

HISTORY OF MEDICINE / ИСТОРИЈА МЕДИЦИНЕ

Development of hematopoietic stem cell transplantation at the Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia

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**SUMMARY**

The first allogeneic hematopoietic stem cell transplantation in children in Serbia was performed in the 1970s at the Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia. In December 1990, a haploidentical hematopoietic stem cell transplantation was performed on a nine-month-old infant suffering from X-linked severe combined immunodeficiency. Seven years later, a Bone Marrow Transplantation Department was established at the Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia. Thanks to the members of the transplantation team, with the help and support of the Ministry of Health of the Republic of Serbia and the Republic Fund of Health Insurance, as well as assistance from several centers in Italy and England, significant success was achieved in the development of transplantation medicine. Each year, the members of the transplantation team at the Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia perform 18–26 hematopoietic stem cell transplantations, both autologous and allogeneic (from an identical related donor, unrelated matched donor, related partially matched donor, related and unrelated cord blood).

Keywords: children; hematopoietic stem cell transplantation; Serbia

INTRODUCTION

Nearly seven decades ago, in 1957, Thomas et al. [1] performed the first hematopoietic stem cell transplantations (HSCT) in patients suffering from leukemia. Two years later, Mathe et al. [2] applied this form of treatment to six patients who had been irradiated in an accident at the Vinča Institute of Nuclear Sciences near Belgrade. Mathe et al. [2] became the most active group in this field during the following years, and in 1968 they reported the first results of the treatment of patients with leukemia. They were also the first to provide a clinical description and the basis for the pathology of graft-versus-host disease, and emphasized the importance of viral and fungal infections in patients after HSCT. The first HSCT in children were performed in 1968, on two boys suffering from primary immunodeficiency [one with severe combined immunodeficiency and the other with Wiskott–Aldrich syndrome] [1–7].

In the 1970s, Dr. Jovan Kezić, founder and first head of the Hematology and Oncology Department, and Dr. Mirko Mikuška, founder and first head of the Immunology Department, performed the first allogeneic HSCT at the Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia (DVCIHPMCS) in a child suffering from severe acquired aplastic anemia. Nearly two decades later, in December 1990, Dr. Mario Abinun and Dr. Dragana Vujić (born Makić), with the great help and support

from Prof. Dr. Miomir Malešević and Prof. Dr. Dese Lilić from the Military Medical Academy in Belgrade, performed the first HSCT from a related partially matched donor (haploidentical HSCT) in a nine-month-old boy suffering from severe combined immunodeficiency. Monoclonal antibody “Campath-1M” (anti-CD52), necessary for bone marrow processing, which was used as the source of hematopoietic stem cells, were obtained as a donation from colleagues in London, Prof. Roland Levinsky and Dr. Gareth Morgan (Institute of Child Health, Great Ormond Street Hospital, Department of Paediatric Immunology, London, UK), thanks to the private contacts of Dr. Mario Abinun. The complicated process of bone marrow processing (removal of T lymphocytes – T-cell depletion) was performed by Prof. Dr. Dese Lilić with her team at the Institute for Experimental Medicine, the Military Medical Academy. This was the first haploidentical HSCT not only in Serbia and the former Yugoslavia, but in the region. Except for a mild chronic form of graft-versus-host disease on the skin, the patient did not have other post-transplant complications [8–12] (Figures 1 and 2).

Recognizing the importance of HSCT in the treatment of congenital and acquired diseases of the lymphohematopoietic system in children, the doctors of the Hematology and Oncology Department (Dr. Jovan Kezić, Dr. Sofija Aleksandrović-Boberić, Dr. Nada

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Figure 1. Photograph of M.A. in 1990 at the age of nine months (photograph obtained from Prof. Dr. Mario Abinun)



Figure 2. M.A. with family and Prof. Dr. Dragana Vujić, in 2024

Rašović-Gvozdenović, and Dr. Petar Ivanovski) and the doctors of the Immunology Department (Dr. Mirko Mikuška and Dr. Mario Abinun) of the DVCIHPCMS, supported by the director Dr. Božidar Vlajić, in 1986 sent a letter to the Republic Fund of Health Insurance requesting the formation of a Bone Marrow Transplant Unit. Virtually, from 1986, an effort to establish the Bone Marrow Transplantation Unit began. The first “sterile unit” was donated by Prof. Wilhelm Friedrich, the Ulm transplantation team, thanks to the private contacts of Dr. Mario Abinun. In October 1991, a letter was sent to the Republic Health and Health Insurance Fund of Serbia with a proposal to establish a Bone Marrow Transplant Unit for children at the DVCIHPCMS. A new letter to the Republican

Fund of Health Insurance requesting the establishment of a Bone Marrow Transplant Unit was submitted on December 16, 1993. The following year, in March 1994, the director of the DVCIHPCMS, Prof. Dr. Miloš Baničević, and the head of the Hematology and Oncology Department, Prof. Dr. Gordana Bunjevački, have prepared the “Program for the Establishment and Operation of the Intensive Care Unit and Treatment Department in the Department of Hematology” and submitted it to the City Fund for Health Insurance. After receiving all necessary approvals and required funds, at the end of 1994, the construction of the future Bone Marrow Transplantation Unit began at the start of 1995, and opened and put into operation on April 18, 1997. On the day the Bone Marrow Transplantation Unit

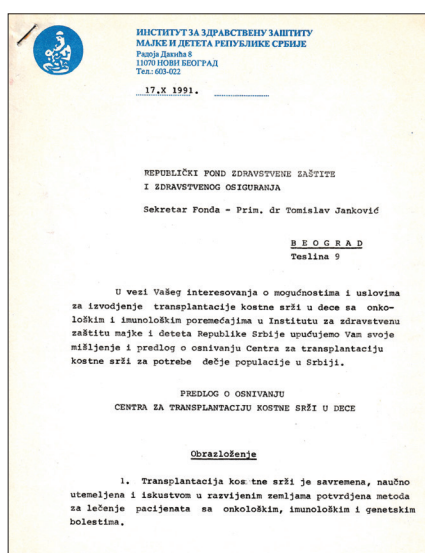


Figure 3. Letter to the Republic Health Insurance Fund dated October 17, 1991

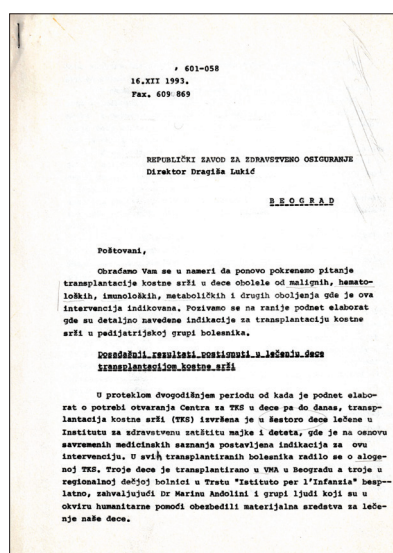


Figure 4. Letter to the Republican Health Insurance Institute on December 16, 1993

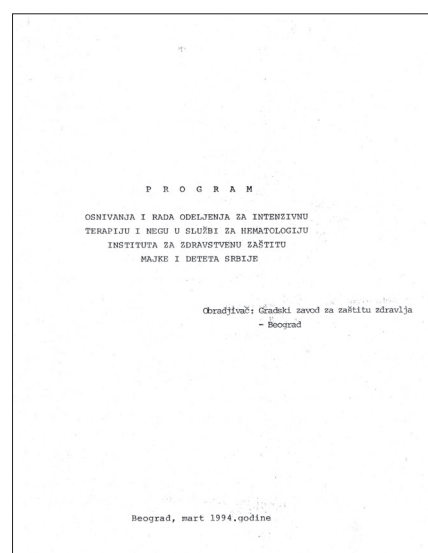


Figure 5. Program for the establishment and operation of the Intensive Care and Therapy Department at the Hematology Department



Figure 6. Health workers and associates who on April 18, 1997, performed the first allogeneic bone marrow transplant in the newly opened sterile unit (from left to right stand Prof. Dr. Srđan Pašić, Prof. Dr. Dragana Vujić)

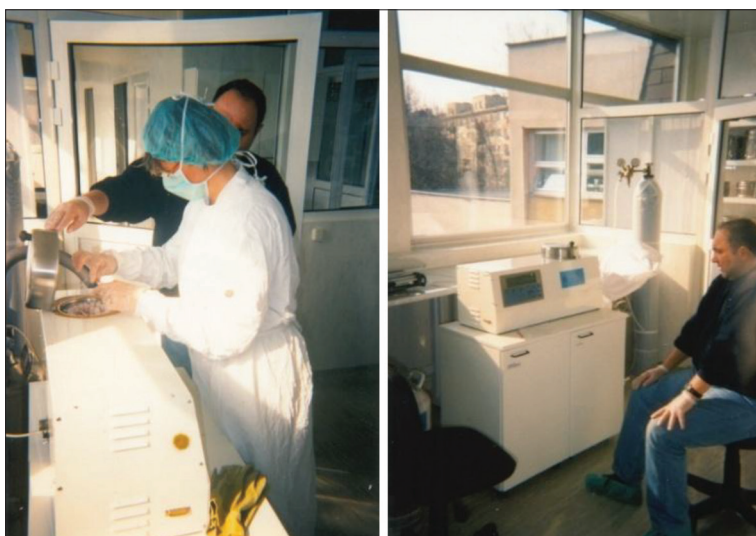


Figure 7. Danko Đurić MSc. and Prof. Dr. Dragana Vujić, 1997, freezing of hematopoietic stem cells

was opened, a HSCT was performed on a six-month-old infant suffering from severe combined immunodeficiency. The bone marrow donor was an older brother. Prof. Dr. Dragana Vujić and Prof. Dr. Srđan Pašić led the transplant team that successfully performed this transplantation. That same year, in August, the first autologous transplantation was performed in a girl who had a relapse of rhabdomyosarcoma. This was also the first autologous HSCT in a child in Serbia where control rate freezing of hematopoietic stem cells was used. The head of the transplantation team was Prof. Dr. Dragana Vujić. From the opening of the Bone Marrow Transplantation Unit until 2004, the transplantation team of the DVCIHPMCS performed 1–3 transplants per year. Thanks to the fact that in 2004 the Ministry of Health of the Republic of Serbia and the Republic Fund of Health Insurance recognized transplantation medicine as one of the priorities, the transplantation team became increasingly active and in 2005 performed eight HSCT. From 2005 to the present the transplantation team performs

between 18 and 26 HSCT per year [8, 13] (Figures 3–6).

Educating the members of the future transplantation team began in 1993 at centers in Italy (Trieste, Perugia, Genoa, Monza, Brescia, and Pavia) and in England (Newcastle upon Tyne). We owe great gratitude to Dr. Marino Andolina (Burlo Garofolo Children's hospital, Trieste, Italy), Dr. Augusto Amici (University of Perugia, Clinic of Pediatrics, Perugia, Italy), Dr. Momčilo Janković (San Gerardo Hospital, Monza, Italy), Dr. Bruno De Bernardi (Giannina Gaslini Institute, Genoa, Italy), Dr. Luigi D Notarangelo (Azienda Ospedaliera Spedali Civili di Brescia, Brescia, Italy) and Dr. Marco Zecca (La Fondazione IRCCS Policlinico "San Matteo," Pavia, Italy), as well as Dr. Mario Abinun (North Children's Hospital, Newcastle upon Tyne, England). The funds for the education of the transplantation team members were provided by colleagues from centers in Italy and England, partly through the project "Creating Conditions for HSCT in Children in Serbia," which has been financed from the budget since 2008 through the Ministry of Health of the Republic of Serbia [13].

Prof. Dr. Dragana Vujić, Prof. Dr. Vujko Drndarević (University of Belgrade, Faculty of Electrical Engineering, Vinča Institute of Nuclear Sciences), Danko Đurić, MSc (Vinča Institute of Nuclear Sciences), Miroljub Arandelović (Vinča Institute of Nuclear Sciences), as well as numerous associates from the Vinča Institute of Nuclear Sciences, in October 1994 started the implementation of a project for the development of a microprocessor for the programmed freezing of hematopoietic stem cells. The

first testing of the microprocessor took place in 1995, when hematopoietic stem cells from laboratory animals were used, and a year later, in 1996, Dr. Dobrila Veljković, the head of the Transfusion Department at the DVCIHPMCS performed the first isolation of human hematopoietic stem cells from peripheral blood, and the obtained cells were used for testing the microprocessor. The donor of the hematopoietic stem cells from peripheral blood was Prof. Dr. Dragana Vujić. The obtained test results confirmed the reliability of the microprocessor, which was successfully used in the period from August 1997 to 2002 [14, 15] (Figure 7).

During 1996 and 1997, Prof. Dr. Dragana Vujić and the head of the Transfusion Department of the DVCIHPMCS, Dr. Sci. Med. Dobrila Veljković, prepared the "Standards for Bone Marrow Transplantation in Children," which were submitted to the Ministry of Health of the Republic of Serbia and the Republic Fund for Health Insurance. A year later, in December 1998, the Ministry of Health made a decision to establish the Republic Center for Bone Marrow

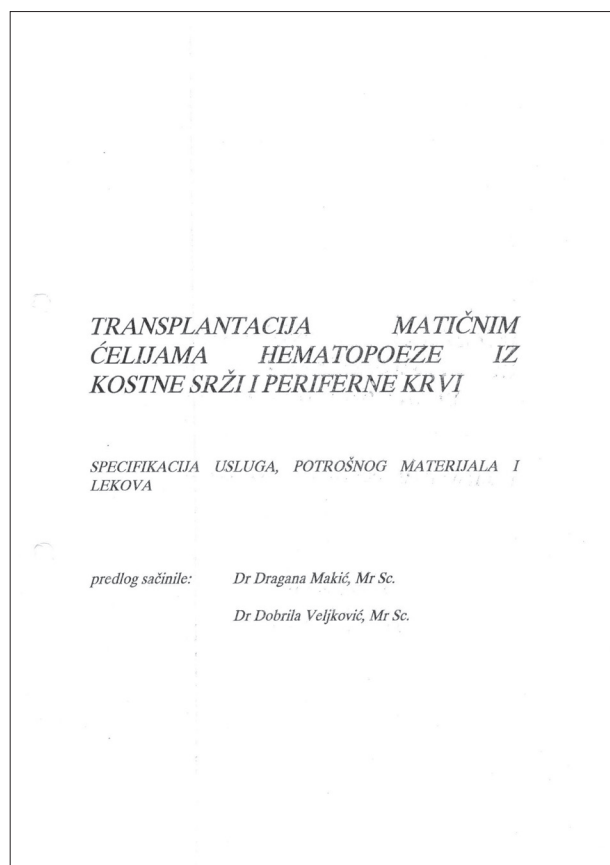


Figure 8. Standards for bone marrow transplantation in children

Transplantation in Children at the DVCIHPMCS. In the same year, we became members of the European Group for Blood and Marrow Transplantation [8, 13] (Figure 8).

The Laboratory for Cryobiology at the Bone Marrow Transplantation Unit was established in 2001 thanks to a donation from the government of the Republic of Italy and the Italian non-governmental organization “Nuova frontiera alisei.” A year later, the non-governmental organization “Gruppo Cesvi L’Espresso” from Italy provided the funds necessary for the acquisition of equipment for the Transfusion Department, the Flow Cytometry Laboratory, and the Cryobiology Laboratory. These two significant donations enabled the further development of HSCT at the DVCIHPMCS [8, 13] (Figure 9).

The project proposal “Creating Conditions for HSCT in Children in Serbia” was prepared in 2007 and submitted to the Ministry of Health of the Republic of Serbia. The project was approved and its implementation began in 2008. The project was prepared by Prof. Dr. Dragana Vujić in collaboration with healthcare workers and associates from the Bone Marrow Transplantation Unit and the Cryobiology Laboratory of the DVCIHPMCS, and from 2008 to 2025 she was the coordinator of the project. The implementation of the project enabled the procurement of the necessary equipment for the successful implementation of the HSCT program at the DVCIHPMCS the preparation of the conceptual, technological, and main project for a new bone marrow transplantation unit and public/

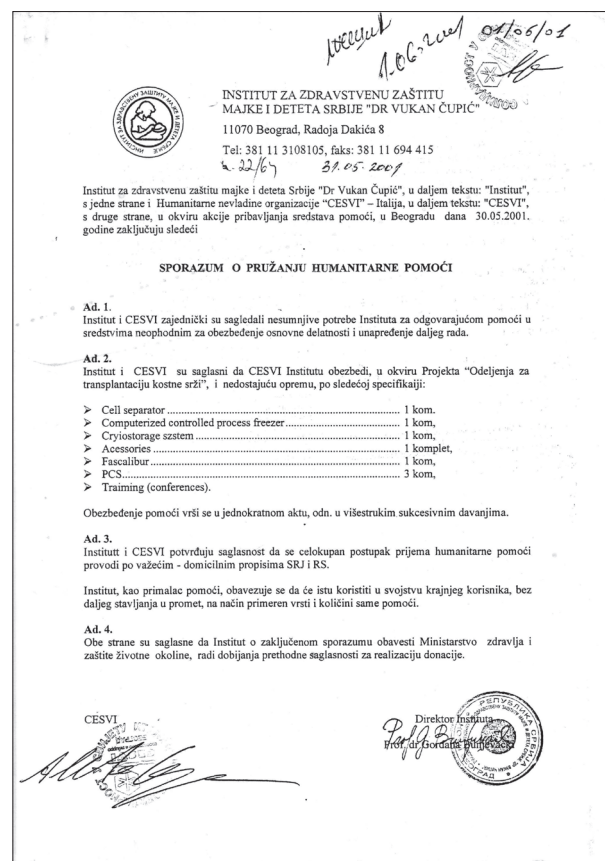


Figure 9. Contract with Gruppo Cesvi L’Espresso

family cord blood bank, the construction and equipping of the public/family cord blood bank, and the procurement of necessary consumable materials for hematopoietic stem cells processing, as well as the preparation of guides for patients, parents, hematopoietic stem cell donors, and healthcare workers and collaborators [8, 13] (Figure 10).

After obtaining the necessary permits, the construction of a public/family umbilical cord blood bank began in April 2013. While the necessary equipment for the future bank was being acquired and team members were undergoing training, the construction of the public/family cord blood bank proceeded in phases. Architectural and construction work was completed in 2020, when, due to changes in legal regulations, the struggle for the legalization of the public/family cord blood bank building began. The public/family cord blood bank building was legalized in September 2023, and in September 2025, with the relocation of the cryobiology laboratory, the public/family cord blood bank building was put into operation [16, 17, 18] (Figure 11).

The first sample of related cord blood was collected, processed, and cryopreserved in 2002 in the newly established cryobiology laboratory. Seven years later, in November 2009, approval was obtained from the Commission for New Technologies of the Ministry of Health of the Republic of Serbia for the establishment of a family cord blood bank, and by 2025, 117 samples had been processed and stored. The procedure for obtaining



Figure 10. Guides created by the transplantation team of Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia (taken from: <https://www.zdravlje.gov.rs/tekst/429156/vodici-dobre-klinicke-prakse-iz-oblasti-transplantacije.php>)

the necessary approvals to operate a public cord blood bank is currently underway [16, 17, 18].

The transplantation team of the DVCIHPMCS provided assistance and support to the transplantation team of the Clinic for Hematology of the University Clinical Center of Serbia from 2008 to 2020 by collecting, processing, and storing patients' hematopoietic stem cells for autologous transplantation [13].

Significant progress has been achieved thanks to the collaboration with the Institute for Medical Research, where the viability of collected and cryopreserved hematopoietic stem cells was assessed, as well as monitoring of Toxoplasma reactivation in the post-transplant period. Prof. Dr. Tanja Jovanović and Prof. Dr. Valentina Arsić Arsenijević from the University of Belgrade, Faculty of Medicine, Institute of Microbiology and Immunology, along with their teams, enabled the monitoring of the virological and mycological status of patients in the peri-transplant period. Thanks to the establishment of the

National Registry of Voluntary Hematopoietic Stem Cell Donors at the Institute for Blood Transfusion of Serbia and the special involvement of Dr. Zorana Andrić, PhD, and Dr. Gloria Blagojević, it became possible to find unrelated voluntary hematopoietic stem cell donors not only in the Serbian registry but also in the worldwide registry [13, 18–21] (Figure 12).

During 2009–2010, the Zvončica Parents' House was built as part of the DVCIHPMCS, intended for the accommodation of children after leaving the Bone Marrow Transplantation Unit, as well as for children from the Hematology and Oncology Department, to ensure adequate monitoring. This significant project was realized through the substantial involvement of the then Director of the Republic Fund of Health Insurance, Mrs. Svetlana Vukajlović [13] (Figure 13).

Significant events for HSCT in children in Serbia are: the first bone marrow transplantation at the DVCIHPMCS, the first haploidentical transplantation with T-cell



Figure 11. Construction of a public/family umbilical cord blood bank; in the photograph, from left to right: Prof. Dr. Dragana Vujić and Emilija Lazić (molecular biologist)



Figure 12. Part of the team that participated in processing the first unrelated bone marrow sample; the donor is from the National Registry of Voluntary Hematopoietic Stem Cell Donors of Serbia, November 2009 (from left to right: Dr. Olivera Šerbić, Dr. Marino Andolina, Prof. Dr. Dragana Vujić, Dr. Dobrila Veljković, Dr. Zorana Andrić)



depletion in December 1990, the opening of the Bone Marrow Transplantation Unit and the first transplantation in the newly opened Unit in April 1997, the first autologous HSCT in August 1997, the first haploidentical transplantation with *ex vivo* treatment of stem cells using vincristine and methylprednisolone in March 2006, the first transplantation from an unrelated matched donor from the Serbian registry in November 2009, approval by the Commission for New Technologies of the Ministry of Health of the Republic of Serbia for the formation of a family cord blood bank in November 2009, processing of haploidentical graft using the alpha/beta TCR/CD19 depletion method in November 2012, the first CD34+ selection in February 2013, the first transplantation from an unrelated donor from the global registry in April 2013, the first transplant with identical related cord blood in May 2017, the first transplant from unrelated cord blood from the world registry in December 2017, administration of



Figure 13. Construction of the Zvončica Parents' House

donor lymphocyte infusion in February 2022, use of extracorporeal photopheresis in 2023 [10, 13, 14, 16, 22–25].

Since the establishment of the sterile unit, members of the transplantation team have introduced new forms of transplantation, immunomodulation, methods for processing hematopoietic stem cells, diagnostic procedures for early recognition, and reduction of the incidence of acute and chronic transplantation complications. Better survival, improved quality of life after HSCT were achieved, and projects and programs were developed aimed at creating a center capable of gaining international accreditation. This significant achievement could not be reached without close cooperation of all members of the transplantation team of the DVCIHPMCS, the Institute of Microbiology of the Faculty of Medicine of the University of Belgrade, the Laboratory for Human Leukocyte Antigen Typing, and the National Register of Voluntary Hematopoietic Stem Cell Donors of the Institute for Blood Transfusion of Serbia, the Institute for Medical Research of the University of Belgrade, as well as the assistance and support of the Ministry of Health and the Republic Fund of Health Insurance, colleagues from foreign centers who helped in

the education of members of the transplantation team and in providing the necessary equipment, and people of good will who provided significant donations.

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Ethics: The author declares that the article was written according to the ethical standards of the Serbian Archives of Medicine as well as the ethical standards of its institution.

Conflict of interest: None declared.

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Развој трансплантације матичних ћелија хематопоезе у Институту за здравствену заштиту мајке и детета Србије „Др Вукан Чупић“

Драгана Вујић

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Еуромедик, Београд, Србија

САЖЕТАК

Прва алогена трансплантација матичних ћелија хематопоезе код деце у Србији урађена је седамдесетих година 20. века у Институту за здравствену заштиту мајке и детета Србије „Др Вукан Чупић“. У децембру 1990. године урађена је хаплоидентична трансплантација матичних ћелија хематопоезе код деветомесечног оdoјчета које је боловало од Х-везане тешке комбиноване имунодефицијенције. Седам година касније отворено је Одељење за трансплантацију коштане сржи у Институту за здравствену заштиту мајке и детета Србије „Др Вукан Чупић“. Захваљујући члановима трансплантационог тима, уз помоћ и подршку Министарства здравља Републике

Србије и Републичког фонда за здравствено осигурање, као и помоћ неколико центара из Италије и Енглеске, постигнут је значајан успех у развоју трансплантационе медицине. Чланови трансплантационог тима Института за здравствену заштиту мајке и детета Србије „Др Вукан Чупић“ годишње изведу 18–26 трансплантација матичних ћелија хематопоезе, како аутологних, тако и алогених (од идентичног сродног даваоца, несродног подударног даваоца, сродног делимично подударног даваоца, сродне и несродне крви пупчанника).

Кључне речи: деца; трансплантација матичних ћелија хематопоезе; Србија