

# Quality of Haemophilia Treatment in Serbia: National Haemophilia Registry Report

Danijela Miković<sup>1</sup>, Ljiljana Rakić<sup>1</sup>, Gordana Janković-Tršnjak<sup>1</sup>, Radmila Baklaja<sup>1</sup>, Ivo Elezović<sup>2</sup>

<sup>1</sup> Haemostasis Department and Haemophilia Centre, Blood Transfusion Institute of Serbia, Belgrade, Serbia;

<sup>2</sup> Institute of Haematology, Clinical Centre of Serbia; School of Medicine, University of Belgrade, Belgrade, Serbia

## SUMMARY

**Introduction** The National Registry of patients with inherited bleeding disorders was established in 1963 and ever since it has been in charge of the Haemophilia Centre, Blood Transfusion Institute of Serbia, Belgrade.

**Objective** Purpose was to assess the quality of haemophilia treatment in Serbia from 2000 to 2008 based on the National Registry data related with the organization of care and quantities, and the choice of products.

**Methods** Analysis of data collected by the National Registry from January 2000 to December 2008.

**Results** The National Registry of patients with hereditary coagulopathy encompasses a database of 392 patients with haemophilia A (HA), 64 haemophilia B (HB), 217 von Willebrand's disease and 19 with rare bleeding disorders. Treatment can be obtained in seven haemophilia treatment centres; haematological and paediatric institutes and hospitals in Belgrade, Niš and Novi Sad, as well as in other twenty local hospitals. From 2000 to 2003 about three million units of FVIII concentrate were administered annually, e.g. 0.25 IU/capita/year. Besides, national cryoprecipitate was available for the treatment. In 2003, National Haemophilia Committee was founded and centralized products supply was introduced. During 2004 and 2005, about five million units of FVIII concentrate were provided: annually, i.e. 0.65 IU/capita/year. The choice of products was also improved. Namely, until 2004 the availability of DDAVP, antifibrinolytic drugs and rFVIIa concentrate was limited, while from 2004 these products became available for haemophilia treatment in Serbia. In order to improve haemophilia care we established international cooperation; education, training, consulting and participation in clinical and research projects. As the result, FVIII concentrate consumption in 2008 was 10.5 million units, e.g. 1.35 IU/capita/year.

**Conclusion** The considerable improvement of treatment is the result of efforts made by health care and regulatory institutions in Serbia. Significant support has been provided by cooperation within twinning programmes between Stockholm and Belgrade Haemophilia Centres in 2003-2004 and Hamilton and Belgrade Haemophilia Centres in 2005-2008.

**Keywords:** haemophilia; registry; quality of treatment

## INTRODUCTION

Haemophilia is an inherited bleeding disorder due to FVIII deficiency (HA) or FIX deficiency (HB). A severe form of haemophilia, with deficient factor level <1%, is characterized by spontaneous bleeding episodes into joints and muscles that, if inadequately treated, are associated with crippling arthropathy pain, severe joint disease and disability and early death [1]. Haemophilia is a relatively rare disease, affecting 400,000 persons worldwide; it has a specific social significance considering the nature of the disease and therapy that requires highly specialized skills and considerable financial means. Haemophilia treatment is complex and expensive resulting in considerable inequity in provision across the world. Optimal care for severe haemophilia includes a developed organization of haemophilia care, with patients being usually followed in haemophilia centres supplied with and adequate drugs, which results in early and optimal factor replacement for bleeding episodes and the provision of prophylaxis from early age to prevent arthropathy [2, 3].

National haemophilia registries are powerful instruments to support health care. The main function of the registries is to provide accurate data on epidemiology, e.g. the number of patients, geographical distribution and adverse events. The registries should also record data on drug supply, treatment costs and social status of

patients with the main purpose to improve the performance of the health care system involving haemophilia [4, 5]. According to the European Association for Haemophilia and Associated Disorders (EHAD), each country should have a national haemophilia patient registry [6].

## OBJECTIVE

The aim of this paper was to assess the quality of haemophilia treatment in Serbia from 2000 to 2008 based on the National Registry data related to the organization of health care, the quantity and choice of products and the frequency of adverse events.

## METHODS

The quality of treatment is presented according to data collected from the National Registry related to the organization of haemophilia care and the choice and quantity of therapeutical products.

The National Registry of patients with inherited bleeding disorders was established in Serbia in 1963 and ever since it has been in charge of the Haemophilia Centre of the Blood Transfusion Institute of Serbia in Belgrade. At the Centre series of activities are carried out; the diagnosis and registration of patients, social,

medical and educational work, follow-up of patients' health condition, out-patient transfusions, prenatal diagnosis, team work organization in the treatment of patients, preparation and follow-up of the national plan for the treatment of patients and national and international cooperation.

From January 2000 to December 2008, we analyzed data covering a total of 9 years. On December 31<sup>st</sup> 2008 the list of the registered alive patients with haemophilia in Serbia included 392 patients with haemophilia A and 64 with haemophilia B. The Registry included both the patients with haemophilia, but also 217 patients with von Willebrand's disease and 19 patients with rare bleeding disorders.

The National Registry also collects and follows data related to the choice and quantity of products for haemophilia treatment. It also contains the record on the supply and usage of drugs in therapy.

## RESULTS

The organization of haemophilia care in Serbia is in accordance with the national programme carried out by the Ministry of Health. Patients with haemophilia are registered in the National Register at the Blood Transfusion Institute of Serbia in Belgrade. The National Haemophilia Committee is in charge of planning and monitoring of the diagnosis and therapy of haemophilia and other inherited coagulation disorders. Treatment can be obtained in seven haemophilia treatment centres; haematological and paediatric institutes and hospitals in Belgrade, Niš and Novi Sad, as well as in other twenty local hospitals. The Programme is financed by the Health Insurance Fund. Centralized drug supply was introduced in 2004.

A total of 392 haemophilia A and 64 haemophilia B patients were registered in the National Registry of patients with inherited bleeding disorders on December 31<sup>st</sup> 2008. Over the last 9 years (2000–2008) the median annual number included 8 newly diagnosed patients with haemophilia (range: 4–15). Table 1 illustrates the number and age of the registered patients.

The control of coagulation factors inhibitor is performed on regular basis. Since 2000, 170 patients with HA were

**Table 1.** Number and age of registered haemophilia patients in Serbia (until December 31<sup>st</sup> 2008)

Disorder	Age (years)				Total
	0-7	8-13	14-18	>18	
Haemophilia A	16	31	48	297	392
Haemophilia B	5	5	8	46	64
Total	21	36	56	343	456

**Table 2.** Products supply for haemophilia treatment in Serbia (2000-2008)

Concentrate	Year									
	2000	2001	2002	2003	2004	2005	2006	2007	2008	
FVIII (IU×10 <sup>3</sup> )	1930	1901	3468	2238	4000	4850	8872	8613	10503	
FIX (IU×10 <sup>3</sup> )	222	450	302	200	400	500	400	675	781	
FVIII-vWF (IU×10 <sup>3</sup> )	-	-	-	-	400	400	293	375	470	
rFVIIa (packs/kutija)	-	985	690	-	700	840	1644	1635	2295	
APCC (IU×10 <sup>3</sup> )	-	-	-	-	-	-	-	120	100	

tested for the presence of inhibitor and 16 of them were found positive. The overall prevalence of the FVIII inhibitor was 9.4% in patients with HA. According to the inhibitor titre 12/16 (75%) were high-responders and 4/12 (25%) were low-responders. In the same period, 20 HB patients were tested, and all were negative.

The therapy of choice for haemophilia patients is treatment with coagulation factors concentrates due to their efficacy and safety. Plasma derived FVIII/FIX concentrates is available in Serbia. From 2000 to 2003 around three million units of FVIII concentrate were administered annually, e.g. 0.25 IU/capita/year. Besides, national cryoprecipitate was also available for the treatment. In 2003, the National Haemophilia Committee was founded which, among other things, resulted in the introduction of centralized products supply. During 2004 and 2005, considerable quantities of concentrate were provided; around five million units annually, i.e. 0.65 IU/capita/year. In order to achieve further improvement in haemophilia care, we also established international cooperation; education, training, consulting and participation in clinical and research projects. Over the past few years, with the support of the World Federation of Haemophilia (WFH), we had cooperation with colleagues from Stockholm, Sweden and Hamilton, Canada. A twinning programme between haemophilia centres Karolinska Hospital, Stockholm and Blood Transfusion Institute, Belgrade took place in 2003-2004. Another twinning programme took place in 2005-2008 with colleagues from Haemophilia Centre Hamilton, Canada. As the result of our activities, FVIII concentrate consumption in 2008 was 10.5 million units e.g. 1.35 IU/capita/year. Compared with the year 2000, the quantity of FVIII concentrate was five times higher in 2008. The use of cryoprecipitate has been decreasing; in 2008 it was used in some cases only, and we hope to completely eliminate it during 2009 by timely supply and distribution of the drugs. The use of FIX concentrate was also increasing and it was three times higher in 2008 as compared to 2000. FIX concentrate consumption in 2000 was 0.03 IU/capita/year, and in 2008 almost 800 thousand units were used, e.g. 0.10 IU /capita/year.

The choice of products for haemophilia treatment was also improved. Namely, until 2004 the availability of DDAVP, antifibrinolytic drugs, rFVIIa and activated prothrombin complex concentrate were limited, while from 2004 onwards these products became available for the treatment of haemophilia patients in Serbia. Haemophilia patients with inhibitors, who are also high-responders, are treated with rFVIIa and activated prothrombin complex concentrate. Table 2 illustrates the choice and quantity of products for haemophilia treatment in Serbia during last nine years.

## DISCUSSION

According to the EHAD, in each country there should be a central organization for haemophilia care supported by centres operating at the local level. This improves disease outcome in both developing and Western countries [6]. Organization of haemophilia care in Serbia is in accordance with that principle. There is the National Registry and the National Haemophilia Committee founded in 2003 by the Ministry of Health, with representatives of haemophilia treatment centres and the National Registry. The Committee and the Registry are in charge of planning and monitoring of the diagnosis and therapy of haemophilia [7, 8].

Each country should have a national haemophilia patient registry [6]. Surveillance systems established to monitor haemophilia population have a substantial impact on haemophilia care around the world [4, 9]. Regarding haemophilia, one of the first registries has been set up in the UK in 1967; it collects complete data on all new diagnoses of coagulation disorders, treatment, complications, viral transmission and mortality rates [10, 11, 12]. Another example is the Canadian clinic registry comprising data on patients with HA, HB, VWD and rare bleeding disorders related to epidemiology, the evaluation of viral infections and treatment [13]. Other national haemophilia registries are currently serving the haemophilia community [14, 15, 16]. From 1963 the Serbian National Registry at the Blood Transfusion Institute of Serbia has been collecting data used for epidemiological surveillance (number of patients, frequency of coagulation factor inhibitors and viral transmission), preparing a plan for drugs supply (drugs utilization, treatment costs) and surveillance of patients' social status [7, 8].

The key issues in the selection of product are its efficacy and safety. The first factor replacement concentrates were derived from human plasma and later factor concentrates were produced by recombinant technologies which became available in highly developed countries since the mid-1990s [1]. None of the currently available recombinant concentrates have ever been shown to transmit infective agents, and according to the United Kingdom Haemophilia Centre Doctors' Organization (UKHCDO) guideline, patients with congenital haemophilia should be treated with recombinant products, particularly, if they have never been exposed to plasma products [17]. However, the use of concentrates, and especially recombinant ones, is limited to the most developed countries due to the high price [3]. Plasma derived FVIII/FIX concentrates are available in Serbia and we plan to introduce recombinant FVIII/FIX concentrate during 2009 for the treatment of haemophilia patients who have never been exposed to plasma products.

People with haemophilia need to have access to safe and effective treatment at optimum levels enabling them to live a normal life [3]. There are wide disparities in the provision of care for people with haemophilia, because of the relatively high cost of treatment and the necessary specialized clinical infrastructure [2, 18]. The national registries should also record data on drug supply with the main purpose to improve haemophilia care. Our data will

be compared with global data gathered by the WFH. The Global Survey 2007 included data from 100 countries, which is 88% of the world population [18].

Regarding the quantity of coagulation factor concentrates 10.5 million units of FVIII concentrate was administered in Serbia in 2008, that is 1.35 IU/capita. Comparing to the Western European countries, where FVIII usage per capita ranges from 2.8 unit in Greece to 8.4 in Sweden, we use less FVIII concentrate. However, in comparison to the year 2000 the quantities of FVIII concentrate increased five times by 2008. FIX concentrate consumption ranges from 0,001 IU/capita in the least developed to 0.39 in highly developed countries. FIX concentrate consumption in Serbia in 2008 was 0.10 IU/capita, which was in accordance with our economic capacity.

Home treatment and prophylactic treatment should be available to people with haemophilia in each country as it has been shown to prevent and improve chronic joint disease [19, 20]. The available quantities of FVIII/FIX concentrates in Serbia enable on demand treatment of acute bleeding episodes partially carried out as home treatment. The availability of prophylactic treatment, physiatric and orthopaedic care is still limited.

The most frequent complication of replacement therapy of haemophilia is the development of inhibitors to the replaced clotting factor. Retrospective studies have shown a prevalence of FVIII inhibitors of 6-20%, while FIX inhibitors are very rare [21]. The prevalence of Serbian HA patients known to have developed an inhibitor is 9.3%. Our data are substantially comparable with those reported in the literature. Patients with inhibitors, who are also high-responders, should be treated with rFVIIa or activated prothrombin complex concentrate. These preparations are licensed in Serbia and provided by a centralized supply.

The sharing of education and management information across countries should be encouraged. The WFH established twinning programmes between haemophilia centres and International Haemophilia Training Centres (IHTCs) more than two decades ago [22, 23]. Within our two twinning projects with Haemophilia Centres in Stockholm and Hamilton a considerable improvement of haemophilia care in Serbia has been achieved. Educational programmes were organized in Belgrade and several physicians, nurses and technologist from Serbia have been trained internationally i.e. in Milan, London and Hamilton IHTCs.

## CONCLUSION

Much has been achieved for haemophiliacs in the last nine years. We have safe effective treatment for our patients so that children with haemophilia can grow with minimal disability, expecting normal lifestyle and employment prospects. Considerable improvement of the treatment is the result of efforts made by colleagues in health care institutions in charge of haemophilia care in Serbia and the support of the Ministry of Health and the Health Insurance Fund. Extensive support has been provided through international cooperation.

## ACKNOWLEDGMENT

The authors acknowledge the following colleagues, who are in charge of the treatment of haemophilia patients, for their collaboration and support in registration and data collection: Predrag Miljić, Institute of Haematology, Clinical Centre of Serbia, Belgrade; Nada Rašović, Dragan Micić. Miloš Kuzmanović, Mother and Child Health Institute

of Serbia “Dr Vukan Ćupić”, Belgrade; Dragana Janić, University Children Hospital., Belgrade; Nebojša Rajić, Clinic of Haematology, Clinical Centre of Vojvodina, Novi Sad; Nada Konstantinidis, Children and Youth Health Care Institute, Novi Sad; Miodrag Vučić, Clinic of Haematology, Clinical Center Niš; Gordana Kostić, Children’s Clinic, Clinical Centre Niš.

## REFERENCES

- Mannucci PM, Tuddenham E. The haemophilias – from royal genes to gene therapy. *N Engl J Med.* 2001; 344:1773-9.
- Evatt BL, Black C, Batorova A, Street A, Srivastava A. Comprehensive care for haemophilia around the world. *Haemophilia.* 2004; 10:9-13.
- Bolton-Maggs PHB. Optimal haemophilia care versus reality. *Br J Haematol.* 2005; 132:671-82.
- Dimichele D. In praise on long-prospective data collection: questions and perspectives. *J Thromb Haemost.* 2004; 2:1044-6.
- Evatt BL, World Federation of Haemophilia Guide to Developing a National Patient Registry. World Federation of Haemophilia 2005. Available at: [http://www.wfh.org/2/doc/Publicatons/Diagnosis\\_and\\_Treatment/Registry\\_Guide\\_2005](http://www.wfh.org/2/doc/Publicatons/Diagnosis_and_Treatment/Registry_Guide_2005) (last accessed 27. 06. 2009).
- Colvin BT, Astemark J, Fischer K, Gringeri A, Lassila R, Schramm W, et al. European principles of haemophilia care. *Haemophilia.* 2008; 14:361-74.
- Mikovic D. Haemophilia healthcare in Serbia – principles and organization. NovoSeven Symposium, Belgrade, November 8<sup>th</sup> 2001. Book of Abstracts, p.14-5.
- Mikovic D, Jankovic G, Rakic Lj, Maslac A, Kovac M. Improvement of the quality of hemophilia and von Willebrand disease treatment in Serbia from 2000 to 2005; XXVII International Congress of the WFH, Vancouver, Canada, 21-25 May, 2006. Book of Abstracts. *Haemophilia.* 2006; 12(s2):45-50.
- Srivastava A, Hoots WK, Soucie JM, Ludlam CA. Linking the world with training and research for improving haemophilia care. *Haemophilia.* 2008; 14(Suppl 3):43-8.
- Hay CR. The UK Haemophilia Database: a tool for research, audit and healthcare planning. *Haemophilia.* 2004; 10(S3):21.
- Darby SC, Kan SW, Spooner RJ, Giangrande PL, Lee CA, Macris M, et al. The impact of HIV on mortality rates in the complete UK haemophilia population. *AIDS.* 2004; 20:525-33.
- Darby SC, Keeling DM, Spooner RJ, Wan Can S, Giangrande PL, Collins PW, et al. The incidence of factor VIII and factor IX inhibitors in the hemophilia population of the UK and their effect on subsequent mortality, 1977–99. *J Thromb Haemost.* 2004; 2:1047-54.
- Walker I. The Canadian Hemophilia Registry. *Haemophilia.* 2004; 10:21-2.
- Ivaskevicius V, Jurgutis R, Rost S, Müller A, Schnitt C, Wulff K, et al. Lithuanian haemophilia A and B registry comprising phenotypic and genotypic data. *Br J Haematol.* 2001; 112:1062-70.
- Kar A, Potnis-Lele M. Haemophilia data collection in developing countries: example of the haemophilia database of Maharashtra. *Haemophilia.* 2004; 10:301-4.
- Iorio A, Olivoecchio E, Morfini M, Mannuccio PM. Italian Registry of Haemophilia and Allied Disorders. Objectives, methodology and data analysis. *Haemophilia.* 2008; 14(3):444-53.
- Keeling D, Tait C, Makris M. Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. *Haemophilia.* 2008; 14:671-84.
- World Federation of Hemophilia Global Survey 2007. Available at: [www.wfh.org](http://www.wfh.org). (last accessed 14.06.09)
- Teitel JM, Banard D, Israels S, Lillicrap D, Poon MC, Sek J. Home management of haemophilia. *Haemophilia.* 2004; 10:118-33.
- Hoots WK, Nugent DJ. Evidence for the benefits of prophylaxis in the management of hemophilia A. *Thromb Haemost.* 2006; 96:433-40.
- Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. *Haemophilia.* 2003; 9:418-35.
- Giangrande P, Mariani, G, Black C. The WFH Haemophilia Centre Twinning Programme: 10 years of growth, 1993–2003. *Haemophilia.* 2003; 9:240-4.
- Poon MC, Luke KH. Haemophilia care in China: achievements of a decade of World Federation of Hemophilia treatment centre twinning activities. *Haemophilia.* 2008; 14:879-88.

## Квалитет лечења хемофилије у Србији: извештај Националног регистра за хемофилију

Данијела Миковић<sup>1</sup>, Љиљана Ракић<sup>1</sup>, Гордана Јанковић-Тршњак<sup>1</sup>, Радмила Баклаја<sup>1</sup>, Иво Елезовић<sup>2</sup>

<sup>1</sup> Одељење за хемостазу и центар за хемофилију, Институт за трансфузију крви Србије, Београд, Србија;

<sup>2</sup> Институт за хематологију, Клинички центар Србије; Медицински факултет, Универзитет у Београду, Београд, Србија

### КРАТАК САДРЖАЈ

**Увод** Национални регистар особа с урођеним коагулопатијама је основан 1963. године и отада се налази у оквиру Одељења за хемостазу и центра за хемофилију Института за трансфузију крви Србије у Београду.

**Циљ рада** Циља рада је био да се процени квалитет лечења особа с хемофилијом у Србији у периоду 2000-2008. године на основу података Националног регистра који се односе на организацију лечења, количину и избор препарата који се примењују у лечењу ове болести.

**Методе рада** Анализа података Националног регистра прикупљених од јануара 2000. до децембра 2008. године.

**Резултати** У Националном регистру особа с урођеним коагулопатијама регистрована су 392 болесника с хемофилијом А, 64 с хемофилијом Б, 217 са Фон Вилебрандовим (*von Willebrand*) обољењем и 19 болесника с ретким урођеним коагулопатијама. Болесници се лече у седам референтних центара (у хематолошким и педијатријским институтима и клиникама у Београду, Новом Саду и Нишу), као и у 20 локалних здравствених центара. Од 2000. до 2003. године око три милиона јединица концентрата *FVIII* је примењивано годишње, односно 0,25 ИЈ по становнику годишње. За лечење је коришћен

и национални криопреципитат. Године 2003. формирана је Републичка стручна комисија за хемофилију и уведено централизовано снабдевање лековима. Током 2004. и 2005. године обезбеђено је око пет милиона јединица годишње, односно 0,65 ИЈ по становнику годишње. Избор препарата је такође унапређен. Наиме, до 2004. године *DDAVP*, анифибринолитици и концентрат *rFVIIa* су били ограничено доступни, али од 2004. ови препарати постају доступни за лечење хемофилије у Србији. Ради унапређења збрињавања особа с хемофилијом, отпочела је међународна сарадња кроз едукацију, усавршавање, консултације и учешће у клиничким и истраживачким студијама. Као резултат, потрошња концентрата *FVIII* у 2008. години је била 10,5 милиона јединица, односно 1,35 ИЈ по становнику годишње.

**Закључак** Значајно унапређење лечења особа с хемофилијом је резултат активности здравствених радника и регулаторних институција у Србији. Значајна подршка овим активностима се одвијала кроз програме стручне сарадње центара за хемофилију из Стокхолма и Београда у периоду 2003-2004. године и Хамилтона и Београда у периоду 2005-2008. године.

**Кључне речи:** хемофилија; регистар; квалитет лечења