnih lekova za sistemsku primenu, i svih lekova uopšte, korišćena je jedinica mere definisana dnevna doza (DDD) na 100 bolesničkih dana (BD). Lekovi su razvrstani po Anatomsko-Terapijsko-Hemijskoj (ATC) klasifikaciji. Ova metodologija omogućava da se upotreba lekova prati bez obzira na dužinu vremenskog perioda praćenjem obima i strukture upotrebe lekova.

Antibiotici (grupa J po ATC klasifikaciji) predstavljali su najzastupljeniju grupu u ukupnoj upotrebi u Nišu sa 263,54 DDD/100 BD (43,05% od ukupne upotrebe). Kotrimoksazol (204,35 DDD), hinoloni (29,81 DDD) i aminoglikozidi (18,88 DDD) bili su najviše propisivane grupe antibiotika. U Novom Sadu, upotreba antiinfektivnih lekova iznosila je 224,85 DDD/100 BD. Slično situaciji u Nišu, i ovde je kotrimoksazol najčešće propisivan (129,03 DDD), zatim cefalosporini (43,54 DDD) i aminoglikozidi (20,5 DDD).

U najvećem broju slučajeva izbor antibiotika za perioperativnu primenu u hirurgiji bio je u skladu sa međunarodnim smernicama. Međutim, primećena je prekomerna upotreba antibiotika s obzirom na njihovo ordiniranje u postoperativnom periodu bez jasnih dokaza o infekciji. Smatramo da treba postaviti jasne indikacije za primenu antibiotika u hirurškoj profilaksi kako bi se u daljem toku izbegla svaka neracionalna upotreba.

**Ključne reči:** Anatomsko-Terapijsko-Hemijska klasifikacija, definisane dnevne doze, hirurška profilaksa, antibiotici