univerzitetni klinični center ljubljana
University Medical Centre Ljubljana

ETIČNI IZZIVI PRI TRANSPLANTACIJI ORGANOV

ETHICAL CHALLENGES IN ORGAN TRANSPLANTATION

UNESCO Chair
in Bioethics, Haifa

Ljubljana, 2019

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UVOD

Transplantacija organov je eden največjih dosežkov medicine 20. stoletja. Strokovno in logistično je transplantacija najbolj kompleksna medicinska intervencija. Združuje mnoge stroke, države in najbolj občutljive podatke posameznikov. Vsi členi domačih ali mednarodnih transplantacijskih verig morajo usklajeno delovati v zelo omejenem času da bi se organ uspešno presadil. Transplantacija je rešila življenja stotinam tisočev bolnikom z dokončno odpovedjo delovanja organa. Omogočila je, da se rodi tisoče zdravih otrok staršem, ki bi bili brez transplantacije obsojeni na smrt. Danes stotine tisočev novih bolnikov v svetu čaka, da jim s transplantacijo rešimo življenje.

Zaupanje v medicino, zdravnike, medicinske sestre in celoten zdravstveni tim je temelj transplantacijske dejavnosti. Brez tega ne bi bilo darovanja organov živih ali umrlih darovalcev. Zaupa nam celotna družba. Zato transplantacijska dejavnost v Sloveniji in mnogih drugih državah uspešno poteka. Tega zaupanja ne smemo ogroziti.

Organov za transplantacijo je izrazito premalo, glede na potrebe bolnikov. Tako je bilo od začetka transplantacijske dejavnosti, tako je danes in bo tudi v prihodnje. Posledica velikega nesorazmerja med potrebami in razpoložljivimi človeškimi organi so tudi etično mejne ali nesprejemljive prakse pri pridobivanju organov. Trgovina z organi ali uporaba organov usmrčenih zapornikov sta obsojeni po vsem svetu kot prakse nesprejemljive za civilizirano družbo. So pa v nekaterih državah tudi prakse, ki so manj znane javnosti, se pa gibljejo po robu ali čez rob etično sprejemljivega.

Nobena od etično kontroverznih praks pridobivanja organov, in tudi ne vse skupaj, ne bodo rešile problema pomanjkanja organov. Nekatere prakse pa imajo lahko za posledico nasproten učinek, izgubo zaupanja v medicino in zdravnike in s tem izgubo zaupanja javnosti v transplantacijo. S tem bomo posledično lahko imeli ne več, ampak manj organov in transplantacij kot jih imamo danes. En sam škandal lahko ima večletne posledice. Nemška transplantacijska dejavnost se še danes ni povsem opomogla od škandala leta 2012, ko se je zaradi nekaj izjemnih in nesprejemljivih dogodkov ogrozilo zaupanje javnosti v celotno transplantacijsko dejavnost. Izgubljeno zaupanje se mukotrpno in počasi obnavlja in gradi naprej.

Slovenija ima na področju transplantacijske dejavnosti edinstven položaj in prednosti. Ima veliko univerzitetno bolnišnico, UKC Ljubljana, ki izvaja vse transplantacije organov in skrbi za vse bolnike od presaditve do odpovedi presajenega organa. Slovenijatransplant, ki skrbi za donorski program v povezavi z 10 slovenskimi donorskimi bolnišnicami ima sedež v UKCL. S tem se omogoča najtesnejša povezava donorskega programa s prejemniškim programom in čakalnimi listami, ki jih vodi UKC Ljubljana. Slovenija je od 1. januarja 2000 članica Eurotransplanta, velike mednarodne mreže, kar ji omogoča izmenjavo organov in s tem možnosti večje izbire pri pridobivanju organov za posameznega bolnika. Te izbire ne bi imeli če bi bili omejeni v okvir majhne države.

Slovenska transplantacijska dejavnost je integrirana v celotno medicino. Slovenski transplantacijski eksperti, ki delujejo v UKC Ljubljana, so široko in globoko seznanjeni z dosežki na področju umetnih organov in regenerativne medicine ter z zdravljenjem kroničnih bolezni. Z integralnim poznavanjem nadomeščanja funkcije organov lahko vsakemu bolniku z napredovalo odpovedjo organa ponudimo najboljše kar sodobna medicina zmore. Ponudimo mu zdravljenje po njegovi meri, to kar personalizirana medicina pravzaprav je. Zdravljenje po meri bolnika, upoštevajoč tako medicinsko stroko kot vse želje, skrbi in strahove posameznega bolnika.

Namen srečanja je predstaviti nekatere od etično mejnih ali težje sprejemljivih praks v transplantacijski medicini, ki so danes realnost ali bodo mogoče v skorajšnji prihodnosti. Prav tako bomo skozi uspešen in kakovosten slovenski transplantacijski program pokazali, da je možno našim bolnikom zagotoviti transplantacijo ob sprejemljivi čakalni dobi, ob sočasnem upoštevanju etičnih načel, ki jih v Sloveniji upoštevamo in negujemo od prve transplantacije ledvic leta 1970 v UKC Ljubljana.

Jadranka Buturović Ponikvar

INTRODUCTION

Organ transplantation is one of the greatest medical achievements of the 20th century. Medically and logistically, transplantation is one of the most complex medical interventions. It involves many professions and spans dozens of countries relying on patients' most sensitive data. In order for an organ to be successfully transplanted, all components of the domestic and international transplant chain must operate quickly and efficiently.

Transplantation saved lives of hundreds of thousands of patients with end-stage organ failure. Transplantation allowed thousands of healthy babies to be born to parents who were sentenced to death without a transplant. Today, hundreds of thousands of patients across the world are waiting for an organ to save their life.

Trust in medicine, doctors, nurses and the entire health team is the foundation of transplantation. Without trust, there would be no donation of organs from living or deceased donors. Transplantation in Slovenia and many other countries is only possible because of trust. We should take every precaution to never jeopardize this trust.

Organ shortage is one of the main challenges of transplantation medicine. This has been the case since the beginning of transplantation and remains so today. A large discrepancy between supply and demand for human organs leads to ethically borderline or outright unacceptable practices in organ harvesting. Organ trafficking or the use of organs of executed prisoners are condemned throughout the world as practices unacceptable to a civilized society. In some countries, however, practices that are less well-known to the public are moving along the edge or sometimes beyond the boundaries of what is ethically acceptable.

While ethically controversial organ harvesting practices will not solve the problem of organ shortage they might also have an opposite effect - a loss of trust in medicine and doctors, and a loss of public trust in transplantation. We could end up with fewer rarther than more organs and transplants than we do today. A single scandal can have long-term consequences. The German transplantation activity been significantly decreased after the scandal in 2012, when, due to a few rare but outrageous events, public trust in the entire transplantation program was threatened.

Slovenia has a unique position and advantages in the field of transplantation. It has a large university hospital, University Medical Center (UMC) Ljubljana, which carries out all organ transplants and takes care of all recipients, from transplantation to failure of the transplanted organ. Slovenijatransplant, responsible for the donor program in conjunction with 10 Slovenian donor hospitals, is based in UMC Ljubljana. This enables a very close connection of the donor program with the recipient program and the waiting lists maintained by UMC Ljubljana. Since January 1, 2000, Slovenia has been a member of Eurotransplant, a large international network, which allows it to exchange organs providing a greater choice in obtaining the best organ for an individual patient. We would not have had this choice if we were limited only to our own country.

Slovenian transplantation is tightly integrated into the rest of the medical system. Slovenian transplantation experts working in UMC Ljubljana are thoroughly acquainted with the achievements in the field of artificial organs, regenerative medicine and treatment of chronic diseases. In light of this comprehensive knowledge, every patient with advanced organ failure can be offered the best treatments that modern medicine can offer: personalized treatment, tailored to each patient, which takes into account both medical knowledge and patients' wishes and concerns.

The purpose of the meeting is to discuss some ethically borderline practices in transplantation medicine. Some of these practices are already reality or on their way to becoming one. We will also show, through a successful Slovenian transplant program, that it is possible for our patients to be provided with transplants within acceptable waiting time, without sacrificing ethical principles that we have nurtured since the first kidney transplantation in the UMC Ljubljana in 1970.

Jadranka Buturović Ponikvar

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PREDAVATELJI / SPEAKERS

Jadranka Buturović-Ponikvar je internistka in nefrologinja. Rodila se je v Puli (Hrvaška). Osnovno šolo, gimnazijo in srednjo glasbeno šolo je končala v Splitu (Hrvaška). Diplomirala je na Medicinski fakulteti v Beogradu (Srbija) kot najboljša študentka v generaciji (povprečna ocena 9.93) in dobila letno nagrado Srbskega zdravniškega društva. Bila je zaposlena (1982-1988) v Centru za transplantacijo in dializo Inštituta za urologijo in nefrologijo Univerzitnega kliničnega centra Srbije v Beogradu. Od leta 1988 do danes je zaposlena v Univerzitetnem kliničnem centru Ljubljana (UKCL), na Kliničnem oddelku za nefrologijo. Od 2015 do 2018 je bila predstojnica Kliničnega oddelka za nefrologijo. Od 3. januarja 2018 je strokovna direktorica UKCL.

Leta 1993 je doktorirala na Medicinski fakulteti Univerze v Ljubljani. V tujini je delovala leta 1998 na Northwestern University, Chicago. Od leta 2004 je redna profesorica za predmet interna medicina na Medicinski fakulteti Univerze v Ljubljani. Od leta 2017 je predsednica Habilitacijske komisije Medicinske fakultete Univerze v Ljubljani.

Od leta 1995 do 1999 je bila vodja Centra za otroško dializo in transplantacijo (dokler se ni preselil na Pediatrično klinikov), od leta 1999-2015 pa je bila vodja Enote za ultrazvok Kliničnega oddelka za nefrologijo. Od leta 2011 je vodja raziskovalne skupine Oddelka za nefrologijo in članica Medicinskega sveta Agencije za raziskovalno dejavnost RS. Od 2011-2019 je bila nacionalna koordinatorica za nefrologijo na Zdravniški zbornici Slovenije. Od 2014 do 2. januarja 2018 je bila pomočnica strokovnega direktorja za raziskovalno dejavnost UKCL. Leta 2019 je bila izvoljena za predsednico Etične komisije Eurotransplanta.

Glavni klinični in raziskovalni interesi so: hemodializa, transplantacija, Doppler ultrazvok, biopsija nativnih in transplantiranih ledvic, antikoagulacija, citrat, žilni pristopi, ledvični registri.

Je članica ERA-EDTA (European renal association – European dialysis and transplant association), ISN (Internatioan Society of Nephrology), ASN (American Society of Nephrology), NKF (National Kidney Foundation), ESOT (European Society for Organ Transplantation), AST (American Society for Organ Transplantation), IPTA (International Society for Pediatric Transplantation), VAS (Vascular Access Society), SZD-Slovensko nefrološko društvo, Slovensko društvo za uporabo ultrazvoka v medicini, Slovenska medicinska akademija (ustanovna članica).

Bibliografija je dostopna na pubmed in *web of science* pod imeni: buturovic j; buturovic-ponikvar j; ponikvar jb; buturovicponikvar j, in na COBISS in SICRIS, številka 10649.

Jadranka Buturović-Ponikvar is an internist and nephrologist. She was born in Pula (Croatia). She completed elementary school, grammar school and the high school of music in Split (Croatia). She graduated from the University of Belgrade Medical School as the best student in the class, being awarded by the Serbian Medical Association (GPA 9.93/10). She was first employed at the Center for Transplantation and Dialysis, Institute of Urology and Nephrology, University Medical Center Serbia, Belgrade, from 1982-1988. Since 1988 she has been employed at the University Medical Center Ljubljana, Slovenia. She was Head of the Department of Nephrology from 2015 -2018. As of January 3, 2018 she is Medical Director of the University Medical Center Ljubljana.

In 1993 she received her PhD at the Medical School of the University of Ljubljana. She spent a sabbatical in 1998 at Northwestern University in Chicago, Illinois. Since 2004 she is a Professor of Medicine at the Faculty of Medicine, University of Ljubljana, Slovenia. In 2017 she was elected President of the Habilitation Commission at the Medical Faculty, University of Ljubljana.

She was Chief of the Center for Pediatric Dialysis and Transplantation from 1995-1999 (until the Center was moved to the Department of Pediatrics), and since 1999 she has been Chief of the Ultrasound Unit at the Department of Nephrology. In 2011 she was appointed Head of the Research Group at the Department of Nephrology, and member of the Council of Medicine at the Slovenian Research Agency. She was a national coordinator for the nephrology fellowship program at the Medical Chamber of Slovenia from 2011-2019. She was Assistant Director of Research at the University Medical Center Ljubljana from 2014-January 2nd 2018. In 2019, she was elected Chair of Eurotransplant Ethical Committee (ETEC).

Her main clinical and research interests include: hemodialysis, kidney transplantation, Doppler ultrasonography, biopsies of native and transplanted kidneys, hemodialysis anticoagulation, citrate, vascular access, and renal registries.

She is a member of ERA-EDTA (European Renal Association – European Dialysis and Transplant Association), ISN (International Society of Nephrology), ASN (American Society of Nephrology), NKF (National Kidney Foundation), ESOT (European Society for Organ Transplantation), AST (American Society for Transplantation), IPTA (International Pediatric Transplant Association), VAS (Vascular Access Society), Slovenian Society of Nephrology, Slovenian Society for the use of ultrasonography in medicine, and the Slovenian Medical Academy (founding member).

Her bibliography is accessible on the pubmed and web of science under the names: buturovic j; buturovic-ponikvar j; ponikvar jb; buturovicponikvar j, and on COBISS and SICRIS, code number 10649.

Danica Avsec je anesteziologinja z več kot dvajsetletnimi izkušnjami s področja donorske medicine. Leta 1982 je diplomirala na Medicinski fakulteti Univerze v Ljubljani in leta 1991 opravila specializacijo iz anesteziologije in reanimatologije. V naziv primarij je bila imenovana leta 2002 in v svetniški naziv leta 2008.

Kot specialistka anesteziologije in reanimatologije se je zaposlila v UKC Maribor na oddelku kirurške intenzivne terapije. Leta 1998 prevzela funkcijo bolnišnične transplantacijske koordinatorice in aktivno sodelovala pri ustanovitvi nacionalnega javnega zavoda za presaditve organov in tkiv Slovenija-transplant.

Leta 2001 je bila imenovana za direktorico Slovenija-transplanta in to funkcijo opravlja še danes. Odgovorna je za nadzor nad nacionalnim donorskim in transplantacijskim programom, koordinacijo donorskih in transplantacijskih dejavnosti na nacionalni in mednarodni ravni, razvoj dejavnosti v Sloveniji in promocijo in podporo programu na nacionalni ravni. V skladu z direktivo 2010/53/EU je bila imenovana za odgovorno zdravnico za program darovanja v Sloveniji. V mednarodni fundaciji za izmenjavo organov Eurotransplant, katero je od leta 2000 vključena tudi Slovenija, je članica odbora Eurotransplant Board (od leta 2016) in članica posvetovalnega odbora za etična vprašanja ETEC (od leta 2014).

Je članica številnih slovenskih in mednarodnih strokovnih združenj. Od leta 2005 je članica Izvršnega odbora Slovenskega združenja za transplantacijo, članica Strokovnega sveta za transplantacijo pri Slovenskem zdravniškem društvu in pridružena članica Razširjenega strokovnega kolegija na MZ RS. Na mednarodnem nivoju je predstavnica Slovenije v odboru CD-P-TO pri Svetu Evrope (od leta 2007), uradna delegatka MZ RS v Evropski komisiji na sestankih nacionalnih odgovornih inštitucij za področje transplantacije organov (od 2007), predsednica odbora Board of transplant coordinators v okviru UEMS Surgery (od leta 2016) in izpraševalka na izpitih za evropskega transplantacijskega koordinatorja (od leta 2011).

Sodelovala je v številnih mednarodnih evropskih projektih kot vodja projekta (EDD), vodja posameznih delovnih sklopov (EUDONORGAN, FOEDUS) ali vodja projekta za Slovenijo (ACCORD, SOHO, MODE, ETPOD, EULID, EUROCET). Kot ključni strokovnjak je sodelovala v projektu Technical Assistance for Allignment in Organ Donation (Turkey).

Kot vabljena predavateljica sodeluje na strokovnih srečanjih in kongresih v Sloveniji in v tujini. Njena bibliografija obsega preko 100 strokovnih člankov in je dostopna v bazi COBISS.

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Danica Avsec is anaesthesiologist with more than twenty years of experience in donor medicine. She graduated from the University of Ljubljana Medical Faculty in 1982 and completed her specialisation in Anaesthesiology and reanimatology in 1991. She was awarded a primarius title in 2002 and councillor title in 2008.

She worked as a specialist of Anaesthesiology and reanimatology at UMC Maribor in surgical intensive therapy unit. In 1998 she took over the role of hospital transplant coordinator and actively cooperated with establishment of national institute for transplantation of organs and tissues Slovenija-transplant.

In 2001 she was nominated for director of Slovenija-transplant and she maintained this position until present. She is responsible for supervision of all transplant activities on national level, coordination of transplant activities on national and international level, development of donor and transplant program in Slovenia and promotion and support of the donor and transplant program on national level. In accordance with the directive 2010/53/EU she was nominated a responsible physician for donor programme in Slovenia. She took over a position of Slovene representative in Eurotransplant Board in 2016 and she is a delegate in Eurotransplant Ethical Advisory Committee ETEC since 2014.

She holds memberships in numerous Slovene and international medical associations. Since 2005 she is a member of executive board of Slovene transplant association, member of medical committee for transplantation at Slovene medical association and associated member of Advisory committee for transplantation program at the Ministry of Health of the Republic of Slovenia (since 2007). On international level she is a member of CD-P-TO at the Council of Europe (since 2007), official national delegate of MoH of the republic of Slovenia for Competent authority meetings for organs, tissues and cells (from 2007), president of the Board of Transplant Coordinators (BTC) in the frame of UEMS Surgery and EDTCO (from 2016) and examiner for EBSQ Transplant coordination exams (from 2011).

She cooperated in many EU projects as a project leader (EDD), work package leader (EUDONORGAN, FOEDUS) or project leader for Slovenia (ACCORD, SOHO, MODE, ETPOD, EULID, EUROCET). She cooperated as a key expert at Technical Assistance for Alignment in Organ Donation (Turkey) project.

Regularly attends medical congresses, professional meetings and seminars and as invited speaker in Slovenia and internationally. Her bibliography includes more that 100 articles and is accessible in COBISS database.

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Doc. dr. Željka Večerić-Haler je zdravnica in specialistka nefrologije zaposlena na Kliničnem oddelku za nefrologijo v Univerzitetnem kliničnem centru Ljubljana, Slovenija. Njeno klinično delo je večinoma povezano s klasično nefrologijo, dializo in presaditvijo ledvic. Je tudi učiteljica s pedagoškimi dejavnostmi, vključno z usposabljanjem domačih in tujih študentov medicine v področju interne medicine. Na oddelku za nefrologijo deluje tudi na področju sistema vodenja kakovosti. Kot nefrolog in koordinator sistema kakovosti se sooča s številnimi izzivi s področja bioetike in človeških odnosov. V času študija medicine je razvila zgodnje zanimanje za medicinske raziskave, predvsem temeljne študije, ki vključujejo delo na živalskih modelih. Za svoje najzgodnejše raziskovalno delo na področju črevesnih tumorjev pri podganah in zdravljenju Crohnove bolezni pri ljudeh je prejela fakultetni Prešernovi nagradi. Zahvaljujoč radovednosti, predvsem pa na podlagi izkušenj pridobljenih na področju raziskav na živalih, se je leta 2010 lotila projekta presaditve matičnih celic v živalskih modelih odpovedi ledvic ter leta 2016 iz tega področja doktorirala na Univerzi v Ljubljani. V nadaljevanju je opravila ustrezno izobraževanje ter pridobila dovoljenje za vodenje in izvajanje poskusov na živalih. Trenutni raziskovalni fokus ji predstavlja humana regenerativna medicina, in sicer deluje na projektih transplantacije matičnih celic pri zavrnitvi transplantirane ledvice in molekularni diagnostiki patologije presajene ledvice. Živi z družino v okolici Ljubljane. V prostem času se ukvarja s plesom in branjem.

Asist. Prof. Željka Večerić-Haler is a Medical Doctor and Specialist of Nephrology at University Medical Center Ljubljana, Slovenia. Her clinical work is majorly associated with classical nephrology, dialysis and transplantation. She is also a teacher with pedagogical activities including training domestic and foreign medical students in internal medicine. She also works on the field of quality management at nephrology department. As a nephrologist and quality system coordinator, she faces numerous challenges from the field of bioethics and human relations. When she was a medical student, Željka Večerić Haler developed an early interest in medical research, especially basic studies involving work on animal models. She received 2 faculty Prešerns` awards for her earliest reserch work on intestinal tumors in rats and Crohns disease in human. Having a curious mind and background in animal research she has completed her PhD from University of Ljubljana, Faculty of Medicine in 2016 working on project of stem cell transplantation in animal models of kidney failure. Afterwards she decided to take up the course obtaining an authorization to guide and conduct animal experiments. Her current research interests include regenerative medicine studies in human, including stem cell transplantation in antibody mediated rejection of transplanted kidney and molecular diagnostics of kidney transplant pathology. Željka resides with her family in the surroundings of Ljubljana. In her free time she practices dancing and spends time reading.

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Lada Zibar, MD, PhD, is a professor at Medical Faculty University Josip Juraj Strossmayer in Osijek and nephrologist at Clinical Hospital „Merkur" Zagreb. She is the president of the Committee for Medical Ethics and Deontology of Croatian Medical Chamber and of the Croatian Society for Transplantation Medicine, resp., and representative of the Republic of Croatia in the Eurotransplant Ethical Committee (Netherlands). She has been active in conferences on medical ethics and medical law, mostly within transplantation sessions. She has mentored numerous medical students researches (some in cooperation with law students) and graduation thesis in the field of transplantation medicine and ethics. She also organizes and holds lectures for high school students and general population to popularize organ donation and transplantation and also to raise health literacy.

Ana M. Pires Silva

- LL.M in Public Law, Portuguese Catholic University, Faculty of Law, Lisbon (Portugal);
- Since 2007 - PRESENT - Legal and ethical adviser in the field of transplantation, National Organization of Transplants of Portugal (currently named Portuguese Institute of Blood and Transplantation);
- Member of the Portuguese Working Group for the transposition of the Council of Europe Convention against Trafficking in Human Organs;
- Member of the international network of National Focal Points on Transplant-Related Crimes, of the Council of Europe;
- Expert in the field of organ, tissues and cells of the European Committee on Organ Transplantation (CD-P-TO), of the Council of Europe;
- Council of Europe expert - consultancy services related to expert examination of the legal regulatory framework on organ and tissue transplantation in Belarus in the framework of the Council of Europe Project "Bioethics: protection of human rights in biomedicine".

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Doc. dr. Blaž Koritnik, dr. med., je od leta 2009 specialist nevrolog na Nevrološki kliniki Univerzitetnega kliničnega centra Ljubljana, od leta 2017 pa predstojnik Kliničnega inštituta za klinično nevrofiziologijo. Pri kliničnem delu se ukvarja predvsem z boleznimi perifernega živčevja in z boleznijo motoričnega nevrona. Raziskovalno se ukvarja s fiziološkimi mehanizmi različnih nevroloških bolezni. Od leta 2012 je docent na Katedri za nevrologijo Medicinske fakultete v Ljubljani. 10 let je član nacionalne ekipe za določanje možganske smrti z elektroencefalografijo. Kot predavatelj in inštruktor je sodeloval na več domačih in mednarodnih srečanjih in delavnicah s področja transplantacijske medicine.

Blaž Koritnik, MD, PhD, is a consultant neurologist at the Division of Neurology of the University Medical Centre Ljubljana since 2009. He is also the Head of the Institute of Clinical Neurophysiology since 2017. His main clinical expertise is peripheral nervous system diseases and motor neurone disease. His research work involves physiological mechanisms of various neurological diseases. He is an Assistant Professor of Neurology at the Faculty of Medicine in Ljubljana since 2012. For the past 10 years, he is a member of the national team for brain death assessment using electroencephalography. He participated at several domestic and international meetings and workshops in the field of transplant medicine as a lecturer and instructor.

Andrej Gadžijev

Rojen 6. 9. 1971 v Ljubljani, kjer je obiskoval tudi osnovno in srednjo šolo. Leta 1990 se je vpisal na Medicinsko Fakulteto v Ljubljani in uspešno diplomiral 24. 1. 2000. V tem času je prejel srebrno Prešernovo nagrado kot soavtor (skupaj z dr. Bojanom Vrtovcem) za delo »Debelina intime in medije karotidnih arterij in koronarni dejavniki tveganja«. Sekundariat je zaključil marca leta 2002 in opravil strokovni izpit iz Urgentne medicine. Tri mesece kasneje je opravil še Licenčni izpit za splošnega zdravnika. Septembra 2002 je začel s specializacijo iz travmatologije in jo zaključil s pohvalo 18. 3. 2009, februarja 2010 pa je postal vodja enote intenzivne nege na Travmatološki kliniki na Zaloški 2. V času čakanja na prosto specializacijo iz kirurških strok je leta 2002 začel z delom kot centralni koordinator za transplantacije pri Slovenija-transplantu, ki ima svoj sedež v UKC Ljubljana. Kot koordinator je poleg specializacije iz travmatologije in kasnejšega dela kot specialist travmatolog delal polnih 10 let, preden se je odločil, da se raje usmeri v delo mentorja mlajšim koordinatorjem. V tem času se je redno izobraževal na obeh področjih, kazal pa je vedno večje zanimanje za transplantacijsko dejavnost. Januarja 2011 je opravil mednarodni izpit in prejel Evropsko diplomo za koordinatorja za transplantacije. Leta 2012 je prevzel vodenje celotnega projekta za zagotavljanje kakovosti in varnosti v sklopu darovanja organov in tkiv (QAP) in s tem postal glavni revizor donorske dejavnosti v vseh donorskih bolnišnicah v Sloveniji. Leta 2017 se je večinsko zaposlil pri Slovenija-transplantu in zasedel mesto pomočnika direktorice za strokovno medicinske zadeve. Redno sodeluje praktično na vseh nivojih delovanja Slovenija-transplanta, od organizacijskih, promocijskih, zakonodajnih do izobraževalnih, tako na nacionalnem kot na mednarodnem nivoju. Je tudi član odbora za področje pridobivanja organov in koordinacijo pri Eurotransplantu, ter član odbora za strokovno medicinska vprašanja pri Zdravniški Zbornici Slovenije. Živi v Ljubljani z ženo in dvema sinovoma.

Andrej Gadzijev

Born on September 6, 1971 in Ljubljana, where he also attended primary and secondary school. In 1990, he registered at the Faculty of Medicine in Ljubljana and successfully graduated on 24 January 2000. At that time, he received a silver Preseren Award as a co-author (together with Bojan Vrtovec) for his work "Thickness of carotid arteries intima and media and coronary risk factors «. He completed his internship in March 2002 and passed the professional examination in Emergency Medicine. Three months later, he passed the Licensing Exam for a general practitioner. In September 2002, he began his specialization in traumatology and finished it with a compliment on March 18, 2009, and in February 2010 he became head of the intensive care unit at the Traumatology Clinic Ljubljana. While waiting for free specialization from the surgical professions, he started work in 2002 as the central transplant coordinator at Slovenia-transplant, which has its headquarters in UMC Ljubljana. As a coordinator, in addition to the specialization in traumatology and later working as a specialist traumatologist, he worked for full 10 years before changing his obligations to becoming a mentor to younger coordinators. During this time, he regularly studied in both areas, and showed an increasing interest in the field of transplantation. In January 2011, he passed the international exam and received the European Diploma for the Transplant Coordinator. In 2012, he took over the overall project for quality and safety assurance as part of the organ and tissue donation (QAP) and thus became the main auditor of donor activities in all donor hospitals in Slovenia. Since 2017, he is mostly employed at Slovenia-transplant and started working as the assistant director for professional medical matters. He regularly participates in all activities guided by Slovenia-transplant, from organizational, promotional, legislative to educational, both at national and international level. He is also a member of the Committee for Organ Procurement and Coordination (OPCC) within Eurotransplant, and a member of the Committee for Expert Medical Questions at the Medical Chamber of Slovenia. He lives in Ljubljana with his wife and two sons.

Izr. prof. dr. Miha Arnol, dr. med. je na Medicinski fakulteti v Ljubljani diplomiral leta 2000. Sprva je bil zaposlen kot asistent na Inštitutu za fiziologijo Medicinske fakultete v Ljubljani kjer je vpisal podiplomski študij Biomedicina. Po končanem magisteriju se je leta 2002 kot specializant interne medicine zaposlil na Kliničnem oddleku za nefrologijo UKC Ljubljana. Že tekom specializacije se je klinično in raziskovalno usmeril v področje transplantacije ledvic. Zadnje leto specializacije se je izpopolnjeval na Oregon Health & Sciences University v ZDA pod mentorstvom prof. Douglas J. Normana. Specializacijo je zaključil leta 2008, istega leta je končal tudi doktorski študij Biomedicine. Od leta 2016 je vodja Centra za transplantacijo ledvic in od leta 2019 predstojnik Kliničnega oddelka za nefrologijo UKC Ljubljana. Je stalni predstavnik Slovenije v Eurotransplant Kidney Advisory Committee, podpredsednik Slovenskega transplantacijskega združenja ter aktivni član ESOT, TTS in AST.

Assoc. Prof. Miha Arnol, MD, PhD, received his medical degree in 2000 at the Faculty of Medicine, University of Ljubljana. As a junior assistant he first joined the Institute of Physiology at the Faculty of Medicine, University of Ljubljana, where he also enrolled in the postgraduate study of Biomedicine. After completing his master's degree in 2002, he continued with clinical training as a resident of internal medicine and then as a fellow in nephrology. During the last year of his clinical training he focused on transplant medicine and in 2007 spent a year as a visiting fellow at the Oregon Health & Science University, Portland, USA under the mentorship of prof. Douglas J. Norman. In 2008, he finished his fellowship training and received a PhD degree in Biomedicine. He is now a medical director of the Centre for Kidney transplantation and head of the Department of Nephrology at the University Medical Centre Ljubljana. He is a representative of Slovenia in the Eurotransplant Kidney Advisory Committee, vice president of the Slovenian Transplantation Association and active member of ESOT, TTS and AST.

IZZIVI TRANSPLANTACIJE ORGANOV V 21. STOLETJU

Jadranka Buturović Ponikvar[1,2]

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Uvod

Transplantacija organov je eden največjih dosežkov medicine 20. stoletja. Strokovno in logistično je transplantacija verjetno najbolj kompleksna medicinska intervencija. Pri vodenju čakalnih vrst, dodeljevanju organov, odvzemu in transportu organov k bolniku tesno sodelujejo številne bolnišnice in države. V mednarodnih zdravstvenih informacijskih sistemih so shranjeni najbolj občutljivi podatki posameznikov: darovalcev, prejemnikov in bolnikov na čakalnih listah. Brezhibno delovanje celotnega sistema (kot npr. v organizaciji Eurotransplant) je nujno da bi donorski in prejemniški program transplantacije delovala hitro, usklajeno in pravično.

Kljub osupljivim uspehom pa se transplantacija 21. stoletja sooča tudi z velikimi izzivi. V nadaljevanju bom govorila predvsem o transplantaciji ledvic, s katero je največ izkušenj med vsemi transplantacijami solidnih organov. Podobni izzivi in problemi kot so pri transplantaciji ledvic so prisotni tudi pri transplantaciji ostalih organov.

Nezadovoljivo dolgoročno preživetje transplantiranih organov

Dolgoročno preživetje transplantiranih ledvic je še vedno nezadovoljivo. V zadnjih desetletjih so doseženi ogromni uspehi na področju izboljšanja rezultatov v prvem letu po transplantaciji. V večini transplantacijskih centrov enoletno preživetje transplantiranih ledvic presega 90 in več odstotkov. Žal takšnega uspeha ni pri dolgoročnem preživetju. Pred nekaj leti so v ZDA v obdobju 1989-2009 objavili analizo pri 252 910 bolnikih s transplantirano ledvico. Ugotovili so, da se je razpolovna življenjska doba transplantirane ledvice umrlega darovalca (čas, v katerem odpove polovica transplantiranih ledvic) povečala iz 6.6 let v letu 1989 na 8.8 let v letu 2005. Najizraziteje izboljšanje je bilo na področju ledvic neoptimalnega darovalca (»expanded criteria donors« - darovalci z razširjenimi kriteriji), iz 3 let 1989 na 6.4 let v 2005. Pri razpolovni življenjski dobi ledvic živih darovalcev skoraj da ni bilo sprememb: iz 11.4 let v 1989 na 11.9 let v 2005 (1).

Med ZDA in Evropo so na področju transplantacije ledvic pomembne razlike. Pokazali so, da je 10-letno preživetje transplantiranih ledvic bistveno boljše v Evropi kot v ZDA: 10-letno preživetje transplantirane ledvice umrlega darovalca v obdobju 2005-2008 je bilo v Evropi 56%, v ZDA pri belcih 46% (2). V nedavni evropski raziskavi, v kateri so v obdobju od 1986-2015 preučevali 108 787 bolnikov s transplantirano ledvico darovalcev umrlih zaradi možganske smrti, so ugotovili, da se je izboljšanje kratkoročnega preživetja transplantirane ledvice upočasnilo od leta 2000, pri dolgoročnem preživetju pa ni bilo sprememb (3). Kot glavne razloge izpostavljajo pomanjkanje inovacij na področju imunosupresivne terapije in tudi drugih inovacij na področju transplantacijskega zdravljenja.

Kakovost organov za transplantacijo se v zadnjih desetletjih slabša. Starost tako darovalcev kot prejemnikov organov v zadnjih desetletjih narašča. Darovalci (oz. organi darovalcev) standardnih kriterijev postajajo manjši del darovalcev. Zaradi napredka v varnosti v prometu in drugih področjih in napredka pri oskrbi poškodovancev se znižuje odstotek mladih in predhodno zdravih darovalcev umrlih zaradi možganske oz. cirkulacijske smrti in povečuje odstotek starejših darovalcev ki imajo več spremljajočih bolezni (4, 5). Danes sprejemamo organe, predvsem ledvice, medicinsko zahtevnih živih darovalcev. Vse te dejavnike moramo upoštevati, ko interpretiramo podatke o preživetju transplantiranih organov.

Kronična humoralna zavrnitev in nesodelovanje pri zdravljenju sta glavna vzroka za odpoved transplantirane ledvice. To so ugotovili pri spremljanju 315 bolnikov, ki so imeli biopsijo presadka med progresom do odpovedi presadka (6). Nesodelovanje je posebej izrazito pri mladostnikih. Ugotovili so, da je najbolj tvegano obdobje za izgubo presadka med 17 in 24 letom, predvsem zaradi nesodelovanja bolnikov (7).

Moramo se tudi zavedati, da pri transplantaciji ledvice posamezni bolnik dobi efektivno manj kot eno ledvico in posledično manj kot polovico mase nefronov. Transplantiramo namreč, razen v zelo redkih primerih, le eno ledvico in ne dveh. Del nefronov te ledvice propade ob samem postopku transplantacije. Razlogi so ishemična okvara ob odvzemu, prezervacijskem postopku, transportu in čakanju na implantacijo ter reperfuzijska poškodba ob transplantaciji. Pozneje transplantirana ledvica utrpi okvaro zaradi nefrotoksičnih učinkov imunosupresivne terapije, akutne in kronične zavrnitve, okužb, rekurence osnovne ledvične bolezni. Vse to so razlogi, da ima transplantirana ledvica, tudi ko je ob sami transplantaciji idealne kakovosti, omejeno življenjsko dobo.

Stranski učinki imunosupresivne terapije

Za preprečavanje zavrnitve transplantiranih organov je nujno trajno jemanje imunosupresivne terapije. Kljub velikemu napredku farmakologije in številnih novih imunospuresivnih zdravil so stranski učinki tega zdravljenja še vedno pomembni. Imunosupresivna zdravila bolniki morajo praviloma jemati ves čas delovanja organa. Če zdravila prenehajo jemati, četudi mnoga leta po transplantaciji ledvice ki dobro deluje, je velika verjetnost, da bo sledila zavrnitev transplantiranega organa. Posamezni poskusi indukcije tolerance, npr. s sočasno transplantacijo ledvice in kostnega mozga istega darovalca, četudi uspešni pri posameznih primerih, niso dosegli širše klinične uporabe. So pa bili postopki precej agresivni in posledično bolnike izpostavljali dodatnim tveganjem (8, 9).

Število zdravil in tablet, ki jih bolniki po transplantaciji ledvice morajo jemati vsak dan, je razmeroma zelo veliko. Poleg imunosupresivnih za preprečevanje zavrnitve, morajo jemati tudi dodatna zdravila za preprečevanje ali zdravljenje stranskih učinkov imunosupresivnih zdravil in številna druga zdravila za zdravljenje spremljajočih bolezni, vključno s kronično ledvično boleznijo različnih stopenj. Dnevno naši bolniki s transplantirano ledvico v povprečju jemljejo 10 zdravil oz. 20 tablet (10). Pri otrocih so te številke še večje (11). Zato ne preseneča, da je sodelovanje pri zdravljenju oz. adherenca eden ključnih razlogov za izgubo presadka (7).

Pomanjkanje organov

Potrebe po organih za transplantacijo daleč presegajo število organov, ki jih imamo na razpolago. Pred leti je bilo ocenjeno, da v svetu opravljene transplantacije ledvic na letni ravni zadostijo le 10% potreb (12).

Glavni vzroki pomanjkanja ledvic za transplantacijo so povečanje števila bolnikov s končno ledvično odpovedjo v mnogih državah (13), povečanje dostopnosti do dializnega zdravljenja bolnikov v manj razvitih državah, širitev indikacij za transplantacijo, opustitev starostne meje za transplantacijo (14) ter nezadovojivo dolgoročno delovanje transplantiranih ledvic. Zaradi tega mnogi bolniki potrebujejo drugo ali tretjo transplantacijo.

Zaključki

Sočasno z zgodbo o uspehu na področju transplantacije organov, ki je rešila mnoga življenja, v se v 21. stoletju soočamo s številnimi izzivi. Glavni izzivi so nezadovoljivo dolgoročno preživetje transplantiranih organov, pomembni stranski učinki imunosupresivne terapije in pomanjkanje organov.

Prav pomanjkanje organov je eden glavnih vzrokov za etično mejne oz. vprašljive ali nesprejemljive prakse, o katerih bomo govorili v tej knjigi.

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CHALLENGES OF ORGAN TRANSPLANTATION IN THE 21ST CENTURY

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Introduction

Organ transplantation is one of the greatest achievements of 20th century medicine. Expertly and logistically, organ transplantation is probably the most complex medical intervention. Different hospitals and countries are closely involved in managing waiting lists, organ donation and allocation, organ harvesting and transportation. International Health Information Systems store the most sensitive data of individuals: donors, recipients and patients on waiting lists. The smooth functioning of the entire system (such as in the Eurotransplant organization) is essential in order for the donor and recipient transplant program to operate in a swift, coordinated and equitable manner. Despite its stunning successes, 21st century transplantation also faces major challenges.

In the following contribution I will primarily discuss kidney transplantation, with which we have the most experience among all solid organ transplants. Similar challenges and problems as with kidney transplantation are also present in other organ transplants.

Unsatisfactory long-term survival of transplanted organs

The long-term survival of transplanted kidneys is still unsatisfactory. In past decades, tremendous success has been achieved in improving results in the first year after transplantation. The one-year survival of transplanted kidneys exceeds 90 percent or more in the vast majority of centers. Unfortunately, there is no such success in long-term survival. Several years ago, an analysis of 252,910 patients with kidney transplants was published in the United States (US). The observational period was from 1989 to 2009. It was found that the transplant half-life from a deceased donor (half-life is the time period in which half of the transplanted kidneys fail) increased from 6.6 years in 1989 to 8.8 years in 2005. The most pronounced improvement was in the area of the non-optimal donor ("expanded criteria donors") – from 3 years in 1989 to 6.4 years in 2005. Very few changes were observed in the half-life of living donors: from 11.4 years in 1989 to 11.9 years in 2005 (1).

There are significant differences between the US and Europe in the field of kidney transplantation. It was shown that 10-year kidney transplant survival was significantly better in Europe than in the US: the 10-year kidney transplant survival rate from a deceased donor in the period from 2005-2008 was 56% in Europe, and 46% in US (Caucasians) (2). A recent European study examining 108,787 transplant patients from brain-dead deceased donors over three decades (1986-2015) found that improving short-term kidney transplant survival has slowed since 2000, with no changes in long-term survival (3). The main reasons were the lack of innovations in immunosuppressive therapy and other innovations in the field of organ transplantation. The quality of transplant organs has deteriorated in recent decades. The age of donors has been increasing. Standard criteria donors have become a smaller proportion of donors. Due to advances in traffic safety and safety in other areas, as well as advances in trauma care, the percentage of young and previously healthy deceased donors is decreasing. The percentage of older donors who may have multiple concomitant diseases is increasing (4, 5). Today we accept organs, especially kidneys, from medically complex living donors. All these factors must be taken into account when interpreting the survival data of transplanted organs.

Chronic humoral rejection and non-adherence were the main causes of kidney graft failure, as shown in a study monitoring 315 patients who had a kidney graft biopsy during progression to graft failure (6). Non-adherence to treatment is particularly pronounced in adolescents. The most risky period for transplant loss was found to be between 17 and 24 years, mainly due to patient non-adherence (7).

It should also be noted that in a kidney transplantation, an individual patient receives effectively less than one kidney and, consequently, less than half the nephron mass. Except in very rare cases, only one kidney is transplanted and not two. Part of the nephrons of this kidney are lost during the transplantation process itself. The reasons are ischemic injury during removal, the preservation procedure, transport and waiting for implantation, and reperfusion injury during the transplantation procedure. After transplantation, the transplanted kidney suffers injury due to the nephrotoxic effects of immunosuppressive therapy, acute and chronic rejection, infections, and recurrence of primary kidney disease. All of these are reasons why a kidney graft, even when being of ideal quality at the moment of transplantation, has a limited life span.

Side effects of immunosuppressive therapy

Induction and maintenance immunosuppressive therapy is essential in order to prevent transplant rejection. Despite the great advances in pharmacology and many new immunosuppressive drugs, the side effects of immunosuppressive therapy are still significant. As a rule, patients must take immunosuppressive drugs throughout the course of the transplanted organ's functioning. If medication is stopped, even after many years of a well-functioning kidney graft, there is a significant risk that rejection of the transplanted kidney will follow. Sporadic attempts to induce immune tolerance (acceptance of the transplanted organ without the need for maintenance immunosuppression), e.g. the simultaneous transplantation of kidney and bone marrow from the same donor, although successful on a case-by-case basis, have not reached wider clinical use. However, the procedures themselves are quite aggressive and have consequently exposed patients to additional risks (8, 9).

The daily medication burden for the patient with a transplanted organ is high. In addition to immunosuppressants to prevent rejection, patients must also take additional medications to prevent or treat the side effects of immunosuppressive drugs, as well as a number of other drugs to treat concomitant diseases, including various stages of chronic kidney disease. Our adult patients with a transplanted kidney take on average 10 medicines and 20 tablets per day (10). In children, the numbers are even higher (11). It is therefore not surprising that adherence to treatment is one of the key reasons for graft loss (7).

Organ shortage

The demand for transplant organs far exceeds the number of organs available. Some years ago, it was estimated that the number of kidney transplantations performed annually in the world satisfied only 10% of the needs (12). The main reasons for organ shortage, specifically kidneys, are the increased numbers of patients with end-stage kidney failure needing renal replacement therapy in many countries (13), better access to dialysis treatment in less developed countries, widening indications for transplantation, abandonment of age limit for transplantation (14), and unsatisfactory long-term kidney graft survival. As a result, many patients require a second or third transplant.

Conclusions

Along with the success story of organ transplantation that has saved many lives, we face many challenges in the 21st century. The most important among them are: the unsatisfactory long-term survival of transplanted organs,

significant side effects of immunosuppressive therapy, and organ shortage. The lack of organs to meet the current needs is one of the main reasons for ethically questionable or unacceptable practices that will be discussed in this book.

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TRGOVINA Z ORGANI IN TRANSPLANTACIJA ORGANOV USMRČENIH ZAPORNIKOV

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Uvod

Presaditev organov in tkiv omogoča pomembno izboljšanje kakovosti in omogoča daljše preživetje bolnikov. Zaradi pomanjkanja razpoložljivih organov pa žal veliko bolnikov umre med čakanjem na presaditev (1). Svetovna zdravstvena organizacija (WHO) v prvi vrsti priporoča presaditev organa umrlega dajalca, vendar pa lahko polnoletne osebe nastopajo v vlogi živega darovalca. Načelno morajo biti takšni darovalci s prejemnikom v sorodstvenem razmerju, izjeme so možne v primeru presaditve kostnega mozga in določenih tkiv.

Smernice WHO o presaditvi človeških organov (2) v primeru živega darovalca v prvi vrsti izpostavljajo neizogibnost/nujnost informirane in prostovoljne odločitve o darovanju svojega organa, brez prisile in nagrajevanja. Trgovina z organi, ki je del širše menarodne kriminalne mreže temelječe na svojevrstnih novodobnih oblikah suženjstva (prostitucija, prisilno delo, nenazadnje tudi na smrt obsojeni zaporniki), predstavlja resno skrb za vse zdravstvene delavce v področju transplantacije.

Opredelitev

V skladu s Palermskim protokolom iz leta 20003, ki je osnova za večino državnih zakonov o trgovini z ljudmi, je trgovina z organi opredeljena v širši definiciji pojma „trgovina z ljudmi" ter pomeni: novačenje, prevoz, skrivanje ali sprejemanje ljudi z nedopustnimi metodami kot so ugrabitev, prisila, goljufija ali zavajanje, zato, da bi jih izkoristili (3). Žrtve trgovine z ljudmi potekajo proti njihovi volji skozi dejanja prisile in so prisiljene delati na zahtevo preprodajalca ali drugih. Delo ali storitve lahko vključujejo vse, od prisilnega dela do komercialnega spolnega izkoriščanja in nenazadnje trgovanja z namenom odstranitve organov.

Podatki

Svetovna finančna zaveza (angl. Global financial integrity) za boj proti korupciji ocenjuje, da se 10 odstotkov vseh presaditev organov, vključno s pljuči, srci in jetri, opravi s posredovanjem trgovcev z ljudmi. Le ti po zadnji oceni ustvarjajo letne dobičke med $840.000 in $1.700.000 (4).

Med najpogosteje »trženimi« organi so ledvice. WHO ocenjuje, da se na črnem trgu vsako leto znajde okoli 10.000 ledvic in se posledično nezakonito presadi ena ledvica vsako uro (2). V tej mednarodni kriminalni mreži so darovalci neredko ne le žrtve trgovine z organi, temveč tudi trgovine z delavci, prostitucije in drugih oblik prisile. Za opisano obliko kriminala se pogosto uporablja izraz "transplantacijski turizem", ki ga natančneje opredeljuje Istanbulska deklaracija (5) "... potovanja z namenom presaditve, ki vključujejo trgovino z organi in/ali komercializacijo presaditve ali če viri (organi, strokovnjaki in centri za presaditev) namenjeni zagotavljanju presaditve spodkopavajo zmožnost države za opravljanje storitev presaditve za svoje prebivalstvo."

Podlaga za liberalnejši pristop

Zaradi stalnega večanja števila bolnikov na čakalnih listah za presaditev organov ter pomanjkanja organov za presaditev so bili že predlagani določeni alternativni viri darovalcev. Med njimi je bila predlagana uporaba organov zapornikov obsojenih na smrtno kazen.

Pomisleki

Poročila o odvzemu organov usmrčenih vaditeljev Falun Gonga (kitajska kigong disciplina, ki vključuje meditacijo in moralno držo izhajajočo iz budistične tradicije) in drugih političnih zapornikov na Kitajskem že leta vzbujajo vedno večjo skrb mednarodne skupnosti. Po nekaterih poročilih so bili politični zaporniki (predvsem pa vaditelji Falun Gonga) usmrčeni "na zahtevo", z namenom odvzema in trgovine z organi. V obsežni raziskavi, ki sta jo o tej pereči temi navkljub velikim oviram in pritiskom opravila Kilgour in Matas (6) sta ugotovila, da je na Kitajskem izvor več kot 41 500 transplantacij za obdobje šestih let (od leta 2000 do 2005) nepojasnjen ter zaključila, da se omenjeno ogromno število organov (glede na sicer izredno slabo razvito transplantacijsko mrežo na Kitajskem) pridobi ilegalno, in sicer od usmrčenih zapornikov. Pričujoča problematika ne zajema zgolj Kitajske ali držav tretjega sveta. V Združenih državah so bili že pred leti podani predlogi za uporabo organov usmrčenih zapornikov (prvi izmed njih je bil podan leta 2003 s strani na smrt obsojenega C. Longo). V javnosti se je razvnela vroča diksusija, pri čemer sta se pri podpornikih predloga oblikovala dva vzorca razmišljanja: prvi, nagnjen k temu, da se zapornikom omogoči darovanje organov po njihovi smrti, in drugi, ki predlaga, da se obsojenim zapornikom ponudi možnost trgovanja z ledvicami ali njihovim kostnim mozgom v zameno za redukcijo smrtne kazni v doživljenjsko zaporno kazen. Pričakovano je bilo, da vsak predlog, ki omogoča osebi trgovanje z lastnim telesom (organom) z namenom zmanjšanje kazni, sploh v primeru smrtne kazni, sproža številna vprašanja, ki so v ZDA večinoma povezana z rasno neenakopravnostjo (večino na smrt obsojenih ujetnikov predstavljajo črnci). Pojavljajo se tudi številni drugi pomisleki, kot npr podaja pisnega soglasja po predhodni poučitvi s strani darovalca in prejemnika ter nenazadnje način usmrtitve (7-11). Pri ustaljenem načinu usmrtitve (uporaba letalne injekcije) je z veliko verjetnostjo pričakovati hudo okvaro organov, ki bodo tako neoptimalni ali celo neprimerni za presaditev. Iz tega razloga so bili podani predlogi, da je metoda izvršitve usmrtitve v primeru darovanja organov dejanje samega darovanja organov, kar pa seveda eksplantacijsko ekipo spreminja v izvedbeno (»eksekucijsko«), čemur večina zdravnikov sodelujočih v transplantacijskih programih odločno nasprotuje. Številne ameriške zdravniške organizacije prepovedujejo sodelovanje zdravnikov v državnih usmrtitvah (12).

Zaključek

Obup prejemnikov kot nasledek negotovosti ob čakanju na listi za presaditev organov, po drugi strani pa ranljivost posameznikov, predvsem njihova materialna odvisnost, so situacije, na katerih temelji mednarodni kriminal trgovine z ljudmi in organi.

Vprašanje, ali je smiselno pristopiti k boju proti nezakonitemu trgovanju z organi na način legalizacije trgovine z organi (delno tudi na način, da se sprejmejo ukrepi za sprejemanje organov usmrčenih zapornikov) je trenutno izredno pereče vprašanje. Gotovo imamo pred tem še mnogo maneverskega prostora v optimizaciji manj spornih metod za povečanje števila darovalcev, kot npr z vlaganjem v večjo ozaveščenost javnosti o darovanju organov in posledično pridobitjem večjega števila organov primernejših, nekontroverznih darovalcev.

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ORGAN TRAFFICKING AND USE OF ORGANS FROM EXECUTED PRISONERS

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Introduction

Organ and tissue transplantation leads to dramatic improvement in patients' quality of life and outcomes. Unfortunately, many people die while waiting for a transplant because of the paucity of available organs (1). Organs for transplantation should be removed preferably from the bodies of deceased persons. However, adult living persons may donate organs, but in general such donors should be genetically related to the recipients. Exceptions may be made in the case of transplantation of bone marrow and other acceptable regenerative tissues (2).

In part, the World Health Organization (WHO) Guiding principles on human organ transplantation 2 were introduced to ensure that living organ donors have made an informed and voluntary decision to donate their organ; free from duress, coercion and reward. Organ trafficking operated by heterogenious acts of modern day slavery (including usage of organs of death row inmates) is a serious concern for all healthcare professionals participating in transplantation associated activities.

Definition

According to the Palermo Protocol of 2000 3 which is the basis for most national laws on human trafficking, organ trafficking is defined within the broader definition as:"Trafficking in persons' shall mean the recruitment, transportation, transfer, harbouring or receipt of persons, by means of the threat or use of force or other forms of coercion, of abduction, of fraud, of deception, of the abuse of power or of a position of vulnerability or of the giving or receiving of payments or benefits to achieve the consent of a person having control over another person, for the purpose of exploitation. Exploitation shall include, at a minimum, the exploitation of the prostitution of others or other forms of sexual exploitation, forced labour or services, slavery or practices similar to slavery, servitude or the removal of organs."(3).

Data

Global Financial Integrity estimates that 10 percent of all organ transplants including lungs, heart and liver, are done via trafficked organs, generating profits between $840 million and $1.7 billion per year (4). However, the most prominent organs that are traded illicitly are kidneys, with the WHO estimating that 10,000 kidneys are traded on the black market worldwide annually, or more than one every hour(2). Cases are emerging where an organ donor may have been a victim of sex trafficking and/or labor trafficking as well as a victim of organ trafficking, creating a multi-level equation of exploitation. The term "transplant tourism" is often utilized in describing this crime, as defined by the Declaration of Istanbul (5) "...travel for transplantation that involves organ trafficking and/or transplant commercialism or if the resources (organs, professionals and transplant centers) devoted to providing transplants to patients from outside a country undermine the country's ability to provide transplant services for its own population."

Rationale for liberation

As the scarcity of suitable organs for transplantation continues to grow, alternative sources for organs have been reported and others suggested. One such suggestion is to recover organs that would otherwise seem to go to waste, such as those from condemned (death row) prisoners.

Controversies

Reports of organ harvesting from Falun Gong practitioners (a Chinese qigong discipline involving meditation and a moral philosophy rooted in Buddhist tradition) and other political prisoners in China have raised increasing concern by some groups within the international community. According to the reports, political prisoners, mainly Falun Gong practitioners, are being executed "on demand" in order to provide organs to recipients. An initial investigation by Kilgour and Matas 6 stated "the source of 41,500 transplants for the six year period 2000 to 2005 is unexplained" and concluded that "there has been and continues today to be large scale organ seizures from unwilling Falun Gong practitioners".

This discussion is, however, not restricted to China or third world countries. In the United States, proposals of this type have come from prominent bodies. While one proposal suggested that prisoners be given the option of donating organs upon their death, another suggests that condemned prisoners be offered the option of trading a kidney or their bone marrow in exchange for a commuted sentence of life in prison without parole (7). However, any law or proposal that allows a person to trade an organ for a reduction in sentence, particularly a sentence from death to life in prison, raises numerous issues, most of them associated with inequity, especially racial discrimination (majority of the death row inmates are black). Furthermore, issues of informed consent of potential donors as well as recipients need to be addressed, as well as method of execution (7-11). It was suggested that the method of execution in case of organ donation is the act of organ donation itself, as the recovery of organs in the usual manner of execution (lethal injection) would produce nonoptimal organs for transplantation. It clearly places the organ recovery team in the role of executioner and many physician groups have prohibited physician participation in state executions on ethical grounds (12).

Conclusion

Desperate situations of both recipients and donors create an avenue ready for exploitation by international organ trafficking parties. The question of whether to legalize and regulate the organ trade, partly in a way to act on strategies to accept organs from executed prisoners to combat illegal trafficking and organ shortage is currently highly questionable. Less controversial methods to increase the number of donated organs can be obtained by increasing public awareness on organ donation and improving organ yield from egligible donors.

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POVEZAVA EVTANAZIJE IN DAROVANJA ORGANOV

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Uvod

Etični izzivi in nedopustna ravnanja v transplantaciji organov so posledica pomanjkanja organov. Na področju transplantacije ledvic so pred časom ocenili, da število opravljenih transplantacij v svetu zadovolji le 10% potreb (1). Trgovina z organi in transplantacija organov pridobljenih od zapornikov obsojenih na smrt sta soglasno obsojeni s strani transplantacijske skupnosti in mednarodne javnosti (2, 3). Sočasno se pa v zadnjih letih, v povezavi z legalizacijo in širjenjem evtanazije, pojavljajo iniciative in pobude v prid še enem kontroverznem viru organov. To so darovalci organov usmrčeni z evtanazijo (4).

Evtanazija in darovanje organov

Eurotransplant je je sprejel uporabo organov pridobljenih od darovalcev usmrčenih z evtanazijo leta 2005. Praktični priročnik postopka je objavljen leta 2016 v najbolj vplivni transplantacijski reviji (5). V Eurotransplantu (na Nizozemskem) kandidata za evtanazijo in darovanje organov sprejmejo v bolnišnico praviloma na dan "posega". Isti dan ga usmrtijo, uradno ugotovijo smrt, in v najkrajšem času ("no touch period" 5 minut) začnejo z odvzemom organov. Usmrtitev se opravi v neposredni bližini operacijske dvorane. Nekateri svojci se želijo prepričati, da je njihov usmrčeni sorodnik res mrtev preden ga odpeljejo v operacijsko dvorano (5).

Etiki iz Oxforda so leta 2012 predlagali korak dlje v primerjavi s postopkom, ki poteka pod okriljem Eurotransplanta: namesto usmrtitve bolnika, razglasitve smrti in temu sledečega odvzema organov predlagajo, da se kandidata za evtanazijo (in darovanje organov) uvede v splošno anestezijo ter da se z odvzemom organov začne dokler srce še bije in je darovalec živ. Srce se odvzame kot zadnji organ. S tem odvzem srca sočasno postane tudi izvedbeni akt evtanazije (6). Kot prednosti tega pristopa navajajo boljšo kakovost organov, manj trpljenja bolnika (splošna anestezija namesto globoke sedacije pri običajni evtanaziji) in spoštovanje bolnikove avtonomije, ki naj bi se za takšen postopek sam odločil.

Da bi odvzem vitalnih organov pri še živemu kandidatu za evtanazijo upeljali v prakso je potrebno opustiti enega temeljnih postulatov transplantacijske dejavnosti - "pravilo mrtvega darovalca" ("dead-donor rule"). Pravilo zahteva, da je pred odvzemom vitalnega organa darovalec dejansko in uradno mrtev (po kriteriju možganske ali srčne oz. cirkulacijske smrti) (10).

Pobude za opustitev "pravila mrtvega darovalca" ("dead-donor rule")

Pobude za opustitev "pravila mrtvega darovalca" potekajo več let (7, 8, 9). Nov zagon so dobile z legalizacijo evtanazije v Kanadi leta 2016 (10). Uvodnik v reviji New England Journal of Medicine iz 6. septembra 2018 poudarja argumente temu v prid - število in kakovost organov bi se maksimizirali če bi se odvzem organov (vključno z vitalnimi organi) začel dokler je kandidat za evtanazijo in darovanje organov še živ (11). Na nekakšen način se v članku implicira (vsaj takšna je moja percepcija), da je samomorilne misli, v smeri biti bolj vreden mrtev kot živ, morda za spodbujati rajši kot zdraviti. Odveč je opozoriti, da tako transplantacijski zdravniki kot prejemniki organov ne bodo želeli organov starih in bolnih.

Kriteriji za evtanazijo postajajo vse bolj sproščeni in široki. Čeprav je bila v začetku evtanazija promovirana le za najbolj bolne med bolnimi (" the sickest of the sick"), je danes na voljo za psihiatrične bolnike (12), prizadete (disabled) in otroke. Znaten del evtanzijskih postopek se izvede brez podpisanega informiranega pristanka (13). Tako evtanazija počasi (morda ne tako počasi) postaja procedura s katero se lahko znebimo nemočnih, zmedenih in finančno obremenjujočih oseb in bolnikov. Transplantacijska skupnost po drugi strani lahko veliko pridobi z nadaljevanjem in pospeševanjem tega procesa. Čakajoči na transplantacijo lahko postanejo še bolj odvisni od obljub novega vira kakovostnih človeških organov. V ozadje se lahko potisnejo alternative transplantaciji kot so regenerativna medicina, umetni in bio-umetni organi, ksenotransplantacija in preprečevanje in zdravljenje kronične (in končne) odpovedi organov.

Slovenski pristop transplantaciji organov

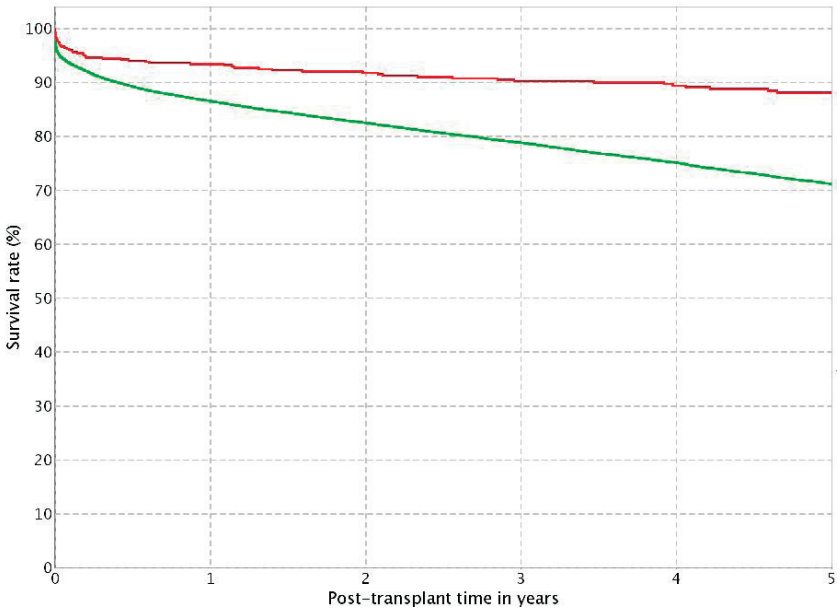
Slovenija je članica Eurotransplanta od 1. januarja 2000. Nenapisani principi slovenske transplantacije organov (kot jih dojemam med 30-letnim delom na področju transplantacije ledvic v UKCL) so: 1) Moramo biti samozadostni: pridobiti dovolj organov darovalcev umrlih možganske smrti, da zadostimo potrebam naših bolnikov ob sprejemljivem čakanju na presaditev 2) Prioriteti transplantacijske dejavnosti sta kakovost in dolgoročno preživetje presajenih organov 3) "Rajši nobena transplantacija kot slaba transplantacija" 4) V Sloveniji ne presajamo organe kontroverznih darovalcev.

Slovenski model transplantacije organov, ki zagotavlja dovolj organov darovalcev umrlih možganske smrti, ob sprejemljivem času čakanja na presaditev (za ledvico umrlega darovalca v povprečju manj kot eno leto), s petletnim preživetjem presajene ledvice ki je pomembno boljše od povprečja Eurotransplanta, je živi dokaz, da je možno organizirati kakovosten transplantacijski program ne da bi presajali organe kontroverznih darovalcev.

Podoben pristop darovanju organov imajo tudi na Hrvaškem. Tam so po številu darovalcev umrlih možganske smrti v svetovnem vrhu.

Komisija za medicinsko etiko R Slovenije se je izrekla proti uporabi organov darovalcev usmrčenih z evtanazijo. V imenu Komisije je podpisan akademik prof. dr. Jože Trontelj, dr. med. (dopis z dne 27. decembera 2012): ***"V Sloveniji je etično in legalno nesprejemljivo uporabljati organe pridobljene od bolnikov usmrčenih z evtanazijo, tudi če so organi pridoboljeni v državah v katerih je evtanazija legalizirana."*** Dopis je posredovan Eurotransplantu.

Slika. 5-letno preživetje presajene ledvice od darovalca umrlega možganske smrti v Sloveniji in (Slovenijatransplant: n=506 and Eurotransplant: n=35717, 2000-2010). Courtesy by Miha Arnol.



Zaključki

Pridobitev organov od bolnikov usmrčenih z evtanazijo in opustitev "pravila mrtvega darovalca" ne bosta rešila globalnega problema pomanjkanja organov. Po drugi strani povezava evtanazije z darovanjem organov lahko ogrozi zaupanje bolnikov in javnosti v transplantacijo, zdravnike in medicino na sploh. Pridobivanje organov lahko postane skriti dejavnik v podporo evtanaziji (14). Slovenski model transplantacije organov je živi dokaz, da je z dobro organizacijo in visoko kakovostjo transplantacijske dejavnosti možno zagotoviti dovolj organov možgansko umrlih darovalcev za potrebe bolnikov, ob sprejemljivi čakalni dobi, ne da bi pri tem uporabljali etično kontroverzne darovalce. Komisija za medicinsko etiko Republike Slovenije se je opredelila proti uporabi organov bolnikov, usmrčenih z evtanazijo v Sloveniji. četudi so usmrčeni v državah v katerih je evtanazija legalizirana.

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LINKING EUTHANASIA WITH ORGAN DONATION

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Introduction

Ethical challenges and unacceptable practices in organ transplantations are mainly the consequence of organ shortage. In the area of kidney transplantation, it has been estimated that the number of transplants in the world satisfy only 10% of needs (1). Organ trafficking and the transplantation of organs obtained from prisoners sentenced to death were unanimously condemned by the transplant community and the international public (2, 3). At the same time, however, in line with euthanasia legalization and expansion, there has been a growing interest in recent years in another controversial source of organs – organ harvesting from donors killed by euthanasia (4).

Euthanasia and organ donation

Eurotransplant accepted the use of organs from donors killed by euthanasia in 2005. A practical manual of the procedure was published in 2016 in the most influential transplant journal - the American Journal of Transplantation (5). In the Netherlands, candidates for euthanasia and organ donation are usually admitted to hospital on the day of the "intervention". On the same day, they are killed by lethal injection, officially declared dead by circulatory criteria, transferred to the operating theatre and, in the shortest period of time ("no touch time" - 5 minutes), organ harvesting is started. The euthanasia procedure is carried out in the immediate vicinity of the operating room. Some relatives want to make sure that their relative is really dead before entering the operating theatre (5).

In 2012, Oxford ethicists proposed a step further than the Eurotransplant procedure: instead of killing the patient first, declaring his/her death, and subsequently harvesting the organs, they suggested that candidates for euthanasia (and organ donation) be introduced into general anesthesia, with the removal of organs beginning while the heart is still beating and the donor is alive. The heart is harvested as the last organ for transplantation. Harvesting the heart simultaneously becomes an implementing act of euthanasia (6). According to the authors, the advantages of this approach include better organ quality, less patient suffering (general anesthesia rather than deep sedation in conventional euthanasia), and respect for the patient's autonomy, who supposedly wants such a procedure.

In order to harvest the organs from the euthanasia candidate while he/she is still alive, it is necessary to abandon one of the basic and long-standing postulates of transplantation - the "dead-donor rule". The rule requires that the donor be actually and officially dead before removal of the vital organ.

Calls for abandoning the dead-donor rule are fully mainstreamed, with a recent article in the New England Journal of Medicine arguing that the number and quality of organs will be maximized if harvesting begins while the donor is still alive (Ball IM et al., NEJM September 6, 2018) (10).

Initiatives to abandon the "dead-donor rule"

The initiatives for abandoning the "dead donation rules" have been in place for many years (7, 8, 9). The new impetus was the consequence of legalizing euthanasia in Canada in 2016 (10). An editorial in the New England Journal of Medicine, dated September 6, 2018, highlights the arguments in favor: the number and quality of organs would be maximized if the procurement of organs (including vital organs) were begun while the candidate for euthanasia and organ donation is still alive (11). The article seems to imply (at least such is my perception) that suicidal thoughts about being more valuable dead than alive may be encouraged rather than treated.

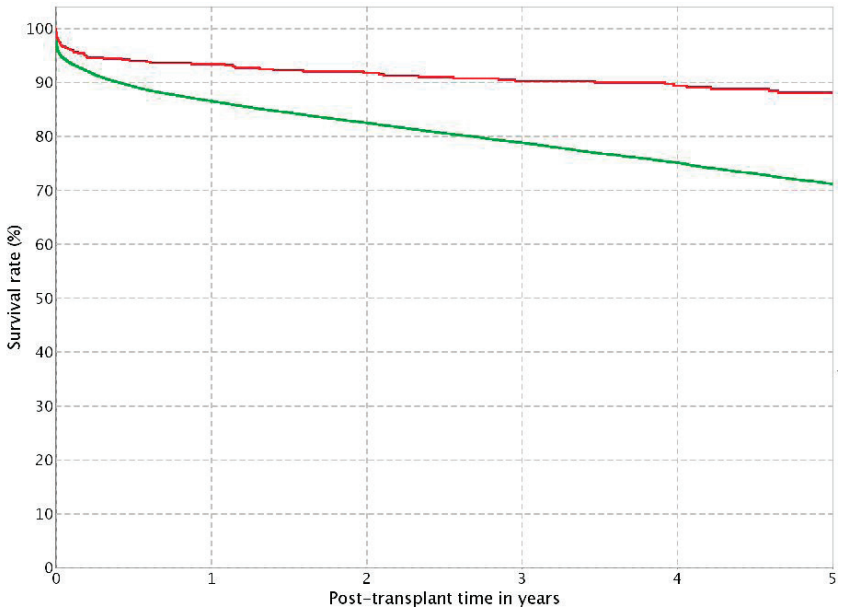
At the same time, the criteria for euthanasia are constantly becoming ever more lax and expansive. While initially advertised as a procedure to be used only for the sickest of the sick, euthanasia is now available to psychiatric patients, disabled persons, and children. It has been reported that a significant number of euthanasia procedures in Belgium are performed without signed informed consent (13). In short, euthanasia may rapidly become a tool for getting rid of the weak, confused and expensive, and the transplant community has way too much to gain from continuing and accelerating this process. Transplant candidates may become even more dependent on the promise of a new source of high-quality human organs. Alternatives to transplantation, such are regenerative medicine, artificial and bio-artificial organs, xenotransplantation, and the prevention and treatment of chronic (and end-stage) organ failure can be pushed back into the background.

Slovenian organ transplant approach

Slovenia is a member of Eurotransplant since 1st January 2000. The unpublished principles of Slovenian organ transplantation (as I perceive them during my 30 years of work in the field of kidney transplantation at UMCL) are: 1) We must be self-sufficient: able to offer sufficient organs of brain-dead donors to our patients with an acceptable waiting time; 2) The high quality and long-term survival of organs and patients are priorities of the Slovenian transplantation program; 3) "Better no transplantation than a bad transplantation"; 4) In Slovenia we do not transplant the organs of ethically controversial donors.

The Slovenian organ transplant model, which provides sufficient organs from brain dead donors at acceptable waiting time for transplantation (on average less than one year for a kidney from a deceased donor), and with a five-year kidney graft survival significantly higher than/above the Eurotransplant average, is living proof that it is possible to organize a high quality transplant program without transplanting the organs of ethically controversial donors. A similar approach to the ethics of organ donation is also employed in Croatia.

Fig. 5-year survival of transplanted kidney from a deceased brain dead donor in Slovenia (Slovenijatransplant: n = 506, red, and Eurotransplant: n = 35717, 2000-2010). Courtesy of Miha Arnol.



The Medical Ethics Commission of the Republic of Slovenia has declared that it is against the use of organs of donors killed by euthanasia. On behalf of the Commission, the declaration was signed by Academician Prof. Dr. Jože Trontelj, MD, with the explanation (letter of December 27, 2012): ***"It would be both ethically and legally inadmissible to use organs retrieved from euthanasia patients for transplantation medicine in Slovenia, even if such organs are harvested in countries where euthanasia is legal."*** The letter has been sent to Eurotransplant.

Conclusions

Harvesting organs from donors killed by euthanasia and abandoning the "dead donor" rule will not solve the global problem of organ shortage. On the other hand, linking euthanasia with organ donation can jeopardize the trust of patients and the public in transplantation, doctors, and medicine in general. Organ donation may become a hidden factor in support of euthanasia (14). The Slovenian model of organ transplantation is living proof that with good organization and high quality of transplantation, it is possible to provide sufficient organs from deceased donors and an acceptable waiting time without using ethically controversial donors. The Medical Ethics Committee of the Republic of Slovenia has opposed the use of organs of patients killed with euthanasia in Slovenia, even if such organs are harvested in countries where euthanasia is legal.

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ŽIVI DAROVALCI ORGANOV: DRUŽBENI PRITISK NA DAROVALCE, MLADI DAROVALCI, KUPON ZA LEDVICO

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Uvod

Živi darovalci, najpogostejše ledvic, so pomemben vir organov za transplantacijo. Prva transplantacija ledvic v svetu leta1954, in v Sloveniji leta 1970, sta bili opravljeni od živega darovalca (1). Prednosti transplantacije od živega darovalca (pred transplantacijo od umrlega) je nekaj: kakovost organov je boljša, zaradi tega tudi daljše dolgoročno preživetje ledvice, čakanje na transplantacijo praviloma krajše, izvedba transplantacije se lahko planira v optimalnem času (tudi pred začetkom dializnega zdravljenja).

Odstotek transplantacij ledvic od živega darovalca, glede na vse opravljene transplantacije, je v mnogih razvitih državah razmerova visok. V letu 2018 je bilo v Eurotransplantu opravljenih skupaj 4805 transplantacij ledvic, od tega1326 (27.5%) od živega darovalca (2). V ZDA je bilo v 2018 opravljenih skupaj 21.167 transplantacij ledvic, od tega 6.442 (30.4%) od živega darovalca (3). Razlike med državama, tudi znotraj Eurotransplanta, so velike. V letu 2018 smo v Sloveniji opravili 2/56 (3.6%) transplantaciji ledvic od živega darovalca, na Hrvaškem 5/183 (2.7%), v Belgiji 57/531 (10.7%), na Madžarskem 45/334 (13.5%), Avstriji 69/413 (16.7%), v Nemčiji 638/2291 (27.8%). Največ transplantacij ledvic od živega darovalca v Eurotransplantu opravijo na Nizozemskem, v letu 2018 510/998 (51.1%) (4).

Poleg ledvic živi darovalci lahko darujejo del jeter (jetra se regenerirajo in lahko ponovno pridobijo celotno funkcijo), del pljučnega krila (pljuča se sicer ne regenerirajo), zelo, zelo redko del črevesja ali trebušne slinavke. Izvaja se, sicer šele v okviru kliničnih raziskav, transplantacija maternice. Prva uspešna transplantacija maternice žive darovalke, ki je rezultirala z rojstvom zdravega otroka, je bila opravljena na Švedskem leta 2014. Prva transplantacija maternice od umrle darovalke, katere rezultat je bil prav tako zdrav otrok, je bila opravljena v Braziliji leta 2017 (5). Izjemoma je možna tudi transplantacija srca od živega darovalca, in sicer pri tako imenovani domino transplantaciji, pri kateri prejemnik zaradi pljučne bolezni dobi pljuča in srce od istega darovalca v "bloku" (ob oceni, da bo uspeh transplantacije tako boljši kot če bi presadili le pljuča). V tem primeru se lahko zdravo srce bolnika, ki je dobil srce in pljuča umrlega darovalca, lahko presadi drugemu prejemniku, ki potrebuje novo srce (6).

Družbeni pritisk na darovanje organov

Pomanjkanje organov je od samega začetka eden največjih izzivov transplantacijske dejavnosti. Organov umrlih darovalcev ni dovolj glede na potrebe, posledica tega je tudi družbeni pritisk na žive darovalce. Na ELPAT kongresu aprila 2019 v Krakowu (ELPAT - Ethical, legal and psychosocial aspects of organ transplantation) je med svojim predavanjem o kuponih za ledvico prof. Gabriel Danovitch iz UCLA (University of California Los Angeles) slušatelje vprašal: "Kateri med vami je daroval ledvico?" Implicitna premisa vprašanja, ki je med slušatelji vzbudilo določeno nelagodje, je bila, da gre za dejanje, katerega bi verjetno vsi bili dolžni narediti.

Predstavila bom nekatere poglede in pristope, ki govorijo v prid družbenem pritisku na žive darovalce ledvice v razvitem svetu.

"Tiranija žrtvovanja"

Ameriška antropologinja Nancy Scheper-Hughes iz Univerze Berkeley, ZDA, ki vodi organizacijo Organ Watch, je pred leti objavila odmevni članek "The tyranny of the gift: sacrificial violence in living donor transplants". V članku zagovarja tezo, da čeprav različno obravnavamo žive darovalce v revnih državah, ki prodajo svojo ledvico in žive darovalce v razvitih državah, ki ledvico darujejo svojim bližnjim, oba fenomena delita podobne družbene elemente: darovalci so pogosto podvrženi pritiskom družine in pozivom, da se žrtvujejo (7).

V članku opozarja na zaskrbljujočo prakso v ZDA in sicer darovanje ledvic otrok in vnukov svojim staršem in starim staršem. Navaja tudi etnografsko raziskavo Sharon Kaufman iz kalifornijske univerze San Francisco (UCSF), ki je identificirala subtilno prakso skozi katero transplantacijski profesionalci/aktivisti rekrutirajo mlade, da darujejo organe starejšim sorodnikom (8).

Mladi živi darovalci

Ledvico lahko darujejo tudi zelo mladi. V nekaterih kanadskih provincah lahko 16-letniki legalno darujejo ledvico. Torej je legalno možno darovati organ (ledvico) še preden je polno dozorela sposobnost oceniti prednosti in tveganja darovanja organa pri še nezreli, razvijajoči se osebnosti. Potencialni mladi darovalci so lahko finančno in psihološko odvisni od starejših, npr. staršev, zato je včasih težko oceniti, koliko je bilo darovanje organa prostovoljno (9).

Otroci, ki so darovali ledvico staršem so bili v letu 2008 znatno številčnejši kot starši, ki so darovali ledvico otrokom, je pokazala analiza živih darovalcev v ZDA. Pred 10 leti je bilo obratno, število staršev, ki so darovali ledvico otrokom je daleč presegalo število otrok, ki so darovali ledvico staršem (10). V letu 2018 je bilo v ZDA živih darovalcev ledvice starostne skupine 18-34 let 1658/6446 (25.7%), v starostni skupini 50-65 let 1728 (26.8%) in le 242 (3.8%) v starostni skupini 65+ let (3).

Po odstranitvi ene ledvice se glomerulna filtracija pomembno zniža. V nedavni prospektivni raziskavi z radioizotopskim določanjem glomerulne filtracije so pokazali, da se prvi dan po enostranski nefrektomiji serumski kreatinin zviša za 79%, peti dan je zvišan za okrog 50%. Po enem letu desna ledvica (najpogostejše se daruje leva ledvica) pridobi okrog 20 ml/min glomerulne filtracije, kar se doda na povprečnih 48.8 ml ml/min, ki jih je imela pred levostransko nefrektomijo (11). V tej smeri govorijo tudi rezultati dolgoročnega sledenja 1901 živih darovalcev ledvice na Norveškem, ki so pokazali da imajo živi darovalci povečano dolgoročno tveganje za končno ledvično odpoved, kardiovaskularno in splošno umrljivost v primerjavi z enako zdravimi vrstniki, ki niso darovali ledvice (12).

Dolgoročni učinek enostranske nefrektomije je razumljivo bolj izrazit pri mladih živih darovalcih. Pokazali so, da je gestacijska hipertenzija in preeklampsija bolj verjetna pri darovalkah ledvice kot pri primerljivih nosečnicah, ki so imele obe ledvici (13). V nadavnem preglednem članku priporočajo, da se zanimanje za žive darovalce usmeri na starejše, ki se bodo soočali z najnižjim tveganjem po enostranski nefrektomiji (14).

Dializni bolniki si, razumljivo, želijo čimbolj kakovosten organ, ki bo dolgoročno dobro deloval. Posamezni starejši in premožnejši dializni bolniki v ZDA ne želijo biti uvrščeni na čakalne sezname za ledvico umrlega darovalca, ker so velike možnosti da bodo dobili organ manjše kakovosti ("expanded" criteria donor) ampak se rajši odločijo za pot in nakup ledvice mladega in zdravega živega darovalca v najpogosteje azijskih državah ("old bodies, young donors") (7).

Pridobivanje organov živih darovalcev prek javnega nagovarjanja

Pridobivanje organov živih darovalcev prek spletnih omrežij in drugih oblik javnega nagovarjanja je del današnje realnosti. Večinoma gre za usmerjeno darovanje. Organ dobi le prejemnik, ki ga darovalec izbere in ki ni v sorodstveni ali čustveni povezavi z darovalcem (vsaj ne od začetka). Javno spodbujeno usmerjeno darovanje organov je dovoljeno le v nekaterih državah, kot so ZDA, Kanada, Velika Britanija, Nizozemska (15). Takšen način pridobivanja organov, pri katerem se bolniki, ki potrebujejo organ lahko ocenjujejo tudi na podlagi osebnega videza in biografije se lahko sprevrže v različico lepotnega tekmovanja. Pri takšnem darovanju organov gre lahko tudi za prikrito trgovino z organi. Altruizem bi vedno moral biti osnova za darovanje organov. Nekateri avtorji zagovarjajo, da bi živi darovalci prek spletnih omrežij oz. javnega nagovarjanja morali darovati organe v pravičen sistem razdelitve organov (kot je to pri umrlih darovalcih), in ne tistemu prejemniku, ki ga sami izberejo. Zato menijo, da bi identiteta bolnikov, ki javno nagovarjajo/prosijo za pridobitev organa, morala biti zakrita (16).

Prositi znance ali tujce da darujejo organ, za posameznega bolnika, ni enostavno. Bolezen je ena najbolj intimnih informacij vsakega posameznika. Prošnja za organ predvideva razkritje osebne ranljivosti širokem krogu znancev in neznancev, V nedavno objavljeni raziskavi so s semi-strukturiranimi intervjuji analizirali pozitivne in negativne aspekte javnega nagovarjaja za darovanje organov prek družbenih omrežij pri 20-ih nizozemskih bolnikih (15). Poleg pozitivnih emocij ob podpori, ki so jo med procesom doživljali in pozitivne interakcije s potencialnimi darovalci, so bile tudi ovire: časovno in emocialno zahteven postopek, negotovost, občutek odvisnosti in obveznosti ter odgovornosti do darovalca. Glavni motiv za odločitev, da bi pristopili k javnemu nagovarjanju za pridobitev organa je bil občutek obupa. Štirje od 20 udeleženih v raziskavi so pred poskusom javnega nagovarjanja za pridobitev ledvice imeli že opravljene 2-4 transplantacije ledvic.V času objave članka so štirje od 20 sodelujočih v raziskavi uspeli pridobiti ledvico prek družbenega omrežja (15).

Kupon za ledvico

Program izmenjave parov živih darovalcev in prejemnikov (KPD – kidney paired donation) je bil uveden leta 2000 v ZDA kot možnost rešitve problema imunološke oz. biološke nekompatibilnosti med živim darovalcem in prejemnikom. Sprva je šlo za izmenjavo organov dveh parov darovalcev in prejemnikov, pri katerih je obstajala recipročna kompatibilnost. Postopek je potekal simultano. Pri sodelovanju več parov je prišlo do verige, pri katerih so odvzemi ledvic in transplantacije sprva potekale simultano pri vseh udeleženih, pozneje pa v sosledju (17). Po uvedbi altruističnega živega darovalca, ki je organ daroval neopredeljenemu prejemniku in se je z njim lahko začela veriga parov živih darovalcev in prejemnikov (2007), se je lahko postopek darovanja in transplantacij celotne verige raztegnil v mesece in je vključeval več centrov v raznih mestih (18).

V ZDA so nedavno uvedli "voucher" program – kupon za bodočo transplantacijo ledvice, ki je nadaljevanje programa izmenjave parov živih darovalcev. Ključna razlika je v tem, da živi darovalec želi darovati ledvico prejemniku, ki trenutno NE potrebuje dialize ali transplantacije ledvice, lahko pa jo bo (ali pa tudi ne) potreboval v prihodnosti. Potencialni živi darovalec pa v prihodnosti ne bo primeren za darovanje. Gre za tako imenovano "kronološko nekompatibilnost". Zato živi darovalec, ko je še v dobrem zdravstvenem stanju, daruje organ neopredeljenemu prejemniku v sistemu razdelitve organov (lahko z darovanjem začne verigo parov živih darovalcev in prejemnikov). Njegov sorodnik, kateremu je sprva želel darovati organ dobi "kupon za ledvico" ki ga bo uveljavljal ko bo organ potreboval. Kupon mu bo omogočil prednostno obravnavo v verigi živih darovalcev in prejemnikov. Kupona ni možno prenesti na na drugo osebo.

Za ilustracijo je v članku opisan primer 19-letne deklice, ki je pri 10-ih letih dobila ledvico živega darovalca, ki po 9-ih letih odlično deluje. Njen oče, star 52 let, ji želi darovati ledvico ("back-up kidney") za primer, da bo njena seda-

nja transplantirana ledvica prenehala delovati. Zato daruje ledvico v verigo transplantacij živih darovalcev, deklica pa dobi kupon za ledvico. Ker je deklica mlada, njeni zdravniki verjamejo, da bo v prihodnosti potrebovala še tretjo transplantacijo. Zato tudi njena 60-letna teta daruje ledvico v verigo transplantacij živih darovalcev, deklica pa dobi še en kupon za ledvico (17).

Vseeno lahko upamo in pričakujemo, da bo napredek transplantacijske, regenerativne in personalizirane medicine, farmakologije in področja umetnih in bio-umetnih organov ter napredek celotne medicine v naslednjih desetletjih omogočil uspešnejše in bolnikom bolj prijazno zdravljenje napredovale kronične ledvične bolezni kot so sukcesivne transplantacije ledvice, pri katerih tudi ledvice živih darovalcev delujejo krajši čas kot ga mnogi bolniki potrebujejo.

Zaključek

Živi darovalci (predvsem ledvic) so bili v preteklosti in bodo v prihodnosti še vedno dragocen vir organov za transplantacijo.

Ob globalnem pomanjkanju organov moramo skrbno spremljati prakse, ki se pojavljajo v nekaterih državah: družbeni pritisk na žive darovalce, rekrutiranje mladih živih darovalcev, javno nagovarjanje in prošnje za organ s strani bolnikov ali njihovih predstavnikov, predvsem prek družbenih omrežij.

Strategija družbenega pritiska na žive darovalce kot vse bolj pomembnega ali glavnega vira organov za transplantacijo se mora spremljati in nadzirati, ker lahko povzroči probleme, s katerimi se bomo soočali v prihodnosti.

Da bi ohranili in spodbujali darovanje ledvic živih darovalcev moramo bolnikom, potencialnim darovalcem in javnosti transparentno predstaviti tako pozitivne plati kot pasti darovanja organa in prakse, ki so prisotne v drugih državah.

Ob tem se moramo zavedati, da je najbolj pomemben cilj nadomestnega zdravljenja končne ledvične odpovedi doseči čimvečji odstotek bolnikov, ki imajo delujočo transplantirano ledvico.

Z dobro organiziranim donorskim programom predvsem umrlih kot tudi živih darovalcev in visoko kakovostjo transplantacije (katere posledica je dobro dolgoročno delovanje transplantiranih ledvic) je za pričakovati, da se bo odstotek bolnikov na nadomestnem zdravljenju, ki imajo delujočo transplantirano ledvico v Sloveniji še naprej povečeval.

V Sloveniji imamo dobre možnosti, da sedanji program transplantacije ledvic od živega darovalca intenziviramo, ne da bi pri tem uporabljali etično mejne ali vprašljive pristope.

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LIVING ORGAN DONORS: SOCIAL PRESSURE TO DONATE ORGANS, YOUNG DONORS, KIDNEY VOUCHER

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Introduction

Living donors are an invaluable source of organs for transplantation, the most common being kidneys. The first kidney transplantation in the world, from a living donor, was performed in 1954 (in Slovenia in 1970) (1). The benefits of transplantation from a living donor (as compared to an organ from a deceased donor) are several: better organ quality and hence a better long-term kidney graft survival, a shorter waiting time for transplantation, and optimal timing for transplantation that can be planned (even before the start of dialysis treatment).

The percentage of kidney transplants from a living donor in relation to all transplants performed is high in many developed countries. A total of 4,805 kidney transplants were carried out at Eurotransplant in 2018, of which 1,326 (27.5%) from a living donor (2). In the United States, a total of 21,167 kidney transplants were performed in 2018, of which 6,442 (30.4%) from a living donor (3). The differences between countries, including within Eurotransplant, are large. In 2018, the number of renal transplants from a living donor performed in Slovenia was 2/56 (3.6%), in Croatia 5/183 (2.7%), in Belgium 57/531 (10.7%), in Hungary 45/334 (13.5%), in Austria 69/413 (16.7%), and in Germany 638/2,291 (27.8%). Most kidney transplants from a living donor at Eurotransplant are performed in the Netherlands, 510/998 (51.1%) (4).

In addition to the kidney, living donors can donate a part of the liver (liver regenerates and can regain full function), part of the lungs (lungs do not regenerate), and very, very rarely a part of the bowel or pancreas. A uterus transplantation is, for now, performed only in clinical trials. The first successful transplantation of the uterus of a living donor, resulting in the birth of a healthy child, was carried out in Sweden in 2014. The first transplantation of the uterus from a deceased donor, which also resulted in the birth of a healthy baby, was carried out in Brazil in 2017 (5). Exceptionally, it is also possible to transplant the heart of a living donor in the case of a "domino transplantation", where a recipient with end-stage lung disease receives both lungs and heart from the same deceased donor (assessing that the result of a combined transplant would be better than transplanting the lungs only). In such case, the healthy heart of the patient who has received the heart and lungs of a deceased donor in block can be transplanted to another recipient who needs a new heart (6).

Social pressure to donate organs

From the very beginning, the lack of organs is one of the biggest challenges of transplantation. The demand for organs largely exceeds organ availability, resulting in social pressure on living donors. At the ELPAT (Ethical, Legal and Psychosocial Aspects of organ Transplantation) Congress in April 2019 in Krakow, Professor Gabriel Danovitch from UCLA (University of California Los Angeles) asked the audience: "Which one of you have donated your kidney?" The implicit premise of this question that aroused certain discomfort in the audience was that kidney donation was in some way an act that was expected.

I will present some views and approaches that may illustrate the social pressure on donation in the developed countries.

"The Tyranny of the Gift"

American anthropologist Nancy Scheper-Hughes from the University of California Berkeley, USA, who founded, together with collaborators, the Organ Watch organization in 1999, published a remarkable article a few years ago, entitled "The tyranny of the gift: sacrificial violence in living donor transplants". The article argues that although we deal differently with living donors in poor countries, who are selling their kidneys, and living donors in developed countries who donate kidneys to their loved ones, both phenomena share similar social elements: the donors are often subjected to family pressure and calls to sacrifice (7).

The article draws attention to a worrying practice in the US, namely, the donation of kidneys of children and grandchildren to their parents and grandparents, as observed by Sharon Kaufman of the University of California San Francisco (UCSF), who identified the subtle practice through which the transplantation professionals/activists recruited children (young adults) to donate organs to older relatives (8).

Young living donors

Kidneys can be donated by very young living donors. In some Canadian provinces, 16-year-olds can legally donate their kidneys. So it is legally possible to donate an organ (kidney) before the fully matured ability to assess the benefits and risks of organ donation is reached by an immature, evolving person. Young donors can be financially and psychologically dependent on the elderly, for example, their parents, and it is sometimes difficult to assess whether organ donation was voluntary (9).

Children who donated a kidney to their parents in 2008 were significantly more numerous than parents who donated a kidney to their children, a study of living donors in America showed. Ten years ago, the number of parents who donated a kidney to their children was far beyond the number of children who donated a kidney to their parents (10). In 2018, the number of living kidney donors in the United States from the age group of 18-34 years was 1,658/6,446 (25.7%), from the age group of 50-65 years 1,728 (26.8%), and only 242 (3.8%) from the age group of 65+ years (3).

After the removal of one kidney, glomerular filtration is significantly reduced. In a recent prospective study with radioisotope determination of glomerular filtration, on the first day after nephrectomy the serum creatinine level increased by 79%, and on the fifth day it increased by about 50%. After one year, the right kidney (the most common is donation of the left kidney) acquires about 20 ml/ min of glomerular filtration, which is added to the average of 48.8 ml/min prior to left nephrectomy (11). The results of the long-term follow-up of 1,901 living kidney donors from Norway showed that living donors have an increased long-term risk of end-stage kidney failure, cardiovascular and all-cause mortality compared to equally healthy non-donors (12).

The long-term effect of unilateral nephrectomy is understandably more pronounced in young living donors. Gestational hypertension and preeclampsia have been shown to be more likely in kidney donors than in comparable pregnant women who have both kidneys (13). For these reasons, it was recently recommended in a review article that interest in living donors should be shifted to elderly donors, who will face the lowest risk after unilateral nephrectomy (14).

Dialysis patients understandably want to receive a kidney of the best quality for transplantation, one that is expected to function well in the long run. Some elderly and wealthy dialysis patients from the United States do not

want to be placed on waiting lists for transplantation from a deceased donor and wait for lower quality "expanded criteria donor" kidney, preferring to buy a kidney from a healthy young living donor, usually in Asian countries ("old bodies, young donors") (7).

Public solicitation for organ donation

Obtaining living donors through social networks and other forms of public solicitation is part of today's reality. It is mostly specific, directed donation. The donor offers a kidney only to a specific recipient who is not in a family or emotional connection with the donor (at least not at the beginning). Public solicitation for organs from living donors is allowed in some countries, such as the United States, Canada, the United Kingdom, and the Netherlands (15). This method of organ providing, in which patients who need organs can also be evaluated on the basis of their personal appearance and biography, can be turned into a version of the "beauty contest". Such organ donation may also involve hidden organ trafficking. Altruism should be the only basis for organ donation. Some authors argue that donors recruited through social networks or in other ways or by public addressing should donate organs to a fair system of organ allocation (as is the case with deceased donors), and not to specific donors. Therefore, they believe that the identity of patients who publicly ask for an organ should be hidden (16).

Asking acquaintances or strangers to donate an organ is not an easy task for patients. Health status is one of the most intimate and sensitive pieces of information for every individual. The request for an organ exposes the vulnerability of the individual to the public. In a recently published study, semi-structured interviews analysed the positive and negative aspects of public solicitation for a kidney from a living donor through social networks in 20 Dutch patients (15). In addition to positive emotions accompanying the support they experienced during the process, as well as positive interactions with potential donors, there were also burdens: a time-consuming and emotionally demanding process, uncertainty about the result, a sense of dependence and obligation, and a sense of responsibility for the donor. The main motive for deciding on a public solicitation address for a kidney was a sense of despair. Four out of the 20 patients studied had had two to four kidney transplants performed before attempting to publicly ask for a kidney. During publication of the article, four out of 20 participants in the study managed to obtain a kidney through the social network.

Voucher for the kidney

The program of exchange between pairs of living donors and recipients (KPD – kidney paired donation) was introduced in 2000 in the United States to address the problem of immunological / biological incompatibility between the living donor and the recipient. Initially, there was an exchange of organs between two pairs of donors and recipients with reciprocal compatibility. The process took place simultaneously. The cooperation of several couples opened the possibility of creating a chain in which kidney removal and transplantation were initially performed simultaneously in all participants, and later in sequence (17). After the introduction of an altruistic living donor for a nonspecific recipient, with a chain followed by pairs of living donors and recipients (2007), the entire chain with organ removal and transplant process could be extended for months and could include several centers in various cities (18).

In the United States, a "voucher" kidney program has recently been introduced – a voucher for future kidney transplantation from a living donor. The key difference compared to the already described kidney paired donation lies in the fact that a living donor wants to donate a kidney to a specific recipient who currently does NOT need dialysis or transplantation, but he/she may (or may not) need transplantation in the future. However, the potential living donor may not be suitable for donation in the future. In this case, we speak of so-called "chronological incompat-

ibility". To resolve the situation, the living donor donates a kidney to an unspecific recipient, starting the chain of kidney paired donation. His relative, to whom he initially wanted to donate the organ, receives the kidney "voucher" for the future. This kidney voucher gives him priority in the future chain of living donors and recipients when he would need a kidney. The kidney voucher cannot be transferred to another person.

For illustration, the article describes the case of a 19-year-old girl who, at the age of 10, received a kidney from a living donor. Nine years afterwards, her kidney graft function is excellent. Her father, aged 52, wants to donate a kidney ("back-up kidney") in case her current kidney transplant fails. So he donates the kidney to the live transplantation chain, and his daughter receives a kidney voucher. Since she is still young, her doctors believe she will need a third transplant in the future. That's why her 60-year-old aunt also donates her kidney to the transplant chain and the girl receives another kidney voucher (17).

It is hoped that the progression of transplantation, regenerative and personalized medicine, pharmacology and the fields of artificial and bioartificial organs, as well as the progress of medicine in general, will contribute to better treatment for advanced chronic kidney disease rather than consecutive kidney transplantations, with kidney grafts even from living donors being in function for a significantly shorter period than young patients may need.

Conclusions

Living donors (mainly of kidneys) have been in the past and will continue to be a valuable source of organs for transplantation in the future.

Global organ shortage requires that practices in living organ donation should be carefully observed and monitored in order to avoid today's and future problems: social pressure on living donors and perception of living donors as an increasingly important or even main source of organs (kidneys), recruitment of young living donors, and public solicitation for organs, primarily through social networks.

In order to preserve and promote donation by living donors, we need to present to patients, potential donors and the public, in a transparent manner, the all aspects of living organ donation and practices that are present in different countries.

Above all, we must be aware that the most important goal for patients needing renal replacement therapy is to achieve the highest possible percentage of patients who have a functioning kidney transplant.

With a well-organized donor program including both deceased and living donors and ensuring a high quality of transplantation (resulting in good long-term graft survival), the percentage of patients with a functioning kidney graft among all renal replacement therapy patients should increase in the next years.

In Slovenia, we have the opportunity and challenge to intensify the current program of kidney transplantation from living donors without significant social pressure or other ethically borderline approaches.

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PRAVNI IN ORGANIZACIJSKI VIDIKI TRANSPLANTACIJSKE DEJAVNOSTI V SLOVENIJI

Danica Avsec

Zavod RS za presaditve organov in tkiv Slovenija-transplant

Uvod

Osnovni dokument za slovensko zakonodajo, ki določa pogoje in pravila za pridobivanje delov človeškega telesa (DČT) in zdravljenje s presaditvijo, je bil Elaborat o organizaciji in delovanju sistema za pridobivanje delov človeškega telesa iz leta 1992 (Elaborat) (1).

V elaboratu je natančno opisan nacionalni donorski program z najpomembnejšimi nalogami in fazami delovanja:

- pridobivanje darovalcev,
- ugotavljanje možganske smrti,
- obveščanje sorodnikov,
- odvzem organov in vodenje uradnih dokumentov o tem.

Poleg tega so bili v elaboratu opredeljeni vzroki za pomanjkanje organov ter podani predlogi za odpravo le-teh. Kot osnovni pogoj za uspešno delovanje je bila navedena povezava med regionalnimi bolnišnicami ter koordinacija nacionalnega donorskega programa iz centralnega mesta. Opredeljene so bile tudi naloge koordinacijske službe na nivoju bolnišnic, naloge in pooblastila koordinatorja na nivoju centralne pisarne ter glavnega nacionalnega koordinatorja. Vseboval je tudi predlog za prehodne ukrepe, ki bi veljali do ustanovitve Zavoda RS za presaditve organov in tkiv, Slovenija-transplant.

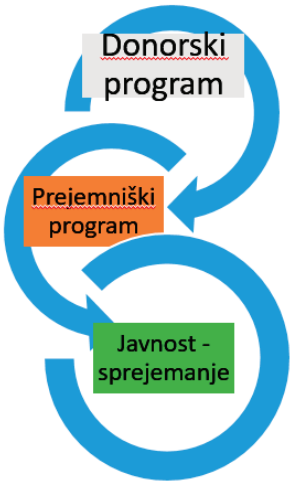
V letu 2000 je bil sprejet prvi slovenski Zakon o odvzemu in presaditvi delov človeškega telesa za namen zdravljenja s presaditvijo (2), ki je povzel vizijo in organizacijo, zapisano v Elaboratu. V zakonu je jasno določena organizacijska shema za delovanje s pooblaščeno institucijo na državni ravni, kar je Evropska unija definirala šele v direktivi iz leta 2010 (3).

Omenjeni zakon upošteva vse etične principe, kar je pomembno dvignilo ugled zakona v Evropi, ter določa financiranje nacionalnega donorskega programa. Zakon definira tudi soglasje za darovanje po principu informiranega soglasja z registrom za opredelitev ter delno uzakonja domnevno soglasje. Zakon ne omenja pogojev in določil v zvezi z raziskavami, ki vključujejo dele človeškega telesa.

Sodobna slovenska zakonodaja in vloga Zavoda za presaditve organov in tkiv RS Slovenija-transplant (3, 4, 2, 6, 7)

Sodobna slovenska zakonodaja povezuje vsa področja, ki jih je treba razvijati, da se transplantacijska medicina lahko izvaja v praksi, kot je prikazano v tabeli 1. Poudarek je na pridobivanju delov človeškega telesa, kakovosti in varnosti v vseh pogledih, natančnemu zapisovanju in sledenju vseh podatkov ter urejanju registrov.

Slika 1: Področja transplantacijske medicine in povezave



Zakon o pridobivanju in presaditvi delov človeškega telesa zaradi zdravljenja (4)

Nastal je na osnovi zahteve, da se Direktiva EU/2010/53 implementira v našo zakonodajo in predstavlja posodobitev osnovnega zakona iz leta 2000. Kot je zahtevano v direktivi, natančneje opredeljuje kakovost in varnost v verigi nalog za pridobivanje, jasno **določa pooblaščeno institucijo** ter način in obseg zbiranja podatkov z različnimi registri.

Glede soglasja za darovanje ne prinaša novosti v primerjavi z zakonom iz leta 2000 in v dveh členih kombinira informirano in domnevno soglasje. Prinaša pa to novost, da omogoča register, v katerem se lahko državljani Slovenije opredelijo proti darovanju, kar predstavlja korak bliže čistemu domnevnemu soglasju.

Definira obveznost imenovanja odgovornih oseb za posamezne programe in zahtevo, da mora biti osebje, ki se ukvarja s to dejavnostjo, primerno izobraženo.

Določa zahteve glede kakovosti prostorov in materiala, ki se uporablja v tej dejavnosti. Prav tako zahteva, da se definirajo parametri, ki določajo sistem kakovosti in nadzor nad spoštovanjem zakonodaje.

Tudi ta zakon ne pokriva področja raziskav na delih človeškega telesa. Natančno pa definira izvajanje sledljivosti v transparentnem okviru, kar pokriva uporabo delov človeškega telesa za zdravljenje ali raziskovanje.

Naloge Zavoda RS za presaditve organov in tkiv Slovenija-transplant so definirane v 40. členu. Zaradi preglednosti vse naloge povzemamo in predstavljamo v treh poglavjih (5):

a) Donorski program:

- strokovni nadzor s svetovanjem donorskim in transplantacijskim centrom v zvezi z vzpostavitvijo in posodabljanjem sistema za kakovost in varnost organov;
- imenovanje pooblaščenih oseb za zbiranje opredelitev darovalcev za časa življenja;
- izdajanje ustreznih strokovnih smernic donorskim in transplantacijskim centrom, ki so vključeni v katerokoli stopnjo postopka od darovanja do presaditve ali uničenja;
- sodelovanje pri proučevanju medicinskih, pravnih, etičnih, ekonomskih in socialnih vprašanj pridobivanja in presaditve;
- koordinacija dejavnosti pridobivanja, presaditve in uničenja med donorskimi in transplantacijskimi centri, laboratoriji, izvajalci prevoza organov, evropsko organizacijo za izmenjavo organov, s katero je sklenjen sporazum,

in mednarodnimi organizacijami za izmenjavo organov;
- zagotavljanje 24-urne dosegljivosti centralnih transplantacijskih koordinatorjev;
- seznanjanje javnosti s pomenom darovanja za časa življenja in po smrti zaradi presaditve drugi osebi.

b) Prejemniški program:

- vodenje čakalnih seznamov prejemnikov,
- sodelovanje z Eurotransplantom,
- koordinacija presaditve organov,
- usklajevanje delovanja donorskih in transplantacijskih centrov ter transplantacijskih koordinatorjev;
- zbiranje in analiziranje podatkov o neuporabljenih organih,
- zbiranje in analiziranje podatkov o neželenih dogodkih in reakcijah,
- svetovanje transplantacijskim centrom.

Področje ureja Pravilnik o uvrstitvi oseb na čakalni seznam zaradi zdravljenja s presaditvijo delov človeškega telesa (UL RS, št. 85/2016)

c) Zagotavljanje kakovosti, varnosti, sledljivosti in preglednosti v sistemu donorske in transplantacijske dejavnosti urejajo številni spodaj navedeni pravilniki. Naloge so sledeče:

- upravljanje sistema za poročanje o hudih neželenih dogodkih in hudih neželenih reakcijah ter obvladovanje takih primerov;
- nadzor nad izmenjavo organov z drugimi državami članicami Evropske unije in tretjimi državami;
- vzpostavitev in upravljanje centralnega registra;
- vodenje evidence o dejavnosti donorskih in transplantacijskih centrov, vključno s številom živih in mrtvih darovalcev, o vrstah in številu odvzetih in presajenih ali drugače odstranjenih organov v skladu s tem zakonom in predpisi o varstvu osebnih podatkov;
- vzpostavitev sistema dodeljevanja in uporabe nacionalne identifikacijske številke;
- vzpostavitev in upravljanje zbirke podatkov o opredeljenih darovalcih;
- vzpostavitev in upravljanje evidence o izdanih dovoljenjih donorskim in transplantacijskim centrom ter evidence o bolnišničnih transplantacijskih koordinatorjih, centralnih transplantacijskih koordinatorjih in kliničnem transplantacijskem koordinatorju;
- dograjevanje in vzdrževanje osrednjega informacijskega sistema za dejavnost pridobivanja, presaditve in uničenja;
- zagotavljanje dograjevanja registra nesorodnih darovalcev kostnega mozga v sodelovanju z Zavodom Republike Slovenije za transfuzijsko medicino;
- priprava in objava letnega poročila o dejavnostih preskrbe z organi na državni ravni in poročanje pristojnim organom Evropske unije ali državam članicam Evropske unije.

10. člen določa odvzem delov telesa po smrti, in sicer od osebe, ki je umrla možganske smrti ali po zaustavitvi srca. Določa, da se smrt ugotovi po postopku, ki ga predpiše minister, in da zdravnik, ki ugotovi smrt, ne sme sodelovati pri odvzemu ali presaditvi.

Zakon zapoveduje, da je treba pri odvzemu delov telesa umrlo osebo obravnavati s spoštovanjem dostojanstva pokojnika in tistih, ki so bili blizu umrlemu, ter z upoštevanjem načel etike in deontologije.

Področje natančneje urejajo ustrezni pravilniki.

Zakon o kakovosti in varnosti človeških tkiv in celic, namenjenih za zdravljenje (ZKVČTC) (6)

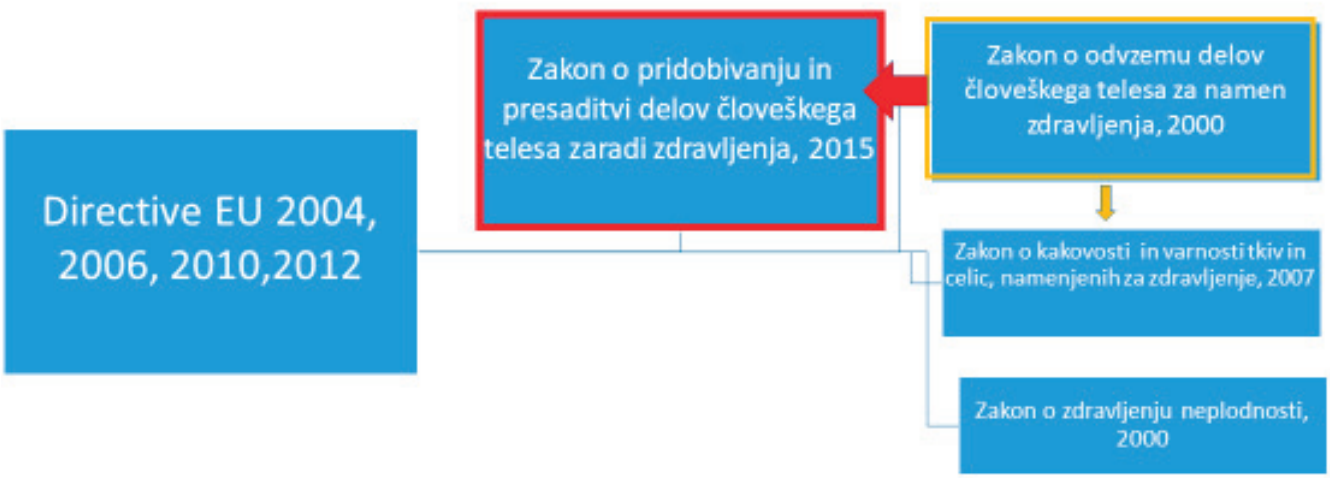
Ta zakon prav tako določa naloge Zavoda RS za presaditve organov in tkiv, s čimer omogoča varnost, sledljivost ter kakovost okvira za delovanje tega tako občutljivega področja, določa pa tudi pogoje za urejen sistem. Glede darovanja in pridobivanja tkiv in celic veljajo splošni principi, določeni v Zakonu o pridobivanju in presaditvi delov človeškega telesa zaradi zdravljenja, 2015 (2).

Zakon določa zahteve pri:

- pridobivanju tkiv in celic v okviru MOO ali po kardio-cirkulatorni smrti;
- promocijske dejavnosti in obveščanje javnosti za podporo darovanja tkiv in celic;
- vodenje osrednjega informacijskega sistema za uporabo človeških celic in tkiv, namenjenih za zdravljenje,
- priprava sprotnih poročil za tkiva in celice ter letno poročilo;
- ustanovitev in vzdrževanje javno dostopnega registra za tkiva in celice, s podatki o dejavnostih ustanov za tkiva in celice;
- zbiranje podatkov v zvezi z ugotavljanjem, sporočanjem in zbiranjem podatkov o hudih nezaželenih dogodkih ali reakcijah pri darovalcih ali prejemnikih tkiv in celic ter njihovo epidemiološko spremljanje.

Povezava med veljavnimi zakoni je prikazana v tabeli 2. Zakon o pridobivanju in presaditvi iz leta 2015 je glede etičnih in ostalih veljavnih principov krovni zakon, medtem ko sta Zakon o kakovosti in varnosti tkiv in celice ter Zakon o zdravljenju neplodnosti usmerjena v tehnične rešitve in določila v omenjenem področju.

Slika 2. Strokovni zakonodajni dokumenti, ki urejajo dejavnost uporabe delov človeškega telesa za namen zdravljenja v Sloveniji in medsebojne povezave (3, 2, 4, 6, 7)



Direktive EU, ki določajo zahteve v transplantacijski medicini (3, 8, 9)

Vsi zakoni so usklajeni z direktivami EU. Na osnovi direktiv morajo države EU zagotoviti, da je uveden okvir za kakovost in varnost, ki zajema celoten postopek, od darovanja do prevoza ali uničenja organov, kot sledi:

- vključevati mora identiteto darovalca in privolitev darovalca ali njegove družine, pa tudi druge pogoje, določene v zakonodaji;
- darovalca izberejo in ocenijo priznani zdravniki in organizacije s primerno usposobljenim zdravstvenim osebjem;
- na voljo so minimalni podatki o darovalcu, kot so starost, teža in pretekla ali sedanja zdravstvena anamneza;

- prevoz organov izpolnjuje nekatere zahteve, kot so pravilno označevanje in identifikacija;
- pridobivanje in presaditev organov sme potekati samo v centrih, ki imajo dovoljenje za ta namen v skladu z zakonodajo EU;
- organe je mogoče slediti najmanj 30 let od darovalca do prejemnika in obratno;
- uveden je sistem za poročanje, raziskovanje, registracijo in pošiljanje ustreznih informacij o hudih neželenih dogodkih ali reakcijah. Informacije se morajo izmenjevati tudi, kadar gre za izmenjavo organov med državami EU;
- darovanje organov mrtvih in živih darovalcev je prostovoljno, brezplačno in treba jim je priložiti potrebno privolitev;
- živi darovalci so skrbno izbrani in pregledani. Zajamčiti jim je treba najvišjo možno raven zaščite;
- temeljna pravica do varovanja vseh osebnih podatkov se 'v celoti in učinkovito spoštuje';
- njihovi pristojni organi redno izmenjujejo informacije v okviru mreže, ki jo vzpostavi Evropska komisija.

Direktiva 2010/53/EU o standardih kakovosti in varnosti človeških organov, namenjenih za presaditev (3)

- Določa pravila za zagotavljanje standardov kakovosti in varnosti za presaditev organov.
- Prizadeva si zagotoviti, da bi bili darovalcem in prejemnikom zagotovljeni enaka kakovost, varnost in pravni standardi ne glede na to, kje živijo.
- Zajema darovanje, testiranje, določanje značilnosti, pridobivanje, konzerviranje, prevoz in presajanje organov.

Direktiva 2004/23/ES – standardi kakovosti in varnosti za darovana človeška tkiva in celice

Direktiva določa standarde kakovosti in varnosti, da bi kar najbolj zmanjšala tveganje okužbe in preprečila prenos bolezni pri presajanju človeških tkiv in celic. Pokriva celotno verigo dejavnosti: od darovanja do pridobivanja, testiranja, predelave, konzerviranja, shranjevanja in razdeljevanja do mesta medicinske uporabe ali do mest, kjer se iz teh človeških snovi izdelujejo industrijski izdelki.

Na osnovi direktive za tkiva in celice so države EU obvezne zagotoviti, da:

- se imenujejo pristojni organi za izvedbo in nadzor izvajanja zakonodaje;
- pridobivanje ter testiranje tkiv in celic izvaja ustrezno usposobljeno in izkušeno osebje;
- so banke tkiv ustrezno akreditirane, imenovane in imajo odobritev ali dovoljenje;
- je zagotovljena sledljivost vseh tkiv in celic, ki so uporabljeni v EU, od darovalca do prejemnika in obratno. Obravnavani podatki se morajo hraniti najmanj 30 let po klinični uporabi;
- so vsi uvozi tkiv in celic iz držav zunaj EU v skladu s podobnimi standardi varnosti in kakovosti;
- so uvedeni sistemi za poročanje, raziskovanje, registracijo in pošiljanje ustreznih informacij o hudih neželenih učinkih ali reakcijah;
- se tkiva in celice zagotavljajo prostovoljno in brezplačno, čeprav je mogoče nekatere stroške poravnati, potem ko je dano obvezno soglasje;
- so vsi podatki anonimni, tako da ni mogoče prepoznati ne darovalca ne prejemnika.

Ta direktiva ne zajema krvi in njenih sestavin, organov in delov organov ali avtologne uporabe.

Konvencija proti trgovanju z organi (9)

Konvencija je bila sprejeta leta 2015 v Španiji in je stopila v veljavo leta 2018. Pripravili so jo strokovnjaki, ki delujejo v okviru strokovne skupine za presaditve organov držav Sveta Evrope. Osnova za konvencijo je Istanbulska deklaracija iz leta 2008. Konvencija poziva vlade, naj kot kaznivo dejanje določijo nezakonito odstranitev človeških organov živim ali umrlim darovalcem:

kadar se odvzem opravi brez prostega, obveščenega in izrecnega soglasja živega ali umrlega darovalca ali, v primeru pokojnega darovalca, ne da bi bila odstranitev odobrena po njenem notranjem pravu;

- če v zameno za odstranitev organov živi darovalci ali tretja oseba prejme finančno korist ali primerljivo korist;
- kadar tretja oseba v zameno za odstranitev organov umrlega darovalca prejme finančno korist ali primerljivo korist.
- Konvencija zagotavlja zaščitne ukrepe in odškodnine za žrtve, pa tudi preventivne ukrepe za zagotovitev preglednosti in pravičnega dostopa do storitev presaditve.

Slovenija jo je podpisala v decembru 2018 in je v postopku ratifikacije konvencije oz. prilagoditve Kazenskega zakonika.

Pogodba med Eurotransplantom in Slovenija-transplantom

Podpisana je bila v letu 2003. V pogodbi je zelo jasno definiran način sodelovanja med Slovenijo in mednarodno organizacijo za izmenjavo organov Eurotransplant.

Način poslovanja in pravila se naslanjajo na nizozemsko zakonodajo, kjer je sedež ustanove.

Medicinska priporočila so sprejeta na osnovi soglasja med delegati vseh držav v posvetovalnih telesih, ki jih končno potrdi izvršni odbor in pooblaščene organizacije v posameznih državah članicah, ki preverijo skladnost priporočila z nacionalno zakonodajo.

V letu 2018 je bila sprejeta nova vodstvena struktura, ki določa nadzorni odbor kot glavno izvedbeno telo. Izvršni odbor se razdeli na odbor za medicinska in strokovna vprašanja ter na odbor za administrativna vprašanja. Implementacija je v postopku.

Osnovni principi in etična pravila (10)

V slovenski organizaciji transplantacijske medicine in programa za pridobivanje DČT smo zelo pozorni na etične zahteve in ostale nujne principe, ki jih je treba vključiti v vsakdanje delo. Za doseganje kakovosti in varnosti mora biti sistem delovanja popolnoma pregleden in sledljiv. Poleg tega je zelo pomembno, da razvijamo zaupanje široke javnosti do tega modernega načina zdravljenja, in to lahko dosežemo z nenehnim izobraževanjem različnih javnosti, predstavitvijo rezultatov zdravljenja in korektnim sodelovanjem z mediji. V zadnjih 20 letih sodelujemo z mediji na partnerski način, opravljamo avtorizacije vseh člankov in zato nimamo večjih problemov s populističnimi negativnimi objavami.

Osnovna pravila, ki jih brezpogojno upoštevamo v transplantacijski dejavnosti:

- Samo umrle osebe so lahko darovalci organov in DČT, t. j. tako imenovani 'dead donor rule'. To velja za oba programa, ki ju izvajamo v pridobivanju DČT, t. j. darovanje po možganski smrti in darovanje po srčni smrti (roženice, koža).
- Izvajanje dejavnosti in možnosti razvoja se nenehno preverjajo z določili v zakonodaji.
- Darovanje je možno le na osnovi altruizma, neprofitnosti in nekomercialnega pristopa.

- Vsi postopki zdravljenja z uporabo DČT in raziskovanje morajo biti v skladu z osnovnimi etičnimi principi.
- Vsako zdravljenje se izvaja na osnovi najboljše klinične prakse in varnih standardov.
- Odgovorni strokovnjaki morajo skrbeti za visoko profesionalno delovanje in nadzorovati izvajanje v skladu s protokoli in navodili.
- Princip samozadostnosti vključuje konstruktivno in odgovorno sodelovanje med odgovornimi regulatorji, strategi in kliniki ter ostalimi, ki spodbujajo, da so bolniki, ki potrebujejo zdravljenje s presaditvijo, na tak način tudi zdravljeni. Biti morajo podrobno informirani o možnostih in rezultatih pri takšnem načinu zdravljenja. Odgovornost vseh odgovornih je, da so po prejetem soglasju vključeni na čakalni seznam ter tudi v sprejemljivem času zdravljeni s presaditvijo.

Zaključek

Skoraj 30 let smo potrebovali, da smo pripravili funkcionalen in varen sistem transplantacijske dejavnosti v Sloveniji. Ta danes predstavlja stabilen okvir za delovanje, ki se nenehno širi na osnovi birokratskih zahtev naše države in novih EU dokumentov. Še najpomembnejši razlog, da se sistem razvija in prilagaja, pa je nagel strokovni razvoj in uvajanje novosti na tem področju medicine.

Slovenija-transplant ima prepoznano vlogo v strokovnih krogih doma in mednarodno, visoko profesionalne sodelavce, sorazmerno stabilen vir financiranja in nenehno nove ambicije, saj v tako natančno in sodobno pravno urejenem sistemu ni težko uspešno delovati.

Seznam zakonskih in drugih pravnih podlag za delovanje Zavoda Republike Slovenije za presaditve organov in tkiv Slovenija-transplant:

Zakon o pridobivanju in presaditvi delov človeškega telesa zaradi zdravljenja (Uradni list RS, št. 56/15)

- Pravilnik o opredelitvi v zvezi z darovanjem delov človeškega telesa (Uradni list RS, št. 29/17)
- Pravilnik o uvrstitvi oseb na čakalni seznam zaradi zdravljenja s presaditvijo človeškega telesa (Uradni list RS, št. 85/16)
- Pravilnik o nalogah transplantacijskih koordinatorjev (Uradni list RS, št. 42/16).
- Pravilnik o vsebini programov izobraževanja in usposabljanja za posamezne postopke preskrbe z organi (Uradni list RS, št. 21/16)
- Pravilnik o načinu konzerviranja in postopkih prevoza človeških organov (Uradni list RS, št. 12/16)
- Pravilnik o sledljivosti in uničenju človeških organov, namenjenih za presaditev, ter o nacionalni identifikacijski številki (Uradni list RS, št. 76/15)
- Pravilnik o poročanju in obvladovanju hudih neželenih dogodkov in hudih neželenih reakcij pri ravnanju s človeškimi organi (Uradni list RS, št. 76/15)
- Pravilnik o spremembah in dopolnitvah Pravilnika o sledljivosti človeških tkiv in celic ter izdelkov in materialov, ki prihajajo v stik s tkivi in celicami (Uradni list RS, št. 17/15)
- Pravilnik o spremembah Pravilnika o darovanju in pridobivanju človeških tkiv in celic (Uradni list RS, št. 79/14)
- Pravilnik o načinu povezovanja s sorodnimi tujimi in mednarodnimi organizacijami in izmenjavi delov človeškega telesa z drugimi državami (Uradni list RS, št. 70/03)
- Pravilnik o sestavi, načinu imenovanja in pravilih za delovanje Etične komisije za presaditve (Uradni list RS, št. 30/02)

- Pravilnik o postopku obveščanja o smrti oseb, ki pridejo v poštev kot dajalci delov človeškega telesa zaradi presaditve (Uradni list RS, št. 85/01)
- Pravilnik o medicinskih merilih, načinu in postopku ugotavljanja možganske smrti ter sestavi komisije za ugotavljanje možganske smrti (Uradni list RS, št. 70/01)
- Pravilnik o načinu varstva osebnih podatkov dajalcev in prejemnikov delov človeškega telesa zaradi zdravljenja (Uradni list RS, št. 75/03)

Zakon o kakovosti in varnosti človeških tkiv in celic, namenjenih za zdravljenje (Uradni list RS, št. 61/07 in 56/15 - ZPPDČT)

- Pravilnik o sprejemu, obdelavi, shranjevanju, sprostitvi in razdeljevanju človeških tkiv in celic (Uradni list RS, št. 70/08)
- Pravilnik o sledljivosti človeških tkiv in celic ter izdelkov in materialov, ki prihajajo v stik s tkivi in celicami (Uradni list RS, št. 70/08)
- Pravilnik o pogojih in postopku za uvoz in izvoz ter vnos in iznos človeških tkiv in celic (Uradni list RS, št. 70/08)
- Pravilnik o darovanju in pridobivanju človeških tkiv in celic (Uradni list RS, št. 70/08)
- Pravilnik o postopkih zbiranja, shranjevanja in uporabe krvotvornih matičnih celic (Uradni list RS, št. 104/03)
- Pravilnik o načinu delovanja in pogojih za razvoj nacionalnega programa zdravljenja s presaditvijo krvotvornih matičnih celic in načinu delovanja registra nesorodnih dajalcev krvotvornih matičnih celic (Uradni list RS, št. 75/03)
- Pravilnik o histovigilanci (Uradni list RS, št. 47/17)
- Pravilnik o pogojih za izdajo dovoljenja za opravljanje dejavnosti preskrbe s človeškimi tkivi in celicami (Uradni list RS, št. 31/17)

Zakon o zdravljenju neplodnosti in postopkih oploditve z biomedicinsko pomočjo (Uradni list RS, št. 70/00 in 15/17 - DZ)

- Pravilnik o obrazcu izjave o privolitvi v postopek oploditve z biomedicinsko pomočjo (Uradni list RS, št. 5/03)
- Pravilnik o obrazcih o pisni privolitvi darovalke in darovalca spolnih celic (Uradni list RS, št. 5/03)
- Pravilnik o sestavi in vsebini poročila o postopkih oploditve z biomedicinsko pomočjo (Uradni list RS, št. 5/03)
- Zakon o zdravstvenih ukrepih pri uresničevanju pravice do svobodnega izločanja o rojstvu otrok (Uradni list RS, št. 11/77)
- Zakon o zakonski zvezi in družinskih razmerjih (Uradni list RS, št. 69/04 – uradno prečiščeno besedilo, 101/07 – odl. US, 90/11 – odl. US, 84/12 – odl. US, 82/15 – odl. US in 15/17 – DZ)

Dodatni zakonski dokumenti, povezani z direktivo, so še:

- Izvedbena direktiva Komisije 2012/25/ES z dne 9. oktobra 2012 o postopkih za pošiljanje informacij pri izmenjavi človeških organov za presaditev med državami članicami (UL L 275, 10. 10. 2012, str. 27–32)
- Delovni dokument služb Komisije o vmesnem pregledu Akcijskega načrta o darovanju in presajanju organov (2009–2015): krepitev sodelovanja med državami članicami (SWD(2014) 147 final, 25. 4. 2014)
- Poročilo Komisije Evropskemu parlamentu in Svetu o izvajanju pooblastila za sprejemanje delegiranih aktov, prenesenega na Komisijo v skladu z Direktivo 2010/53/EU Evropskega parlamenta in Sveta z dne 7. julija 2010 o standardih kakovosti in varnosti človeških organov, namenjenih za presaditev (COM(2015) 123 final, 10. 3. 2015)

Dodatni zakonodajni dokumenti, povezani z osnovno direktivo za tkiva in celice, so sledeči:

- Direktiva Komisije 2006/17/ES z dne 8. februarja 2006 o izvajanju Direktive 2004/23/ES Evropskega parlamenta in Sveta o nekaterih tehničnih zahtevah za darovanje, pridobivanje in testiranje človeških tkiv in celic (UL L 38, 9. 2. 2006, str. 40–52; glejte prečiščeno besedilo).
- Direktiva Komisije 2006/86/ES z dne 24. oktobra 2006 o izvajanju Direktive 2004/23/ES Evropskega parlamenta in Sveta o zahtevah po sledljivosti, obveščanju o hudih in neželenih reakcijah in pojavih ter nekaterih tehničnih zahtevah za kodiranje, predelavo, konzerviranje, shranjevanje in razdeljevanje človeških tkiv in celic (UL L 294, 25. 10. 2006, str. 32–50; glejte prečiščeno besedilo).
- Sklep Komisije 2010/453/EU z dne 3. avgusta 2010 o oblikovanju smernic glede pogojev za inšpekcijske preglede in nadzorne ukrepe ter glede usposabljanja in izobraževanja uradnikov na področju človeških tkiv in celic v skladu z Direktivo 2004/23/ES Evropskega parlamenta in Sveta (notificirano pod dokumentarno številko C(2010) 5278) (UL L 213, 13. 8. 2010, str. 48–50)
- Direktiva Komisije (EU) 2015/565 z dne 8. aprila 2015 o spremembi Direktive 2006/86/ES v zvezi z nekaterimi tehničnimi zahtevami za kodiranje človeških tkiv in celic (UL L 93, 9. 4. 2015, str. 43–55)
- Direktiva Komisije (EU) 2015/566 z dne 8. aprila 2015 o izvajanju Direktive 2004/23/ES v zvezi s postopki za preverjanje ustreznosti standardov kakovosti in varnosti uvoženih tkiv in celic (UL L 93, 9. 4. 2015, str. 56–68)

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2. Zakon o odvzemu delov človeškega telesa za namen zdravljenja, ZOPDC (Uradni list RS, št. 12/00)
3. Direktiva 2010/43/EU Evropskega parlamenta in Sveta z dne 7. julija 2010 o standardih kakovosti in varnosti človeških organov, namenjenih za presaditev
4. Zakon o pridobivanju in presaditvi delov človeškega telesa zaradi zdravljenja (Uradni list RS, št. 56/15).
5. Letno poročilo o delovanju Zavoda RS za presaditve organov in tkiv 2018
6. Zakon o kakovosti in varnosti človeških tkiv in celic, namenjenih za zdravljenje (Uradni list RS, št. 61/2007)
7. Zakon o zdravljenju neplodnosti in postopkih oploditve z biomedicinsko pomočjo (Uradni list RS, št. 70/00 in 15/17 – DZ)
8. Direktiva 2004/23/ES Evropskega parlamenta in Sveta z dne 31. marca 2004 o določitvi standardov kakovosti in varnosti, darovanja, pridobivanja, testiranja, predelave, konzerviranja, shranjevanja in razdeljevanja človeških tkiv in celic
9. Izvedbena direktiva Komisije 2012/25/EU z dne 9. oktobra 2012 o postopkih za pošiljanje informacij pri izmenjavi človeških organov za presaditev med državami članicami
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LEGISLATIVE AND ETHICAL ASPECTS IN TRANSPLANT MEDICINE IN SLOVENIA

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Introduction

The first document that defined the conditions for organ procurement and consequentially transplant medicine in Slovenia was prepared and adopted in 1992. It was called the Elaborate on the Organization of the System for Procurement of Human Body Parts (1).

The elaborate detailed the national donor programme with the most important tasks in the phases of operation:

- Donors and organ procurement;
- Identification of brain death;
- Informing relatives;
- Removal of organs and keeping official documents about it.

In addition, a number of reasons were listed in the document for the lack of organs intended for use in treatment and solutions suggested to eliminate them. The link between regional hospitals and the coordination of the national donor programme from a central place was indicated as a prerequisite for successful operation. Coordination was identified as a basic task at the level of hospitals, which should be connected to the central office and the main national coordinator. The Elaborate contained proposals for transitional measures that should have been taken into account for a successful organ transplantation programme in Slovenia.

In 2000, the first Slovenian law on the procurement of body parts (2) was adopted, which was based on suggestions and solutions about organisational and ethical aspects described in the Elaborate. The law defined an organisational scheme with authorised institutions at the state level, which the EU only identified in 2010.

It provides also funding for the national donor programme.

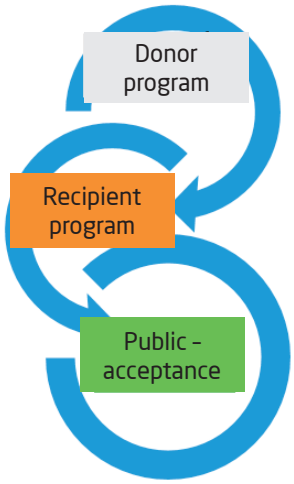
This law defines the consent for donation according to the principle of informed consent with the opting-in register, in part, as well as to the principle of presumed consent.

The law does not mention terms and conditions relating to research involving parts of the human body.

Current Slovenian Legislation and the role of the Institute for the Transplantation of Organs and Tissues of the Republic of Slovenia, Slovenija-transplant (3,4,5)

Current Slovenian legislation connects all the areas that need to be developed so that transplant medicine can be implemented in practice (Figure 1). The emphasis is on acquiring parts of the human body, quality and safety in all respects, and accurately recording and tracking all the data and editing registers.

Figure 1: Areas of transplant medicine and connections



Act on Procurement and Transplantation of Human Body Parts for Treatment (4)

The Act was prepared based on the requirement that Directive EU / 2010/53 should have been implemented in national legislation and represents an update of the Basic Law of 2000. As required by the Directive, quality and safety in the chain of procurement orders is more precisely defined. The competent authority is clearly defined, as well the method and scope of data collection with various registers.

With regard to the consent for donation, it does not bring innovations in comparison with the 2000 law, and it also merges two articles on informed and presumed consent. It brings an innovation in the form of an opt-out register, in which citizens of Slovenia can oppose donation. The opt-out register is a step closer to purely presumed consent, which is our plan for the future.

It defines the obligation to appoint responsible persons for individual programmes and the requirement that the personnel involved in these activities must be appropriately educated.

The requirements regarding the quality of premises and material used in this activity are laid down.

Likewise, the law requires defining the parameters that determine the quality system and the control over compliance with the legislation.

This law does not cover the field of research on parts of the human body either. It accurately defines the implementation of traceability in a transparent framework, which covers the use of parts of the human body for treatment or research.

The tasks of the Institute for Transplantation of Organs and Tissues in Slovenia, Slovenija-transplant are defined in Article 40. For the sake of transparency, all the tasks are summarised and presented in three chapters (5).

a) Tasks related to the donor programme:

- Expert supervision by advising donor and transplantation centres in connection with the
- establishment and updating of the system for the quality and safety of organs;
- Appointment of authorised persons to collect declarations for donation for lifetime;
- Issuing appropriate professional guidelines to donor and transplant centres that are involved in any stage of the procedure from donation to transplantation or destruction;

- Participation in the study of medical, legal, ethical, economic and social issues concerning procurement and transplanting of human body parts;
- Coordination of procurement, transplantation and disposal activities between donor and transplant centres, laboratories, organ transport, the European or international organ exchange organisation. The cooperation with previously mentioned organisations is based on the agreement;
- Ensuring 24-hour accessibility of central transplant coordinators;
- Informing the public about the importance of donation during life and after death due to transplantation to another person.

b) Tasks related to the Recipients programme:

- Keeping recipients' waiting lists;
- Cooperation with Eurotransplant;
- Coordination of organ transplantation;
- Coordination of the functioning of donor and transplantation centres and transplant coordinators;
- Collecting and analysing data on unused organs;
- Collecting and analysing data on adverse events and reactions;
- Counselling to transplant centres.
- The field is governed by the Rules on the classification of persons on the waiting list for the treatment of transplantation of parts of the human body (OJ No. 85/2016)

c) The tasks related to assurance of quality, safety, traceability and transparency in the donor and transplantation system are monitored by a number of the following policies:

- Management of the system for reporting of serious adverse events and serious adverse reactions and the management of such cases;
- Monitoring the exchange of organs with other Member States of the European Union and third countries;
- Establishment and management of the Central Register;
- Keeping records of the activity of donor and transplantation centres, including the number of living and dead donors, the types and number of organs taken and transplanted or otherwise disposed of in accordance with this Act and the rules on the protection of personal data;
- The establishment of a system for the allocation and use of the national identification number;
- Setting up and managing a database of identified donors;
- The establishment and administration of records on the authorisations issued to donor and transplant centres and records of hospital transplant coordinators, central transplant coordinators and clinical transplant coordinators;
- Upgrading and maintaining a central information system for the activity of extraction, transplantation and destruction;
- Ensuring the upgrading of the register of unrelated bone marrow donors in cooperation with the Institute of Blood Transfusion Medicine;
- Preparing and publishing an annual report on state-level procurement activities and reporting to the competent authorities of the European Union or to the Member States of the European Union.

Article 10 provides for the removal of parts of the body after death, namely from a person who died of cerebral death or heart failure. It determines that death is to be determined by a procedure prescribed by the minister and that a doctor who establishes death must not participate in the chain of procurement or transplantation.

The law stipulates that the body of a deceased person should be treated with respect for the dignity of the deceased and those who were close to the dead, as well as the principles of ethics and deontology.

The field is more closely regulated by the relevant policies.

Act on the Quality and Safety of Human Tissues and Cells Intended for Treatment (6)

This Act also defines the tasks of the Institute for the Transplantation of Organs and Tissues in the Republic of Slovenia, Slovenija-transplant thus ensuring the safety, traceability and quality of the framework for the operation of this sensitive area and determining the conditions for a regulated system. As regards the donation and procurement of tissues and cells, the general principles laid down in the Act on the Acquisition and Transplantation of Human Body Parts for Treatment, 2015 (2) apply.

The law sets out requirements for:

- The production of tissues and cells within the framework of the multiorgan procurement or after cardio-circulatory death;
- Promotional activities and publicity to support the donation of tissues and cells;
- The management of a central information system for the use of human cells and tissues for the treatment;
- Preparation of on-line reports for tissues and cells and an annual report;
- The establishment and maintenance of a publicly accessible register for tissues and cells with information on the activities of tissue and cell establishments;
- The collection of data relating to the identification and reporting on serious adverse events or reactions to donors or recipients of tissues and cells and their epidemiological monitoring.

EU directives setting requirements in transplant medicine (7, 8)

All abovementioned Slovenian laws are in line with EU directives. Based on directives, EU countries must ensure a quality and safety framework covering the whole process, from donation to transport or disposal of organs.

- This must include the identity of the donor and the consent of the donor or his family, as well as other conditions laid down in the legislation,
- The donor is selected and evaluated by authorised doctors and organisations with suitably qualified health personnel,
- Minimum donor data such as age, weight and past or current medical history are available,
- The transport of organs meets certain requirements, such as proper marking and identification,
- Organ harvesting and transplantation may only take place in centres authorised for this purpose in accordance with EU law,
- The authorities can be traced for at least 30 years from the donor to the recipient and vice versa,
- A system is introduced for reporting, researching, registering and sending relevant information on serious adverse events or reactions. Information should also be exchanged when it comes to the exchange of organs between EU countries,
- The donation of organs of dead and living donors is voluntary, based on altruism and must be accompanied by the necessary consent,
- Living donors should be carefully selected and reviewed. Donors should be guaranteed the highest possible level of protection,

- The fundamental right to the protection of all personal data is "fully and effectively respected",
- Their competent authorities regularly exchange information within the network set up by the European Commission.

Directive 2010/53 / EU on standards of quality and safety of human organs intended for transplantation (6)

- It lays down rules to ensure standards of quality and safety for organ transplantation;
- It seeks to ensure that living donors and recipients receive the same quality, safety and legal standards regardless of they live.
- It covers donation, testing, characterisation, procurement, preservation, transport and transplantation of organs.

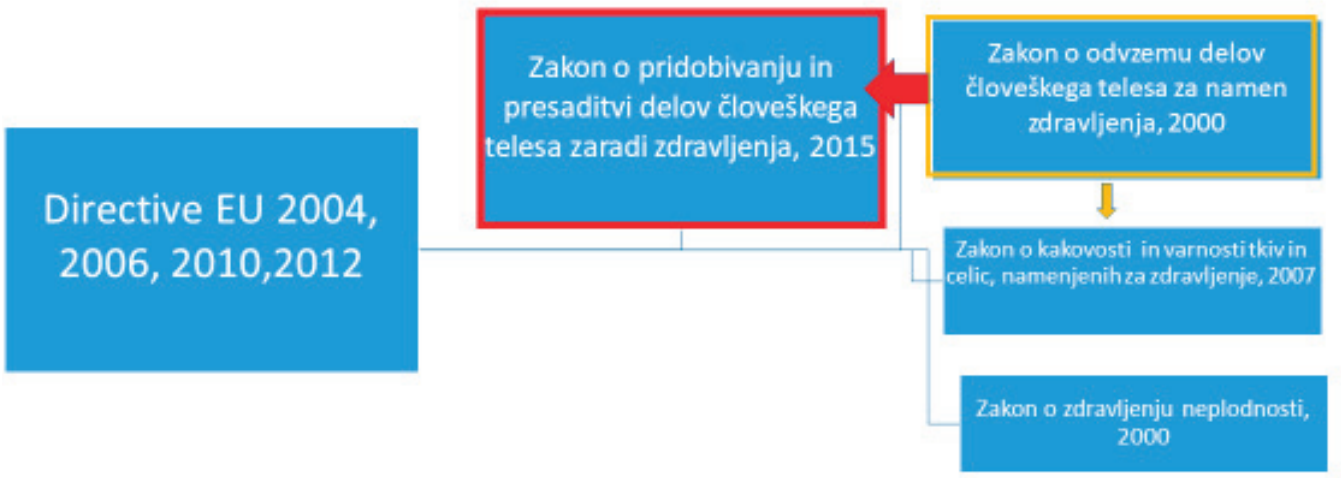
Directive 2004/23 / EC - quality and safety standards for donated human tissues and cells (7)

The Directive sets quality and safety standards in order to minimise the risk of infection and prevent the transmission of disease in the transplantation of human tissues and cells. It covers the entire chain of activities from donation to procurement, testing, processing, preservation, storage and distribution to the site of medical use or to places where industrial products are produced from these human substances.

- Based on the Tissues and Cells Directive, EU countries are obliged to ensure that:
- Competent authorities are appointed to carry out and monitor the implementation of legislation;
- The acquisition and testing of tissues and cells by properly trained and experienced staff;
- Tissue establishments are appropriately accredited, appointed and approved or licensed.
- Traceability of all tissues and cells used in the EU, from the donor to the recipient and vice versa, is ensured. The data under consideration must be kept for at least 30 years after clinical use;
- All imports of tissues and cells from non-EU countries comply with similar safety and quality standards;
- Systems are introduced for reporting, researching, registering and sending relevant information on serious adverse reactions or reactions;
- The tissues and cells are provided on a voluntary and free basis, although some costs may be settled after the compulsory consent is given;
- All data is anonymous so that neither the donor nor the recipient can be identified.

This Directive does not cover blood and its constituents, organs and parts of organs or autologous use.

Figure 2. Legislative documents regulating the activity of using human body parts for the purpose of treatment in Slovenia and their interconnections (3,4,6,7,8,9).



Convention against human organs trafficking (10)

The Convention was adopted in 2015 in Spain and entered into force in 2018. It was prepared by the expert group on organ transplantation in the countries of the Council of Europe. The basis for the convention is the Istanbul Declaration of 2008. The convention calls on governments to establish as a criminal offence the unlawful removal of human organs from living or deceased donors:

- Where the removal is carried out without the free, informed and explicit consent of the living or deceased donor, or, in the case of the deceased donor, without the removal being granted under its domestic law;
- If, in exchange for the removal of organs, the live donor or a third person receives a financial benefit or comparable benefit;
- Where a third party, in exchange for the removal of the organs of the deceased donor, receives a financial benefit or comparable benefit.
- The Convention also provides safeguards and compensation for victims, as well as preventive measures to ensure transparency and fair access to transplant services.

Slovenia signed it in December 2018 and we are in the process of the ratification of the Convention with the adjustments to the Criminal Code.

Basic principles and ethical rules (11)

In the Slovenian organisation of transplantation medicine and the programme for procurement of human body parts, we pay great attention to ethical requirements and other principles that need to be included in everyday work. In order to achieve quality and safety, the operating system must be fully transparent and traceable. In addition, it is very important that we develop the trust of the general public to this modern method of treatment, and this can be achieved through continuous education of various publics, presentation of the results of treatment, and proper cooperation with the media. Over the past 20 years, we have been working with the media in a partnership manner, we are authorising all articles, and therefore we have no major problems with populistic negative publications.

The basic rules unconditionally taken into account in the Slovenian transplantation activity:

- Only deceased persons can be organ donors. It is the so-called Dead Donor rule and applies to both programmes that we perform as donation after brain death and donation after cardiac death - corneas, skin;
- The implementation of the activities and the possibilities of development are constantly checked by the provisions of the legislation;
- Donation is possible only based on altruism, non-profit and non-commercial approach
- All treatment procedures using the human body parts and research must be in accordance with the basic ethical principles;
- Each treatment should be based on the best clinical practice and safe standards
- Responsible professionals should ensure high professional standards and monitor implementation in accordance with protocols and instructions;
- The principle of self-sufficiency involves constructive and responsible co-operation between responsible regulators, strategists and clinics, as well as others that encourage patients requiring transplant treatment. It is necessary that the patients be thoroughly informed about the possibilities and outcomes of this type of treatment. The responsibility of leading professionals and regulators is that they ensure the system that all patients are put on the waiting list after receiving the consent and are treated with a transplant at an acceptable time.

Conclusion

We needed almost 30 years to prepare an operating, functional and safe transplantation system in Slovenia. Today it represents a stable framework for action, which is constantly expanding based on the bureaucratic requirements of our country and the new EU requirements. The most important reason for developing and adapting the system is the rapid development of professional aspects and the introduction of innovations in this field of medicine.

Slovenija-transplant has a recognised role in professional circles at home and abroad, highly professional associates, a relatively stable source of funding and a constantly new ambition, since it is not difficult to operate successfully in such a precise and modern legal system.

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9. Izvedbena direktiva Komisije 2012/25/EU z dne 9. oktobra 2012 o postopkih za pošiljanje informacij pri izmenjavi človeških organov za presaditev med državami članicami
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LEGAL AND ETHICAL FRAMEWORK OF ORGAN TRANSPLANTATION IN CROATIA

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History

Since the first kidney transplantation (TX) in Croatia in 1971 in Rijeka *(Vidović M, Pasini J, Orlić P. Acta Chir Iugosl. 1990;37 Suppl 1:125-31. In Croatian.)* the national organ TX has been improving with time, aiming to the best and comprehensive medical care in the field. Nowadays, kidney, pancreas (simultaneously with kidney), liver and heart TX are routine procedures in several TX centers in Croatia. The results have increased during the last decade, parallel to joining Eurotransplant (ET) in 2007 *(Langer RM, Cohen B, Rahmel A. History of Eurotransplant. Transplant Proc. 2012;44(7):2130-1.)*, placing the country to the highest European and global level *(Gómez MP, Arredondo E, Páez G, Manyalich M. International Registry in Organ Donation and Transplantation 2010. Transplant Proc.* 2012;44(6):1592-7.). ET regulations rendered even better transparency within the system.

Law

Croatian law allows organ TX form living and from deceased donors. Living donors could be related or unrelated. The deceased comprise of only brain dead donors. Organ trade has been forbidden by law. Personal declaration about organ donation by Croatian law is so called opt-out (necessity to opt if willing to be out of the donors' pool), or the presumed consent (Act since 1988). *(*Živčić- Ćosić, S. et al. Development of the Croatian model of organ donation and transplatation, Croatian Medical Journal, Vol. 54, No. 1, 2013., 65-70.) Since the beginning of current millennium hospital coordinators have become obligatory within the system and they bear the major burden and responsibility for donor recruitment, brain death confirmation, preparing and maintaining the donor for organ harvesting and also for communication with donor's family. *(The Law on TX of human body parts for medical treatment purpose, NN 144/12. In Croatian)* Along with the opt-out law, there is a rule defined by the Codex of Medical Ethics and Deontology which obliges physicians to ask for donor's family permission for organ donation. *(Code of Medical Ethics and Deontology. NN 139/15. Available at www.hlk.hr In Croatian. Last access 04 May 2019)* The refusal rate has been around 15 %. The Law on TX of human body parts for medical treatment purpose from 2012 defines the rules of donor and recipient recruitment, procurement and other relevant areas of the TX related procedures. *(The Law on TX of human body parts for medical treatment purpose, NN 144/12. In Croatian)* Allocation of organs from deceased donors has been performed according to the ET rules.

Ethical concerns

Croatian citizens are mostly Catholics and Catholic Church approves organ donation and TX. *(Pope John Paul II.Address of John Paul II to the 18th International Congress of the Transplantation Society. Med Etika Bioet.* 2001 Spring-Summer;8(1-2):12-4.) However, the knowledge about the law and about the attitude of the Church has not been universal among the citizens and there is much to be done in terms of education of the public about the issue. *(Zibar L. et al. Informedness on the opt-out law on organ donation after brain death in Croatia. 1st Congress of Croatian Society for Transplantation Medicine, Zagreb, 2016).*

Pretransplantation management of recipients includes patient's autonomy by decision making, which is inevitable feature of any medical care. However, insufficient health literacy could be the reason for sometimes poor compliance of the patients on their way to the waiting list. *(Zibar L. SAHLSA questionnaire, 2014, Osijek, Croatia, personal unpublished data.*

Living donor TX might be more encouraged, irrespective of the deceased donors' relative availability and the following TX success. Unrelated donations sometimes bear suspicion on organ trade and thus discourage performing the TX. *(Zibar L. How to deal with unprovable suspicion of organ trade? 5th ELPAT Congress, Krakow, Poland, 2019)*

Donation after circulatory death (DCD) would offer further improvement in combating donors shortage (although the shortage has not been a respectable current feature of Croatian organ TX system). The option has been only an unofficial idea for future, so far. Legal and ethical framework for DCD is lacking, as well.

Public insight into the TX activities should be more engaged. The trust is a relevant ground for the success of the program. Wrong premises could be extremely incongruent with the real situation and it is rather unethical not to pursue and to combat them. *(Zibar L et al. What do Croatian chronic hemodialysis patients think about illegal kidney transplantations? ISCB; Jerusalem, Israel, 2016.)*

Further concerns might be related to the TX of seniors, psychiatric patients, patients with HIV, history of addiction to alcohol or drugs, history of losing previous organ transplant due to nonadherence to the therapy, use of marginal donors (with comorbidities), TX in Jehovah's witnesses, in obese patients etc. Improvement in end of life decisions regulations might be closely related to the ethics in organ donation and TX. International relations with neighboring non-ET countries open a distinct set of ethical dilemmas, including the question of insurance and cost as well as distributive justice.

IMPLEMENTATION OF ANTITRAFFICKING CONVENTION

The Portuguese experience in the development of a legal framework for the implementation of the Convention against Trafficking in Human Organs, management of patients who return home after receiving an organ transplant abroad, and for reporting suspicious cases to law enforcement authorities.

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Abstract

The existence of a world-wide illicit trade in human organs for the purposes of transplantation is a well-established fact, and various means have been adopted to combat this criminal activity, in particular the recent Council of Europe Convention against Trafficking in Human Organs. This Convention is the first international legal instrument that criminalizes all illicit transplant practices. Healthcare professionals who treat patients in pre transplant and post-transplant play a crucial role in prevention, detection and reporting organ trafficking. However, healthcare professionals face with medical, legal, and ethical problems when confronted with suspected or confirmed cases of organ trafficking due to their duty to preserve medical confidentiality. We present the recently developed Portuguese Model for the implementation of the Convention against Trafficking in Human Organs. First, we present the legislative changes that are occurring, such as the framework developed to allow healthcare professionals to disclose information on organ trafficking. Secondly, we present a code of conduct developed for healthcare professionals to address such challenges and provide guidelines for the management of those patients, including indicators to identify suspicious, and a reporting mechanism for the communication of suspected cases of organ trafficking to law enforcement authorities for the purposes of criminal investigation.

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MOŽGANSKA SMRT

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Uvod

Koncept možganske smrti, kot ga poznamo danes, se je razvil skupaj z nastankom intenzivne medicine in transplantacijske dejavnosti. Predpisani postopek določanja možganske smrti je namenjen temu, da se možgansko smrt nezmotljivo prepozna in potrdi, se pa od države do države razlikuje v nekaterih podrobnostih. Zato so pomembna prizadevanja za razvoj smernic in priporočil na mednarodnem nivoju.

Koncept možganske smrti

Fiziološke mehanizme nastanka smrti pri človeku so raziskovali že konec 18. stoletja. Vendar pa so šele v začetku 20. stoletja pričeli ugotavljati, da je nepovratna okvara možganov samostojen vzrok za smrt človeka. Odpoved dihanja, delovanja srca in možganov namreč brez intervencij sodobne medicine nastopi skoraj hkrati oziroma v zelo kratkem časovnem obdobju. Šele razvoj moderne intenzivne medicine z nastankom oddelkom za intenzivno terapijo in pričetkom uporabe mehanske ventilacije je prinesel možnost, da se z umetnim vzdrževanjem dihanja vzdržuje delovanje notranjih organov kljub nepovratni odpovedi delovanja možganov. Razvoj intenzivne medicine v sredini prejšnjega stoletja pa sovpada tudi s pričetkom transplantacijske medicine s prvimi transplantacijami organov v 60. letih.

Mollaret in Goulon (1) sta leta 1959 opisala skupino pacientov v "ireverzibilni komi" (coma dépassé), za katero so bili značilni neodzivnost, neizzivni refleksi možganskega debla, odsotnost spontanega dihanja in odsotnost možganske aktivnosti na EEG posnetku. Leta 1968 je komisija Harvardske medicinske fakultete pripravila prvo definicijo možganske smrti (2) z jasno opredeljenimi kriteriji: neodzivnost, odsotnost gibov, apneja, odsotnost refleksov, izoelektričen EEG; najdbe naj bi bile še enkrat potrjene najmanj 24 ur kasneje. Podoben princip ugotavljanja možganske smrti je v uporabi še danes. V Veliki Britaniji je nastal nekoliko drugačen koncept možganske smrti, ki kot zadosten pogoj upošteva ireverzibilno prenehanje delovanja možganskega debla (3). Vse do danes se v različnih državah za definicijo možganske smrti uporablja ali koncept prenehanja delovanja velikih možganov in možganske debla ali pa koncept prenehanja delovanja možganskega debla.

Postopek določanja možganske smrti

Pomembno je, da se za določanje možganske smrti uporablja jasno definiran protokol, ki ne dovoljuje zmote in s katerim lahko izključimo vse možne potencialno reverzibilne dejavnike (4). Določanje se lahko prične, če je pacient v aponični neodzivni komi. Najprej je treba preveriti, ali veljajo določeni predpogoji: jasen mora biti vzrok kome, izključena morajo biti druga možna stanja, ki izgledajo podobno kot možganska smrt, pacient mora biti hemodinamsko stabilen in brez pomembnejših metabolnih motenj, s telesno temperaturo nad 35 °C ter brez pomembnega vpliva zdravil, ki delujejo na osrednje živčevje ali na živčnomišični stik. Glavni del postopka določanja možganske smrti je klinično ocenjevanje odsotnosti refleksov možganskega debla. S testiranjem refleksov se preveri delovanje posameznih se-

gmentov možganskega debla v kranio-kavdalni smeri: reakcija zenic na osvetlitev, kornealni refleks, odziv na bolečino v področju trigeminusa, cefalo-okularni refleks, okulo-vestibularni refleks, žrelni refleks in refleks kašljanja. Na koncu sledi še test apneje. Upoštevati je treba, da se lahko pojavljajo nekateri klinični fenomeni tudi pri možgansko mrtvem človeku, saj so le odraz delovanja drugih delov živčevja (hrbtenjače, perifernega živčevja), kot na primer nekateri spontani in refleksni gibi. Za dokazovanje odsotnosti delovanja možganske skorje se uporabljajo različne instrumentalne preiskave, ki temeljijo na ugotavljanju odsotnosti prekrvavitve (scintigrafija, CT in klasična angiografija, transkranialna dopplerska ultrasonografija) ali električne aktivnosti možganov (elektroencefalografija).

Ugotavljanje možganske smrti v Sloveniji

V Sloveniji je ugotavljanje možganske smrti predpisano s Pravilnikom o medicinskih merilih, načinu in postopku ugotavljanja možganske smrti ter sestavi komisije za ugotavljanje možganske smrti, objavljenem leta 2001 v Uradnem listu Republike Slovenije (5). Možganska smrt je po tem pravilniku definirana kot dokončno in nepovratno prenehanje delovanja celotnih možganov (možganskega debla in možganskih hemisfer) pri osebi, ki se ji ob umetnem dihanju vzdržuje delovanje srca in krvnih obtočil. Ugotavljanje obsega tako dokaz kliničnih znakov možganske smrti kot potrdilni izvid dopolnilne instrumentalne preiskave – elektroencefalogram brez možganske električne aktivnosti ali dokaz zaustavitve znotrajlobanjskega obtoka krvi s perfuzijsko scintigrafijo ali z dopplersko ultrasonografijo. Možganska smrt se ugotavlja z dvema zaporednima kliničnima pregledoma, med prvim in drugim pregledom mora biti predpisani najkrajši presledek, ki je odvisen od bolnikove starosti in vrste okvare možganov (6 do 72 ur). V pravilniku je predpisana sestava komisije za ugotavljanje možganske smrti: dva zdravnika, od katerih je eden zdravnik specialist anesteziolog ali zdravnik specialist internist ali zdravnik specialist pediater, ki dela na področju intenzivne medicine in je izkušen v zdravljenju bolnikov s hudimi poškodbami možganov, drugi pa je zdravnik specialist nevrolog ali zdravnik specialist nevrokirurg ali zdravnik specialist z izkušnjami na področju intenzivne medicine in zdravljenja hudih poškodb možganov, in zdravnik, ki opravi instrumentalne preiskave.

Dileme in izzivi pri ugotavljanju možganske smrti

Čeprav sta koncept in definicija možganske smrti jasna, se v strokovni in laični javnosti večkrat pojavljajo različne dileme in dvomi, ki so verjetno predvsem posledica slabe informiranosti. Zato je pomembno izobraževanje strokovnjakov in ozaveščanje laične javnosti ter transparenten način dela zdravstvenih delavcev, vključenih v postopke ugotavljanja možganske smrti.

Med zdravstvenimi delavci predstavlja poseben izziv prepoznavanje in razumevanje različnih spontanih in refleksnih gibov, ki so kompatibilni z diagnozo možganske smrti in so večinoma posledica refleksne aktivnosti hrbtenjače. Takšni gibi so na primer plantarni umaknitveni refleks, kitni refleksi, krčenje trebušnih mišic, Lazarjev znak in gibi, podobni dihalnim (6). Nerazumevanje izvora in pomena teh gibov lahko povzroči precejšnjo stisko pri svojcih in nezaupanje v postopke določanja možganske smrti pri zdravstvenih delavcih.

Tako znotraj Evrope kot tudi drugod po svetu postopki za določanje možganske smrti niso enotni. Razlikujejo se v predpisanih kliničnih testih (v nekaterih državah na primer uporabljajo atropinski testi, razlikujejo se protokoli testa apneje), uporabi instrumentalnih preiskav, sestavi komisije za ugotavljanje možganske smrti (7). Omenjene razlike odražajo pomanjkanje konsenza na mednarodnem nivoju in je pričakovati postopno poenotenje z razvojem in uporabo smernic in priporočil (8, 9).

Ker je fenomen možganske smrti na stičišču medicinskih, nevroznanstvenih, etičnih, pravnih, religioznih in filozofskih razprav, so nova medicinska in znanstvena spoznanja s tega področja pogosto zanimiva za širšo javnost in medijski prostor. Nedavno je bila na primer objavljena študija, v kateri so opisali vzpostavitev mikrocirkulacije ter metabolne in celične aktivnosti v prašičjih možganih nekaj ur po smrti (10). Rezultate takšnih študij je potrebno kritično vrednotiti (11).

Zaključki

Koncept in pravila za določanje možganske smrti so temelj, da lahko kljub umetnemu vzdrževanju dihanja in cirkulacije zanesljivo potrdimo, da je oseba z nepovratnim in dokončnim prenehanjem delovanja možganov mrtva. Postopek določanja je enak ne glede na to, ali je oseba potencialni donor organov ali ne. Dobro razumevanje teh konceptov in zaupanje strokovnjakov in javnosti v predpisane postopke je pomembno tako za intenzivno medicino kot za transplantacijsko dejavnost. Pri tem ima pomembno vlogo razvoj mednarodnih smernic in priporočil.

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BRAIN DEATH

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Introduction

The concept of brain death, as we know it today, developed along with the emergence of intensive care medicine and organ transplantation. The brain death determination procedure is regulated to recognize and validate brain death without a possibility of error, but it differs from country to country in some detail. Therefore, efforts are being made to develop guidelines and recommendations at the international level.

The concept of brain death

The physiological mechanisms of human death have been investigated at the end of the 18th century. However, it was not until the beginning of the 20th century that they began to realise that irreversible brain damage was an independent cause of human death. Discontinuation of breathing, cardiac and brain activity occurs without interventions of modern medicine almost simultaneously or within a very short interval. Only the development of modern intensive care medicine with the emergence of intensive care units and the beginning of the use of mechanical ventilation brought about the possibility of maintaining the function of internal organs using mechanical ventilation despite the irreversible cessation of brain function. The development of intensive care medicine in the middle of the last century coincides with the beginning of organ transplantation in the 1960s.

Mollaret and Goulon (1) described in 1959 a group of patients in an "irreversible coma" (coma dépassé), characterized by non-responsiveness, absent reflexes of the brainstem, absence of spontaneous breathing, and no brain activity on EEG. In 1968, the Harvard Medical College Commission prepared the first definition of brain death (2) with clearly defined criteria: non-responsiveness, absence of movements, apnoea, absence of reflexes, isoelectric EEG; the finds should be confirmed again at least 24 hours later. A similar principle of brain death determination is still in use today. In the United Kingdom, a slightly different concept of brain death developed, which, as a sufficient condition, considers the irreversible cessation of the brainstem function (3). To this day, in the various countries, the definition of brain death uses either the concept of the cessation of brain and brainstem function, or the concept of the cessation of brainstem function.

The process of brain death determination

It is important that a clearly defined protocol is used to determine brain death, which does not allow for error and with which we can exclude all potentially reversible factors (4). Determination can begin if the patient is in an apnoeic non-reactive coma. First of all, it is necessary to check if certain preconditions apply: the cause of the coma should be clear; other possible conditions that resemble brain death should be excluded; the patient should be hemodynamically stable and without significant metabolic disorders, with a body temperature above 35 °C

and without the significant effect of drugs that act on the central nervous system or on neuromuscular junction. The main part of the process of brain death determination is the clinical assessment of the brainstem reflexes. By testing the reflexes, the functioning of the individual segments of the brainstem in the cranio-caudal direction is examined: the reaction of the pupils to light, the corneal reflex, the response to pain in the trigeminal region, the oculocephalic reflex, the oculovestibular reflex, the pharyngeal reflex and the cough reflex. This is followed by the apnoea test. It should be noted that some clinical phenomena may also occur in a brain-dead person, as they only reflect the function of other parts of the nervous system (spinal cord, peripheral nerves), such as some spontaneous and reflex movements. Various ancillary tests based on the determination of the absence of blood flow (scintigraphy, CT and classical angiography, transcranial Doppler ultrasonography) or electrical activity of the brain (electroencephalography) are used to prove the cessation of cerebral cortex activity.

Brain death determination in Slovenia

In Slovenia, the assessment of brain death is regulated by the *Ordinance on medical criteria, the method and procedure for determining brain death and the composition of the committee for the assessment of brain death*, published in 2001 in the Official Gazette of the Republic of Slovenia (5). According to this rule, brain death is defined as a complete and irreversible cessation of the functioning of the whole brain (brainstem and cerebral hemispheres) in a person with maintained functioning of the heart and circulation using mechanical ventilation. The determination consists of both the evidence of clinical signs of brain death as well as the confirmatory result of a ancillary instrumental investigation – electroencephalogram without electrical brain activity or evidence of cessation of intracranial blood flow using perfusion scintigraphy or Doppler ultrasonography. Brain death is determined by two consecutive clinical examination with a prescribed shortest interval between the examinations, depending on the patient's age and type of brain damage (6 to 72 hours). The Committee for brain death determination consists of: two doctors, one of them a consultant of anaesthesiology or a consultant of internal medicine or a consultant of paediatrics who works in the field of intensive care medicine and is experienced in the treatment of patients with severe brain injury, the other one a consultant of neurology or a consultant of neurosurgery or a consultant with experience in the field of intensive care medicine and the treatment of severe brain injury, and a consultant who performs the ancillary instrumental investigation.

Dilemmas and challenges in brain death determination

Although the concept and definition of brain death is clear, there are various dilemmas and doubts that often arise in the professional and lay public, which are probably due to inadequate knowledge. It is therefore important to educate the experts and to raise awareness of the lay public. Also, the work of health professionals involved in the process of diagnosing brain death should be transparent.

Among health professionals, the challenge is to recognise and to understand the various spontaneous and reflex movements that are compatible with the diagnosis of brain death and are mainly due to the reflex activity of the spinal cord. Such movements are, for example, plantar withdrawal reflex, tendon reflexes, contraction of the abdominal muscles, Lazarus sign and respiratory-like movements (6). Misunderstanding of the origin and significance of these movements can cause considerable distress in relatives and mistrust in the procedures for brain death determination among health workers.

In Europe and elsewhere, procedures of brain death determination are not uniform. They differ in the prescribed clinical tests (for example, atropine tests are used in some countries, apnoea test protocols differ), instrumental investigations, the composition of the Committee for the assessment of brain death (7). These differences reflect

the lack of consensus on the international level. Further development and application of guidelines and recommendations is needed and expected (8, 9).

Since the phenomenon of brain death is at the juncture of medical, neuroscientific, ethical, legal, religious and philosophical debates, new medical and scientific knowledge in this field is often of interest to the general public and the media. Recently, for example, a study was published describing the emergence of microcirculation and metabolic and cellular activity in the pig brain a few hours after death (10). The results of such studies should be critically evaluated (11).

Conclusion

The concept and rules for brain death determination enable to firmly confirm that a person with irreversible and definite cessation of brain function is dead, despite artificial maintenance of breathing and circulation. The same procedure is used regardless of whether the person is a potential organ donor or not. A good understanding of these concepts and the trust of professionals and the public in is important for both the intensive care and the transplantation medicine. The development of international guidelines and recommendations is of great importance to achieve in this.

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NOVI TRENDI V TRANSPLANTACIJSKI MEDICINI – DAROVANJE PO ZAUSTAVITVI SRCA IN SPREJEM V ENOTO INTENZIVNE TERAPIJE Z NAMENOM KASNEJŠEGA DAROVANJA ORGANOV IN TKIV

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Povzetek

Za dobro izvedbo u-DCD in c-DCD programa so potrebni natančni protokoli, podprti z jasnimi smernicami v skladu s sprejeto zakonodajo in usklajeno delovanje vseh sodelujočih ekip, da čim bolj zmanjšamo čas tople ishemije in na ta način omogočamo boljše in daljše preživetje tako presajenih organov, kot prejemnikov. S pomočjo teh programov se je v državah, ki te programe uporabljajo, število darovalcev dvignilo za pomembnih 25 % (Španija) do 50 % (Nizozemska). Najboljši rezultati so bili doseženi na področju transplantacije tako pridobljenih ledvic in pljuč. Nekoliko več komplikacij je pri presaditvi tako pridobljenih jeter, kjer pa se stanje preživelih presadkov po 10 letih izravna s tistimi, pridobljenimi od možgansko mrtvih darovalcev.

Metodologija

V donorski in transplantacijski dejavnosti se, tako kot drugje po svetu, tudi v Sloveniji srečujemo z večjim številom prejemnikov na čakalni listi, kot pa je število razpoložljivih organov za presaditev. Sami smo daleč od samozadostnosti, ki bi po trenutnih izračunih pomenila, da bi moralo na leto od vseh umrlih 0,5 % postati darovalcev organov in tkiv po smrti. V letu 2017 smo dosegli izračunani indeks samozadostnosti 0,187 in še vedno se, tako kot druge države članice Eurotransplanta, soočamo s kruto realnostjo – umiranjem prejemnikov na čakalnem seznamu (približno 10 vsako leto).

Da bi se samozadostnosti lahko čim bolj približali, moramo izkoristiti vse razpoložljive vire darovalcev organov in tkiv po smrti.

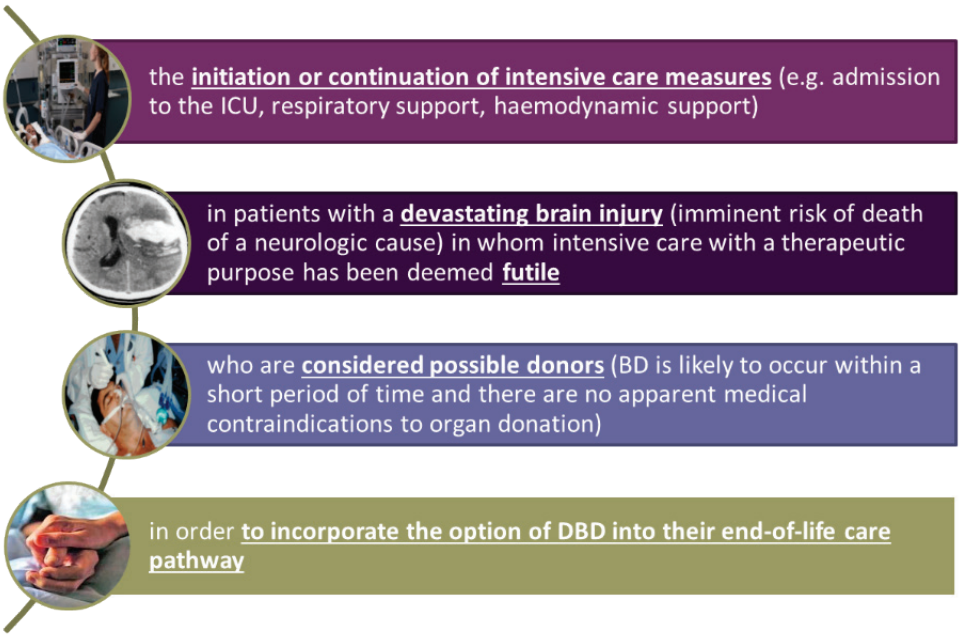
V zadnjih letih smo se že naučili, kako ravnati z mejnimi darovalci (angl. *expanded criteria donors*) in prenekatera kontraindikacija tudi za nas ni več absolutna. Poleg tega so prisotne še precejšnje rezerve v neizkoriščenem potencialu zaradi visoke stopnje zavrnitve svojcev v zadnjem letu in težav s pravočasnim sporočanjem potencialnih darovalcev transplantacijskim koordinatorjem.

Kot novi trend pa se v nekaterih državah članicah Eurotransplanta že pojavljata dva nova programa in sicer sprejem infaustnih pacientov v enoto intenzivne terapije z namenom kasnejšega darovanja organov in tkiv (angl. *ICOD program – Intensive Care admission for Organ Donation*), ter program darovanja organov in tkiv od umrlih darovalcev po ugotovljeni srčni smrti (angl. *DCD program – Deceased after Cardiac Death*).

Obema programoma je skupno to, da posegamo na področje zdravljenja pacientov ob koncu življenja (end-of-life care). Za uspešno izvedbo obeh programov bo potrebno spisati jasno zakonodajo in smernice, ki se bodo na zakonodajo naslanjale, poleg tega pa bo potrebno odgovoriti tudi na vsa, za nepoučene strokovnjake morda sporna, etična vprašanja. Pri tem se naslanjamo na smernice Sveta Evrope, ki govorijo o načinih zdravljenja in odločitvah ob koncu pacientovega življenja. V vseh takih primerih bi namreč lečeči zdravnik moral upoštevati v naprej izraženo voljo

posameznika, med katere sodi tudi želja, postati darovalec organov in tkiv po smrti.

Pri ICOD programu gre za nadaljevanje ali šele uvedbo intenzivnih ukrepov (sprejem v EIT, respiratorna in hemodinamska podpora) pri pacientih z infaustno prizadetostjo možganov (poškodba, krvavitev, ishemična okvara, tumor), pri katerih je bilo intenzivno zdravljenje v terapevtske namene izčrpano. Gre za paciente, pri katerih predvidevamo razvoj klinične slike možganske smrti v naslednjih 48 urah, s tem programom pa želimo vključiti možnost darovanja po možganski smrti v sklop odločitev o zdravljenu ob koncu življenja.



O ICOD lahko razmišljamo šele po tem, ko konzilij specialistov različnih strok, ki so odgovorni za zdravljenje pacienta z dokončno okvaro možganov, sklene, da ne bodo začeli ali stopnjevali zdravljenja, pač pa bodo prenehali z intenzivnim zdravljenjem in prešli na paliativno terapijo in postopke zdravljenja ob koncu življenja. Koordinator za transplantacije ni vključen v konzilij. Prav tako konzilij specialistov različnih strok pomisli na razvoj klinične slike možganske smrti in prisotnost/odsotnost kontraindikacij za darovanje pri takem pacientu. Šele v naslednjem koraku se kontaktira koordinator za transplantacije, kar pa že pomeni integracijo darovanja po smrti v postopke zdravljenja ob koncu življenja. Koordinator za transplantacije dokončno oceni primernost takega pacienta za kasnejše darovanje.

V ICOD program lahko vključimo tako paciente, ki so že v EIT in pri katerih je nadaljnje zdravljenje izčrpano, kot paciente z dokončno okvaro možganov na oddelkih (ki so že ali še niso intubirani). V zadnjih dveh primerih po oceni konzilija in obveščanju koordinatorja sledi pogovor s svojci še pred smrtjo pacienta, in če se odločijo za darovaje (ali pa je bila že za časa življenja jasno izražena želja pacienta, da želi po smrti postati darovalec organov in tkiv), se takega pacienta sprejme v EIT in vključi v ICOD program. V primeru, da nastopi v naslednjih 48 urah možganska smrt, se po kliničnih testih in inštrumentalni potrditvi smrti opravi drugi pogovor s svojci, v katerem se razloži možgansko smrt in še enkrat išče privolitev svojcev za odvzem organov in tkiv. Če pri prvem pogovoru privolitve za vključitev v ICOD program ne dobimo, se nadaljuje z ukrepi ob koncu življenja, kar konkretno pomeni zmanjševanje intenzivnosti zdravljenja in prehod na paliativne ukrepe pred smrtjo (LLST – limitation of life sustaining therapy).

Če znotraj EIT po 48 urah ne nastopi možganska smrti, svojci pa se kljub temu strinjajo z darovanjem, nadaljujemo z odtegnitvijo intenzivnega zdravljenja in v tem primeru lahko tak pacient vstopi v drug program – program darovanja po nadzorovani zaustavitvi srca (cDCD program – controlled DCD).

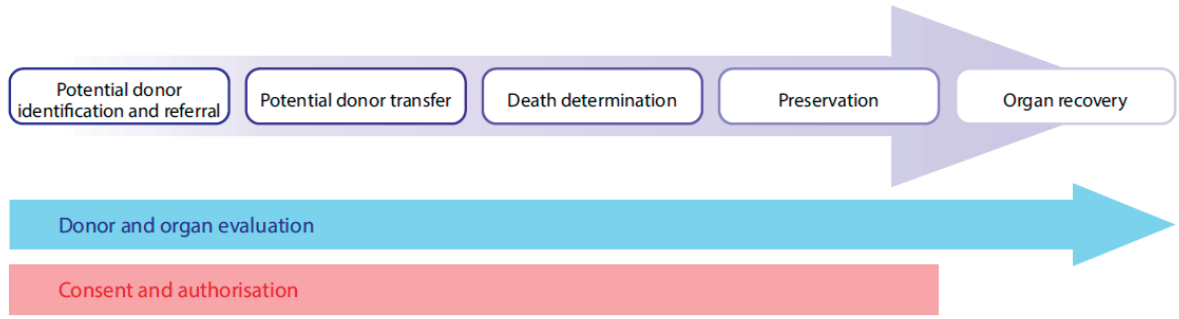
DCD program – gre za program darovanja organov in tkiv po nadzorovani ali nenadzorovani zaustavitvi srca. Glede na Maastrichtsko klasifikacijo poznamo 4 različne kategorije darovalcev po dokazani srčni smrti.

Table 12.1. **Maastricht classification for DCD donors, as modified in Paris (February 2013)**

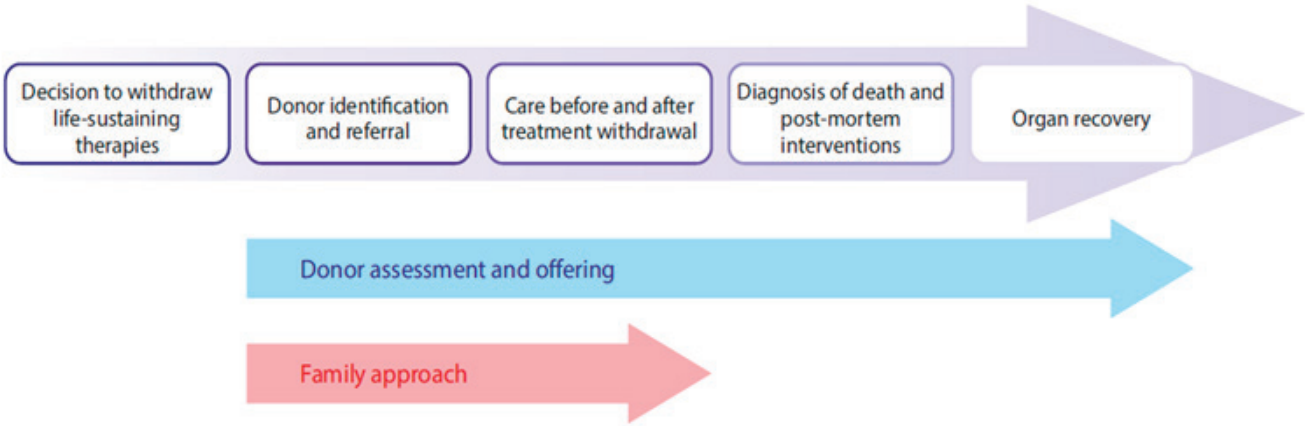
Maastricht Category and type of DCD	Observations
I: Found dead (uncontrolled) I a out of hospital I b in hospital	Sudden unexpected cardiac arrest, with no attempt at resuscitation by a medical team.
II: Witnessed cardiac arrest (uncontrolled) II a out of hospital II b in hospital	Sudden unexpected irreversible cardiac arrest, with unsuccessful attempt at resuscitation by a medical team.
III: Withdrawal of life-sustaining therapy* (controlled DCD)	Planned, expected cardiac arrest, following the withdrawal of life-sustaining therapy.
IV: Cardiac arrest while brain dead (uncontrolled or controlled)	Sudden or planned cardiac arrest after brain death diagnosis process, but before organ recovery.

* This category mainly refers to the decision to withdraw life-sustaining therapies. Legislation in some countries allows euthanasia (medically-assisted cardiac arrest), and subsequent organ donation is then described as an additional category.

Darovanje po nenadzorovani zaustavitvi srca (u-DCD): največkrat smrt nastopi zunaj bolnišnice, prisotne so priče, ki pokličejo reševalno ekipo. Z reanimacijo je potrebno pričeti po največ 15 minutah, če želimo od takega darovalca pridobiti jetra, oziroma maksimalno 30 minutah, da lahko še varno odvzamemo obe ledvici. Reanimacija mora trajati najmanj 30 minut, potem pa že sama poučena in ustrezno izobražena reševalna ekipa pomisli na možnost darovanja po srčni smrti in takega pacienta napove ekipi urgentnih zdravnikov pred prihodom v bolnišnico. Z reanimacijskimi ukrepi nadaljujemo do prihoda v bolnišnico, kjer se določi ura smrti. Pred proglasitvijo ireverzibilne zaustavitve srca s strani neodvisne ekipe strokovnjakov (ki ne sodelujejo v donorskem ali transplantacijskem programu), se preneha z vsemi reanimacijskimi ukrepi in počaka 5 minut (ang. *»no touch period«*). Da zmanjšamo uničevalni učinek tople ishemije na organe, ki bi bili primerni za presaditev, po prihodu v bolnišnico posebna kirurška ekipa po potrditvi smrti nastavi kanile na femoralne žile za vzpostavitev normotermne regionalne perfuzijie (NRP) skozi organe. Vsi zgoraj našteti koraki ne smejo preseči skupnega časa 150 minut (od zaustavitve srca na terenu, do začetka NRP). V tem času se že kontaktira svojce in transplantacijskega koordinatorja, ki oceni primernost pokojnika in organov za darovanje, ter opravi zelo zahteven pogovor s svojci (ker je smrt nastopila nenadoma, pogosto pri predhodno povsem zdravi osebi). NRP lahko traja 4 ure, »in situ« perfuzija s hladnimi tekočinami pa največ 3 ure. Če v tem času dobimo privolitev svojcev za darovanje, oziroma najdemo pozitivno opredelitev pokojnega za darovanje v nacionalnem registru, sledi hladna perfuzija s posebnimi tekočinama za shranjevanje in transport organov do končnega prejemnika, ter postopna eksplantacija organov v operacijski dvorani (kot pri darovanju po možganski smrti). Po odstranitvi iz telesa lahko take organe priključimo na posebne mašine z normotermno perfuzijo, s katerimi njihovo funkcijo precej izboljšamo, tako da so rezultati presaditve takih organov primerljivi s tistimi od možgansko mrtvih darovalcev. V nasprotnem primeru pa vse nadaljnje postopke ustavimo in do odvzema organov ne pride.



Darovanje po nadzorovani zaustavitvi srca (c-DCD) se odvija v EIT, kjer se konzilij zdravnikov, podobno kot v ICOD programu, odloči za odtegnitev intenzivnega zdravljenja (ang. withdrawing life support treatment, WLST) pri kritično bolnih pacientih (poleg pacientov z infaustno prognozo okvare možganov sem sodijo še pacienti z napredovalimi neuromuskularnimi boleznimi in napredovalimi respiratornimi okvarami, kjer ni možnosti ozdravitve). Pred tem se pomisli na možnost darovanja in o takem pacientu obvesti koordinatorja za transplantacije. Po jasnem načrtu sledi pogovor s svojci, ki ga najprej opravijo lečeči zdravniki in ki svojcem razložijo stanje pacienta ter sklep konzilija o nesmiselnosti nadaljnjega zdravljenja. Nato sledi pogovor s koordinatorjem, ki svojcem predstavi možnost darovanja organov po kontrolirani zaustavitvi srca. Pogovor s svojci se pogosto odvija po tem, ko se je pacientu nastavilo kanile za vzpostavitev NRP, če to omogoča ustrezno pripravljena zakonodaja. Ker so tudi organi takega darovalca dodatno ogroženi zaradi tople ishemije, se pogovor s svojci odvija blizu operacijske dvorane, kamor se umrlega pripelje takoj po privolitvi in prične z NRP. Svojci so pogosto prisotni pri odklopu od aparatur in ob pacientu med agonalno fazo do asistolije. Nato sledi 5 minutno »no touch« obdobje, po katerem je srčna smrt dokončno potrjena. Tudi v tem programu srčno smrt potrdi skupina zdravnikov specialistov, ki niso vključeni v donorski ali transplantacijski program. NRP tudi pri c-DCD programu lahko traja 4 ure, v tem času pa nadaljujemo z oceno primernosti posameznih organov za darovanje in alokacijo (dodelitvijo organov do končnih prejemnikov), kar se nadaljuje med hladno perfuzijo, odvzemom organov in priključitvijo organov na mašine z normotermno perfuzijo (kot pri u-DCD programu).



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4. Uncontrolled donation after circulatory death: comparison of two kidney preservation protocols on graft outcomes; Claire Delcus et al; BMC Nephrology (2018) 19:3

NEW TRENDS IN TRANSPLANTATION MEDICINE – DONATION AFTER HEART FAILURE AND ADMISSION TO THE INTENSIVE CARE UNIT WITH THE INTENTION OF SUBSEQUENT ORGAN AND TISSUE DONATION

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Summary

Precise protocols are needed to ensure the proper implementation of the u-DCD and c-DCD programs, supported by clear guidelines in accordance with the adopted legislation and the coordinated operation of all participating teams in order to minimize the warm ischaemia time, thus enabling better and longer survival of the transplanted organs and recipients. With the help of these programs, the number of donors increased by 25% (Spain) to 50% (Netherlands) in the countries that use these programs on daily basis. The best results were achieved in the field of transplantation of both kidneys and lungs obtained. Several more complications are involved in the transplantation of the liver thus acquired, but the state of surviving grafts is comparable with those obtained from brain dead donors after 10 years.

Methodology

In donor and transplantation activities, as elsewhere in the world, we are also faced with a greater number of recipients on the waiting list compared with the number of available organs for transplantation. We are far from self-sufficiency, which, according to the current calculations, would mean that 0.5 per cent of all deaths should become donors of organs and tissues after death every year. In 2017 we achieved the calculated self-sufficiency index of 0.187 and still, like other Eurotransplant countries, we are faced with a harsh reality - dying of recipients on the waiting list (approximately 10 each year).

In order to make the self-sufficiency as close as possible, we must take advantage of all the available sources of donors of organs and tissues after death.

In recent years, we have already learned how to handle extended criteria donors, and a lot of contraindications are no longer absolute for us. In addition, significant reserves in unused potential are present due to a high level of family rejection in the past year and problems with timely referral of potential donors to transplant coordinators.

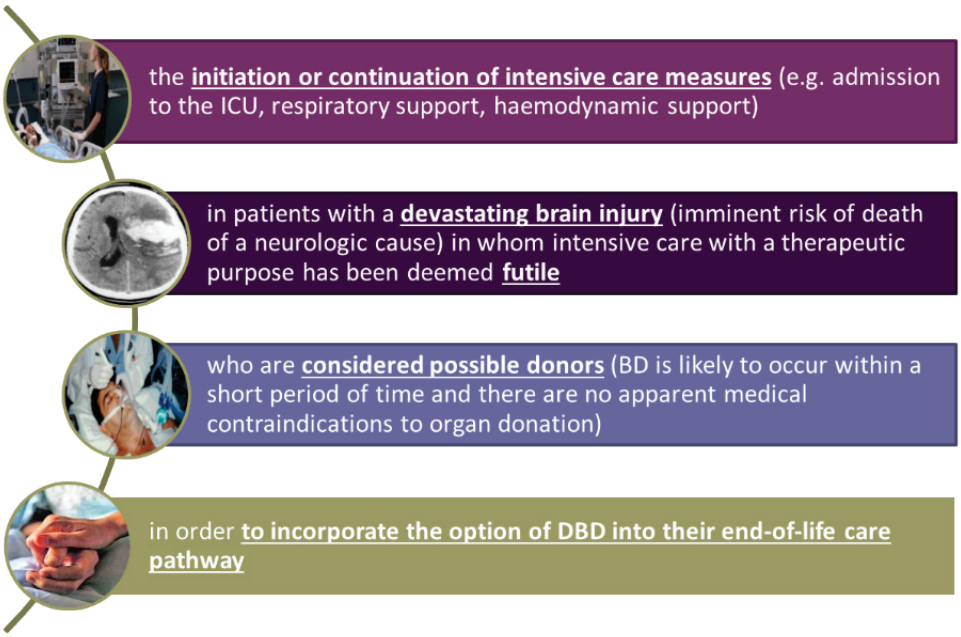
As a new trend, in some Eurotransplant countries they have already implemented two new programs, namely the acceptance of critically ill patients into an intensive care unit with a possibility to the subsequent donation of organs and tissues (ICOD program), and the organ and tissue donation program of deceased donors after a confirmed cardiac death (DCD program - Deceased after Cardiac Death).

Both programs are the part of end-of-life care. For the successful implementation of both programs, it is necessary to prepare clear legislation and guidelines that will lean on the legislation, and it will also be necessary to answer all, for some unconfessed experts, perhaps disputable, ethical issues. In doing so, we rely on the guidelines of the

Council of Europe, which discuss ways of treatment and decisions at the end of the patient's life. In all such cases, the treating physician should take into account the expressed will of the individual, including the desire to become the donor of organs and tissues after death.

The ICOD program involves the continuation or the initiation of intensive care measures (admission to the ICU, respiratory and haemodynamic support) in patients with devastating brain injury (trauma, bleeding, ischemic failure, tumour) in which intensive treatment for therapeutic purposes has been exhausted. These are patients in whom the development of a clinical picture of brain death in the next 48 hours is predicted, and with this program we would like to incorporate the option of donation after brain death (DBD) into their end-of-life care pathway.

Picture 1:



ICOD can only be considered after consultations of multidisciplinary team of experts, who are responsible for the treatment of a patient with an deadly brain prognosis, on decision that they will not start or step up treatment, but they will cease intensive treatment and switch to palliative therapy and treatment procedures at the end of life. The transplant coordinator is not included in the consilium. Similarly, consultations of specialists from different disciplines are concerned with the development of a clinical picture of brain death and the presence / absence of contraindications for donation in such a patient. As a next step that a transplant coordinator is contacted, which already implies the integration of post-mortem donation into end-of-life care protocols. The transplant coordinator completes the assessment of the suitability of such a patient for later donation.

In the ICOD program we can include patients who are already in the ICU and where further treatment is exhausted and patients with devastating brain damage in departments (who are already or not yet intubated). In the last two cases, after evaluating the consilium and informing the coordinator, a conversation with the family is held before the patient's death, and if they decide to donate (or the patient's desire to become a donor of organs and tissues after death has already been clearly expressed during his lifetime) such a patient is admitted to the ICU and included in the ICOD program. If the brain death occurs within the next 48 hours, a second interview with family members is completed after clinical tests and the instrumental confirmation of brain death, in which the brain death is explained and once again we seek for the consent of relatives to remove organs and tissues. If we do not get the first

consent to join the ICOD program, the end-of-life measures continue, which in turn means reducing the intensity of treatment and moving to palliative measures before death (LLST – limitation of life sustaining therapy).

If, within 48 hours, brain death does not occur within the ICU, and the family nevertheless consent to donation, we continue with the withdrawal of intensive treatment, and in this case, such a patient can enter another program - a program of donation after controlled cardiac arrest (cDCD program - controlled DCD) .

Table 1:

Maastricht Category and type of DCD	Observations
I: Found dead (uncontrolled) I a out of hospital I b in hospital	Sudden unexpected cardiac arrest, with no attempt at resuscitation by a medical team.
II: Witnessed cardiac arrest (uncontrolled) II a out of hospital II b in hospital	Sudden unexpected irreversible cardiac arrest, with unsuccessful attempt at resuscitation by a medical team.
III: Withdrawal of life-sustaining therapy* (controlled DCD)	Planned, expected cardiac arrest, following the withdrawal of life-sustaining therapy.
IV: Cardiac arrest while brain dead (uncontrolled or controlled)	Sudden or planned cardiac arrest after brain death diagnosis process, but before organ recovery.

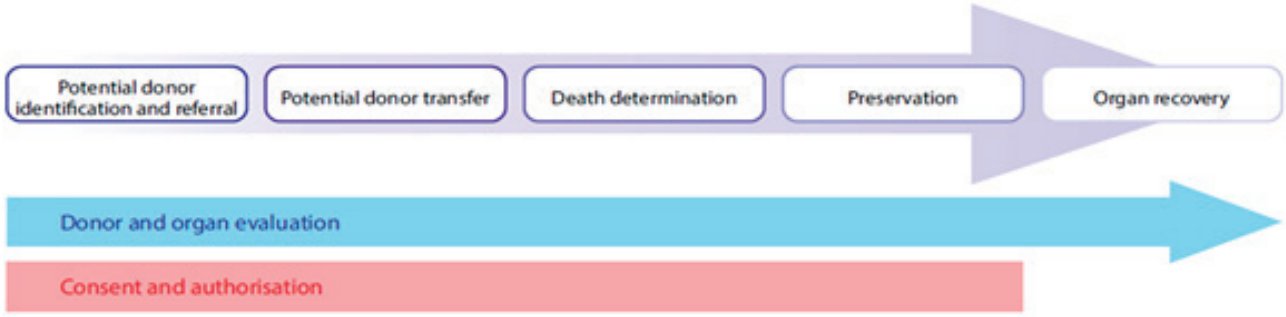
* This category mainly refers to the decision to withdraw life-sustaining therapies. Legislation in some countries allows euthanasia (medically-assisted cardiac arrest), and subsequent organ donation is then described as an additional category.

DCD program - it is a program for donating organs and tissues after a controlled or uncontrolled heart failure. According to the Maastricht classification we know 4 different categories of donors after proven cardiac death.

Donation after uncontrolled cardiac death (u-DCD): Most often death occurs outside the hospital, there are witnesses who call the rescue team. Resuscitation should be started after a maximum of 15 minutes if we want to obtain a liver from such a donor, or a maximum of 30 minutes so that we can safely take both kidneys. Reanimation must last at least 30 minutes, and then a trained and adequately educated rescue team will consider the possibility of donation after cardiac death and reports such a patient to a team of emergency physicians before coming to the hospital. With reanimation measures, we continue to arrive at the hospital where the time of death is determined. Before announcing irreversible heart failure by an independent team of experts (who do not participate in the donor or transplant program), they stop with all the reanimation measures and wait for 5 minutes ("no touch period"). In order to reduce the destructive effect of hot ischemia on organs suitable for transplantation, upon arrival at the hospital, a special surgical team, after confirming death, sets the cannulas on the femoral vessels to establish normothermic regional perfusion (NRP) through the organs. All of the above steps must not exceed the total time of 150 minutes (from cardiac arrest to the beginning of the NRP). At that time, the relatives are informed and the transplant coordinator is contacted, who also assesses the suitability of the deceased and the donor organs, and performs a very demanding conversation with the relatives (because the death occurred suddenly, often with a previously perfectly healthy person). The NRP may take 4 hours, and in situ perfusion with cold liquids for a maximum of 3 hours. If during this time we obtain the consent of the donor's relatives or we find a positive definition of the deceased for the donation in the national register, a cold perfusion with special fluids for the storage and transport of organs to the final recipient has started, as well as the gradual exploration of organs in the operative hall (as for the donation after brain death). After removal from the body, such organs can be connected to special machines with normothermic perfusion, with which their function is greatly improved, so that the results of transplantation of such organs are comparable to those of the brain-dead donors. Otherwise, all subsequent procedures will be stopped and no organs will be recovered.

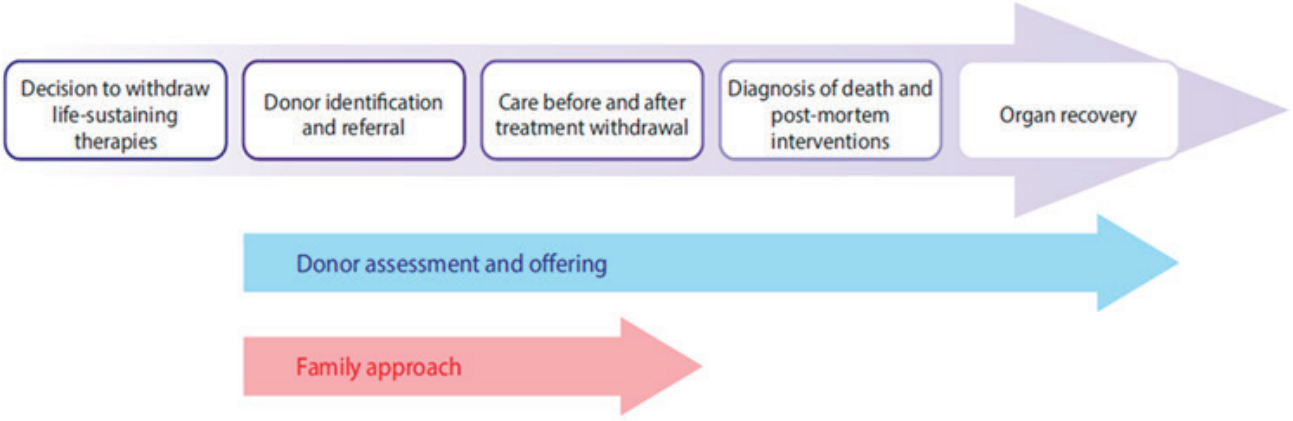
Picture 2:

Picture 2:



Controlled (c-DCD) donation takes place in the ICU, where multidisciplinary team of doctors, similar to the ICOD program, decide to withdraw life sustaining therapy (WLST) in critically ill patients (in addition to patients with prognosis of irreversibly devastating brain injury, with advanced neuromuscular diseases and advanced respiratory failure, where there is no possibility of recovery). Prior to this, think about the possibility of donation and inform the transplant coordinator about such a patient. A clear plan is followed by a family interview, which is first performed by treating physicians explaining the patient's condition and the decision to stop any further treatment. The conversation with the coordinator follows, who presents to patient's relatives the possibility of organ donation after controlled cardiac death. Conversation with relatives often takes place after the patient has been given cannulae to set up the NRP, if this is provided for by properly prepared legislation. Since the organs of such a donor are further compromised by warm ischemia, the family interview often takes place near the operating room, where the deceased is immediately transported upon consent and the NRP begins. The relatives are often present when WLST starts and the patient goes from agonal phase to asystole. Then there is a 5-minute "no touch" period after which cardiac death is finally confirmed. In this program, cardiac death is also confirmed by a group of specialist doctors not included in the donor or transplant program. The NRP can also take 4 hours for the c-DCD program, and at this time we continue with the validity of organs for transplantation and start with the allocation processes (organ allocation to final recipients), which continues also during cold perfusion, organ recovery and ex situ use of normothermic or hypothermic machine perfusions (as in the u-DCD program).

Picture 3:



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4. Uncontrolled donation after circulatory death: comparison of two kidney preservation protocols on graft outcomes; Claire Delcus et al; BMC Nephrology (2018) 19:3

PRESADITEV LEDVIC V SLOVENIJI: MODEL ZA ZGLED?

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Uvod

Transplantacija organov, celic in tkiv je mlada veja medicine. Ključni napredki v transplantacijski medicini so se zgodili v zadnjih 60. letih. Zgodba o presajanju organov je predvsem zgodba o ovirah in o tem, kako je moderna eksperimentalna in klinična medicina uspešno premagala te ovire. Ključni napredki, ki so omogočili preživetje presajenih organov in bolnikov ter zagotovili dologoročni uspeh po presaditvi ledvice so odkritje humanih levkocitnih antigenov (HLA) in usklajevanje v HLA med darovalci in prejemniki, izboljšave dializnih in kirurških tehnik, ohranitvenih raztopin in postopkov za shranjanje organov zunaj telesa ter odkritje učinkovitih in varnih imunosupresivnih zdravil. V prispevku je prikazana uspešna zgodba presaditve ledvic v Sloveniji. Predstavljeni so glavni vzroki za izgubo presajene ledvice in naš model za izboljšanje dolgoročnih rezultatov po presaditvi ledvice.

Zgodovinski pregled presaditve ledvic v Sloveniji

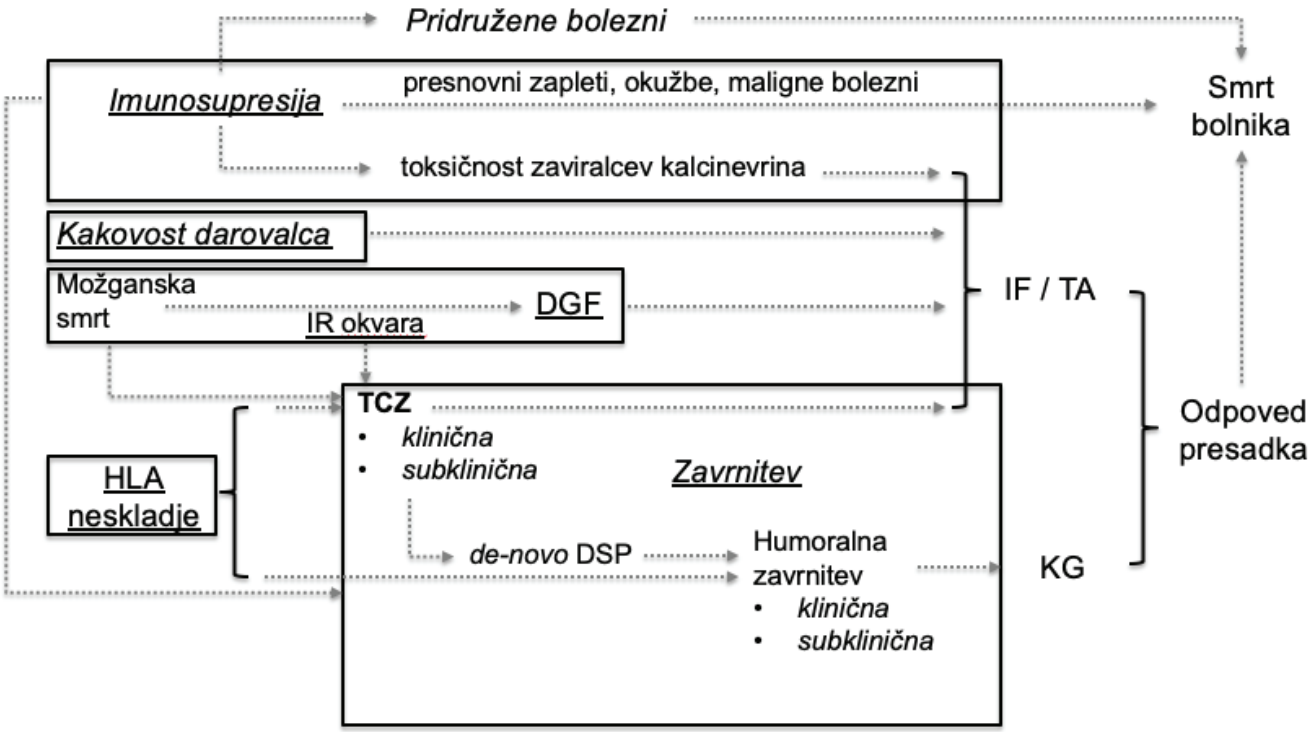
Pomemben zgodovinski dosežek je bila uvedba hemodializnega zdravljenja v Univerzitetnem kliničnem centru (UKC) Ljubljana. Že pred šestdesetimi leti, leta 1959, so urologi na Klinčnem oddelku za urologijo začeli zdraviti bolnike z akutno ledvično okvaro. Njihovo pionirsko delo je leta 1970 omogočilo odprtje prvega centra za kronično hemodializo, ki je bil sestavni Klinčnega oddelka za nefrologijo (1). Odprtje oddelka za kronično hemodializo je bilo ključno za ustanovitev programa presaditve ledvic. Tako je bila že istega leta, aprila 1970, v Univerzitetnem kliničnem centru Ljubljana napravljena prva presaditev ledvice živega darovalca (2). Dejavnost presaditve ledvic živih darovalcev se je uspešno nadaljevala, v obdobju med 1970 in 2018 je bilo opravljenih 132 tovrstnih presaditev (3). Ker so se presaditve ledvic živih darovalcev najpogosteje izvajale pri bolnikih iz drugih republik nekdanje Jugoslavije, se je število teh presaditev izrazito zmanjšalo po osamosvojitvi Slovenije. Po letu 2000, ko se je Slovenija pridružila Eurotransplantu, se je število presaditev ledvic živih darovalcev še dodatno zmanjšalo, predvsem zaradi povečanja števila presaditev ledvic umrlih darovalcev (4).

Program presaditve ledvic umrlih darovalcev se redno izvaja od leta 1986. Leta 1998 je v Sloveniji prišlo do pomembnih organizacijskih sprememb pri darovanju in transplantaciji organov, ustanovljena je bila Nacionalna transplantacijska mreža (5). Poleg UKC Ljubljana je bilo v nacionalni program za presaditev organov umrlih darovalcev vključenih še deset donorskih bolnišnic. Z ustanovitvijo Nacionalne transplantacijske mreže, ki jo sestavljajo Center za transplantacijo ledvic, donorske bolnišnice, Center za tipizacijo tkiv, nacionalni čakalni seznam za presaditve in osrednja koordinacijska institucija, Slovenija-transplant, se je izrazito povečalo število presaditev organov umrlih darovalcev (4,5). Po tej uspešni organizacijski spremembi je bila Slovenija leta 2000 sprejeta v organizacijo Eurotransplant. Vstop Slovenije v Eurotransplant predstavlja zgodbo o uspehu, saj je prinesel številne pozitivne spremembe v organizaciji transplantacijske dejavnosti, ki so vodile v nadaljnje povečanje števila darovalcev in presaditev organov našim bolnikom (6).

Danes je v Sloveniji, ki ima površino 20.000 km^2 in približno 2 milijona prebivalcev, en nacionalni Center za transplantacijo ledvic, ki deluje v okviru Kliničnega oddelka za nefrologijo UKC Ljubljana. Od prve uspešne presaditve ledvice leta 1970 so naši urologi opravili že 1308 presaditev ledvic. V obdobju med 1970 in 2018 je 132 bolnikov prejelo ledvico živega darovalca, 1176 bolnikov pa ledvico umrlega darovalca. Velika večina živih transplantacij ledvic (124) je bila izvedena pred vstopom Slovenije v Eurotransplant. Po drugi strani je do konca decembra 1999 le 239 bolnikov prejelo ledvico umrlega darovalca. Od leta 2000, ko se je Slovenija pridružila Eurotransplantu, je 937 bolnikov prejelo ledvico umrlega darovalca. Skupno število presaditev ledvic je bilo v zadnjih 18 letih kar 2-krat večje od števila presaditev ledvic v 30-letnem obdobju pred letom 2000. To pomeni, da smo po pridružitvi Eurotransplantu na letni ravni opravili 2,8-krat večje število presaditev. Poleg tega je članstvo v uspešni organizaciji tudi trajna spodbuda za sledenje drugim uspešnim članicam organizacije. S približno 60 transplantacijami ledvic, ki so bile opravljene na letni ravni v zadnjih letih, smo dosegli in tudi presegli povprečno število presaditev ledvic na milijon prebivalcev Eurotransplanta. Zaradi dobrega nacionalega donorskega programa je mediani čas od uvrstitve na čakalni seznam do presaditve krajši od enega leta. Do 31. decembra 2018 je bilo 1-letno in 5-letno preživetje bolnikov 98 % oziroma 94 %. Sočasno preživetje presadka je bilo 94 % oziroma 87 %. Ti rezultati so odlični, boljši kot je povprečje vseh članic Eurotransplanta in popolnoma primerljivi z najuspešnejšnejšimi državami v razvitem svetu.

Model za izboljšanje rezultatov po presaditvi ledvice

Najpomembnejši izzivi sodobne transplantacije ledvic so pomanjkanje kakovostnih darovalcev organov, jemanje imunosupresivnih zdravil in njihovi neželeni učinki ter neučinkovito zdravljenje kronične zavrnitve. Kljub boljšim rezultatom se je v zadnjih desetletjih izboljšalo predvsem kratkoročno (1- in 3-letno) preživetje, v bistveno manjši meri pa se je izboljšalo dolgoročno (5- in več-letno) preživetje (7). Izboljšanje kratkoročnega preživetja je povezano z odkritjem novih imunosupressivnih zdravil, predvsem ciklosporina, takrolimusa in mikofenolat mofetila, ki učinkovito preprečujejo akutno zavrnitev presajene ledvice (8). Medtem ko akutna zavrnitev predstavlja glavno oviro za kratkoročni uspeh presaditve, je slabše dolgoročno preživetje po presaditvi ledvice posledica številnih imunoloških in neimunoloških dejavnikov (9). Glavne vzroke za odpoved presajene ledvice, na katerih temelji naš model za izboljšanje preživetja po presaditvi, prikazuje Slika.



Slika. Vzroki za odpoved presajene ledvice in smrti bolnika po presaditvi. V okvirih so prikazane glavne možnosti našega delovanja za izbojšanje rezultatov po presaditvi.

Okrajšave: HLA, humani levkocitni antigeni; IR okvara, ishemično-reperfuzijska okvara; DGF (angl. delayed graft function), odloženo delovanje presadka; TCZ, T-celična zavrnitev; DSP (donor-specifična protitelesa), protitelesa proti HLA darovalca; IF / TA, intersticijska fibroza / tubulna atrofija; KG, kronična glomerulopatija.

Presaditve ledvic živih darovalcev

Povprečna starost umrlih darovalcev organov v Eurotransplantu je vedno višja, najstarejši so prav umrli darovalci ledvic in so bili leta 2017 v povprečju stari 54 let (10). Danes presajamo tudi ledvice darovalcev, ki so starejši od 70 let. Starejši darovalci imajo pogosto pridružene bolezni (npr. arterijsko hipertenzijo, sladkorno bolezen), ki zmanjšujejo kakovost organov in skrajšujejo preživetje presajene ledvice.

Zaradi večanja starosti in manjše kakovosti odvzetih ledvic umrlih darovalcev se v večini držav članic Eurotransplanta povečuje število presaditev ledvic živih darovalcev (10). Glavna prednost presaditve ledvic živih darovalcev je daljše dologoročno preživetje presadka. Tako pet let po presaditvi deluje približno desetina presajenih ledvic živih darovalcev več, kot deluje presajenih ledvic umrlih darovalcev (11). Poleg boljše kakovosti ledvice in krajšega časa hladne ishemije je pomembna prednost presaditve ledvice živega darovalca možnost načrtovane presaditve še pred pričetkom nadomestnega zdravljenja z dializo. V Centru za transplantacijo ledvic UKC Ljubljana smo ledvice živih darovalcev presajali predvsem v obdobju pred vključitvijo v Eurotransplant leta 2000. Po tem obdobju je program presajanja ledvic živih darovalcev skoraj v celoti zastal. Leta 2016 smo ga znova oživili in v zadnjih dveh letih izvedli 6 tovrstnih presaditev.

V Sloveniji je živi darovalec ledvice lahko z bolnikom sorodstveno ali čustveno povezan. Presaditev ledvice živega darovalca spodbujamo pri mlajših bolnikih, saj bodo s presajeno ledvico morali živeti daljše obdobje, zato je pomembno, da dobijo čim bolj kakovostno ledvico. Ne spodbujamo darovanja ledvic otrok ali mladih odraslih staršem

ali starim staršem ali darovanja ledvic darovalcev s pridruženimi boleznimi, ki dolgoročno lahko okvarijo preostalo ledvico (npr. zvišan krvni tlak ali sladkorna bolezen).

Zmanjšanje okvare presajene ledvice zaradi ishemične-reperfuzijske okvare

Daljši je čas hladne ishemije, torej dlje časa ko je ledvica zunaj telesa neprekrvljena, krajše je preživetje presadka in bolnika (12). Hladna ishemija povzroči ishemično-reperfuzijsko okvaro, ki je glavni dejavnik tveganja za razvoj odloženega delovanja presajene ledvice (DGF, *angl.* delayed graft function). Ker ledvica neposredno po presaditvi ne prične delovati, bolniki potrebujejo eno ali več dializ. Dolgoročno je DGF povezana s slabšim delovanjem in krajšim preživetjem presadka. Pri nekaterih ranljivih skupinah bolnikov (predvsem starejših in tistih s povečanim srčno-žilnim tveganjem) je DGF lahko vzrok zgodnje umrljivosti po presaditvi. Nenazadnje DGF povečuje stroške zdravljenja zaradi potrebe po dializi, dodatnih preiskavah, biopsiji presadka, zdravljenju zavrnitve in posledično daljšega bolnišničnega zdravljenja po presaditvi. Ledvico je zato potrebno presaditi čim preje po odvzemu darovalcu, najkasnje pa v 36 urah. Pri naših prejemnikih je bil po pridružitvi Eurotransplantu čas hladne ishemije pri 90 % presaditev daljši od 12 ur, pri 20 % presaditev pa daljši od 24 ur.

Za zmanjšanje neugodnega vpliva hladne ishemije in tveganja za razvoj DGF številni razviti centri v svetu danes namesto hipotermičnega statičnega shranjevanja odvzetih ledvic uporabljajo strojno perfuzijo. Med strojno perfuzijo je ledvica nameščena v posebni posodi, kjer je s pomočjo perfuzijske črpalke kontinuirano perfundirana s posebno ohranitveno raztopino na stalni temperaturi (2-5°C) in pri določenem perfuzijskem tlaku. Strojna perfuzija dokazano zmanjšuje pogostnost DGF. Že leta 2009 so v randomizirani raziskavi primerjali hipotermično strojno perfuzijo in statično shranjevanje ledvic. Rezultati so pokazali, da ohranjanje odvzetih ledvic zunaj telesa s pomočjo strojne perfuzije zmanjšuje pogostnost in trajanje DGF ter izboljša preživetje presajenih ledvic (13).

V Centru za transplantacijo ledvic smo leta 2018 kupili dva aparata LifePort® za strojno perfuzijo ledvic umrlih darovalcev. Prvo strojno perfuzijo ledvice umrlega darovalca smo izvedli septembra 2018. Do konca leta 2018 smo strojno perfuzijo uporabili pri 10 presaditvah ledvic. Pri namestitvi ledvic v transportni sistem ni bilo zapletov, zaradi katerih bi strojno perfuzijo morali prekiniti. Le pri eni presaditvi (10 %) je prišlo do razvoja DGF.

Skladnost v HLA

Zaradi pomanjkanja organov se zmanjšuje tkivna skladnost, ki pogosto vodi v razvoj protiteles proti neskladnim HLA darovalca (14). Novo-nastala protitelesa proti neskladnim HLA darovalca so glavni dejavnik tveganja za razvoj kronične humoralne (s protitelesi posredovane) zavrnitve, ki je najpogostejši vzrok odpovedi delovanja presajene ledvice (15).

V Sloveniji zaradi dobrega donorskega programa ne presajamo ledvic HLA popolnoma neskladnih darovalcev in prejemnikov. Minimalno skladnost v lokusu HLA-DR zahtevamo tudi pri presaditvah ledvic starejšim prejemnikom v okviru seniorskega programa Eurotransplanta. Eurotransplant v okviru programa sprejemljive tkivne skladnosti (AM, *angl.* acceptable mismatch) omogoča tudi presaditve ledvic visoko senzibilziranih prejemnikov s številnimi protitelesi proti HLA. Z izogibanjem nesprejemljvim HLA darovalca preprečujemo zgodnjo humoralno zavrnitev in s tem zgodnjo odpoved presajene ledvice.

Ukinjanje, zmanjšanje in optimizacija imunosupresije

Optimizacija imunosupresijskega zdravljenja je eden največjih izzivov moderne transplantacijske medicine. Poleg okvare presajenega organa, dolgotrajno imunosupresijsko zdravljenje povzroča druge zaplete, saj bolniki bolj nagibajo k okužbam, razvoju malignih bolezni ter srčno-žilnim zapletom. Imunosupresija je najmočnejša v zgodnjem obdobju, predvsem prve 3 mesece po presaditvi. V kasnejšem obdobju imunosupresijskega zdravljenja odmerke imunosupresijskih zdravil pogosto znižujemo, posamezna zdravila tudi ukinemo. S tem zmanjšamo toksičnost zdravljenja, kar lahko podaljša preživetje bolnika in presadka. Po drugi strani pa zmanjšanje imunosupresije lahko vodi v nastanek protiteles proti neskladnim HLA darovalca, ki povečajo tveganje za razvoj kronične zavrnitve presadka (15).

V Centru za transplantacijo ledvic v zadnjih letih bolnikom z ugodnim pooperativnim potekom in dobrim delovanjem presajene ledvice v prvem tednu po presaditvi ukinemo glukokortikoid. Naši rezultati kažejo, da zgodnja ukinitev glukokortikoida v prvem tednu po presaditvi ne poslabša delovanja presajene ledvice in ne poveča tveganja za razvoj zgodnje zavrnitve ali nastanka novih protiteles proti neskladnim HLA darovalca v prvem letu po presaditvi. Poleg tega imajo bolniki po zgodnji ukinitvi glukokortikoidov manjšo incidenco novo-nastale sladkorne bolezni, osteoporoze in nekaterih oportunističnih okužb (16).

Težava, s katero se soočajo v vseh transplantacijskih centrih v svetu je, da bolniki nezadostno sodelujejo pri zdravljenju in ne upoštevajo dosledno navodil o jemanju imunosupresijskih zdravil ter odmerke zdravil sami znižajo ali katerega od zdravil celo ukinejo. Neustrezno jemanje imunosupresivnih zdravil je eden glavnih dejavnikov tveganja za nastanek protiteles proti neskadnim HLA darovalca in kronične humoralne zavrnitve (17). Ker imamo v Sloveniji en nacionalni transplantacijski centrer, se lahko s tem problemom spopadamo bolje kot druge države s številnimi transplantacijskimi centri, ki svoje bolnike po določenem času po presaditvi pogosto preusmerijo k nefrologom ali splošnim zdravnikom.

K optimizaciji imunosupresijskega zdravljenja je pripomogla zamenjava imunosupresijskega zdravila ciklosporin za takrolimus, pri katerem nastaja manj protiteles proti neskladnim HLA (18). Slovenskim bolnikom smo takrolimus v standardni imunosupresijski protokol uvedli leta 2013. Takrolimus s podaljšanim sproščanjem dodatno poenostavlja zdravljenje, ker ima podaljšano delovanje in ga bolniki lahko jemljejo samo enkrat dnevno zjutraj. Z manj dnevnimi odmerki je manj možnosti, da bolniki odmerek izpustijo, s doslednejšim jemanjem zdravil pa se poveča sodelovalnost pri zdravljenju, kar zmanjša tveganje za razvoj protiteles proti neskladnim HLA in kronične zavrnitve (19).

Zaviralci mTOR (*angl.* mammalian target of rapamycin) omogočajo varno zmanjšanje odmerka zaviralca kalcinevrina, kar lahko zmanjša neželene učinke imunosupresivnega zdravljenja. Rezultati večcentrične raziskave Transform, v kateri je sodeloval tudi Center za transplantacijo ledvic kažejo, da je učinkovitost zdravljenja z everolimusom in znižanim odmerkom zaviralca kalcinevrina v primerjavi z mikofenolat mofetilom in standardnim odmerkom zaviralca kalcinevrina podobna, vendar povezana z značilno manjšo incidenco oportunističnih okužb z virusom Polioma BK in virusom citomegalije (20).

V uporabo prihaja novo imunosupresijsko zdravilo belatacept s katerim lahko nadomestimo zaviralec kalcinevrina. Belatacept je fuzijska beljakovina, ki selektivno zavira aktivacijo limfocitov T z blokado kostimulacijske signalne poti. Leta 2016 so 7-letni rezultati raziskave BENEFIT pokazali, da je bilo pri bolnikih zdravljenih z belataceptom relativno tveganje za smrt ali odpoved delovanja presadka za 47 % manjše v primerjavi z zdravljenjem s ciklosporinom (21). Pri zdravljenju z belataceptom se je delovanje presajene ledvice v povprečju izboljšalo, pri zdravljenju s ciklosporinom pa poslabšalo. Nenazadnje je bilo zdravljenje z belataceptom povezano z manjšo pogostnostjo razvoja protiteles proti neskladnim HLA darovalca ter manj srčno-žilnimi dogodki. Nekaj slovenskih bolnikov to zdravilo že prejema. Žal je njegovo predpisovanje omejeno, saj je zdravilo drago, povpraševanje po njem pa tako veliko, da proizvajalec ne zmore proizvesti dovolj zdravila.

Zgodnje prepoznavanje okvare presajene ledvice

V Centru za transplantacijo ledvic od leta 2014 poleg kliničnih pokazateljev okvare presadka v prvem letu po presaditvi pri vseh bolnikih ugotavljamo morebiten nastanek protiteles proti neskladnim HLA darovalca in napravimo nadzorno ledvično biopsijo. Z nadzorno biopsijo želimo prepoznati zgodnjo (subklinično) zavrnitveno reakcijo ali druge bolezenske spremembe, ki jih v zgodnjem obdobju po presaditvi lahko uspešno zdravimo. Žal so ponavljajoče biopsije presajene ledvice povezane z zapleti zaradi invazivnosti, težavno organizacijo pri velikem številu bolnikov in visoko ceno.

V svetu številni raziskovalci odkrivajo nove molekularno-genetske biološke označevalce v krvi, urinu in tkivu presajene ledvice, ki razkrijejo zgodnjo okvaro presadka in najverjetnejši vzrok okvare. Poleg tega pokažejo, ali bolnik prejema prenizke ali previsoke odmerke imunosupresijskih zdravil, kar lahko vodi v odpoved delovanja presadka ali pa zbolevnost zaradi neželenih učinkov imunosupresijskega zdravljenja (22). Žal je določanje molekularno-genetskih označevalcev drago in zahteva laboratorijsko opremo, ki v klinični medicini pogosto ni dostopna. Nenazadnje moramo za prepoznavanje okvare presadka z biološkimi označevalci zagotoviti standardiziran odvzem krvi, urina in tkiva ter poskrbeti za ustrezno hranjenje bioloških vzorcev za prihodnost. Ker bomo tovrstno biobanko težko zagotovili sami, smo v letu 2019 vzpostavili sodelovanje z Inštitutom za biokemijo Medicinske fakultete Univerze v Ljubljani s katerim razvijamo standardiziran informacijski sistem za vodenje bioloških vzorcev v biobanki. Vzpostavili smo tudi sodelovanje z Alberta Transplant Applied Genomic Centre (ATAGC) v Kanadi za molekularno analizo biopsijskih vzorcev (MMDx, Molecular Microscope Diagnostic System), ki omogoča preciznejšo diagnozo in prognozo okvare presajene ledvice. Upamo, da bo to v prihodnje omogočilo nova odkritja na področju zgodnjega prepoznavanja okvare presajene ledvice, učinkovitejšega zdravljenja in s tem daljšega dolgoročnega preživetja po presaditvi ledvice.

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KIDNEY TRANSPLANTATION IN SLOVENIA: A MODEL TO FOLLOW?

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Introduction

Transplantation medicine is a recent phenomenon. Many of the big developments in this discipline have taken place within the past 60 years. Much of the story of transplantation is a story of barriers and how modern scientific medicine overcame those barriers. Major developments being perfected that helped keep kidney patients alive and kidney transplantation a story of success are identification and matching in the human leukocyte antigens (HLA) of donors and recipients, the development and refinements of dialysis and surgical techniques, organ preservation solutions, and anti-rejection immunosuppressive drug medications. This overview gives a brief outline of how transplantation progressed in Slovenia and became a story of success. Our model on how to improve kidney transplant outcomes is also presented.

A historic overview of the kidney transplantation in Slovenia

An important historic achievement was the introduction of dialysis treatment at the University Medical Centre (UMC) Ljubljana. Sixty years ago, in 1959, the urologists at the Department of Urology started treating patients with acute kidney injury. Based on their pioneering work, the first chronic hemodialysis unit was opened in 1970. This hemodialysis center was part of the Department of nephrology (1). The existence of the hemodialysis unit was an important prerequisite to start with the regular transplantation program. In April 1970 first living-related kidney transplantation was performed at the UMC Ljubljana (2). Since the first successful case, regular transplant activity from living-related donors continued and 132 transplant procedures from living donors were performed between 1970 and 2018 (3). Because living-related kidney transplants were most commonly performed in the patients from other republics of former Yugoslavia, the number of these procedures decreased after Slovenia declared independency. Living donation dropped further after January 2000 when Slovenia joined Eurotransplant and the number of deceased donor kidney transplants significantly increased (4).

Deceased donor kidney transplants have been regularly performed since 1986. In March 1998 a National Transplant Network was established and there has been a significant organizational change in deceased donation and solid organ transplantation in Slovenia (5). Besides the UMC Ljubljana, ten donor hospitals have been included in the national program for deceased donor organ transplantation. The establishment of a National Transplant Network composed of a centrally located kidney transplant center, donor centers, a tissue-typing center, a national transplant waiting list, and a central coordinating institution, Slovenija-transplant, resulted in a significant increase in the number of deceased-donor organ transplants (4,5). After this successful organizational change Slovenia was accepted into Eurotransplant in January 2000. Joining Eurotransplant meant positive changes and is regarded as a success story. Both donor numbers and transplant possibilities increased and equal chances are assured for our patients on the common Eurotransplant waiting list (6).

Nowadays in Slovenia, which has an area of 20,000 km^2 and a population of 2 million, there is one national Kidney transplant centre located at the Department of Nephrology of the UMC Ljubljana. Since the first successful kidney transplant in 1970, our urologists have performed 1308 kidney transplant procedures. In the period between 1970 and 2018, 132 patients received living donor and 1176 patients received deceased donor kidney transplants. The great majority of living donor kidney transplants (124) were performed before joining Eurotransplant. On the other hand, until the end of December 1999, 239 patients received kidney grafts from deceased donors, while 937 patients were transplanted from deceased donors after January 2000 when Slovenia joined Eurotransplant. The total number of kidney transplants in the last 18 years was 2 times higher than the number of kidney transplants in the 30 years before 2000. This also means a 2.8 times higher number of transplants per year in the last period. Furthermore, membership in a successful organization is a permanent incentive for keeping pace with the other members of such an organization. With approximately 60 deceased donor kidney transplants performed yearly during the last years, we have reached and also exceeded the average number of these transplants per million population of the Eurotransplant. Due to a good national donor program, the median time from ranking on the kidney waiting list to transplant is less than one year. Up to December 31, 2018, the 1-year and 5-year patient survival rates were 98% and 94%, respectively. The concomitant graft survival rates were 94% and 87%, respectively. These results have been excellent, better than average survival rates in the Eurotransplant member states and entirely comparable to those presented by the most successful countries worldwide.

A model to improve kidney transplant outcomes

The most important challenges for modern kidney transplant medicine are the lack of quality organ donors, the use of immunosuppressive drugs and their adverse effects, and the ineffective treatment of chronic rejection. Although short-term (1- and 3-year) graft survival improved over the last decades, long-term (5- and more-year-long) survival improved to a substantially lesser extent (7). Better short-term survival is associated with the discovery of new immunosuppressive drug medications, especially cyclosporine, tacrolimus and mycophenolate mofetil, which effectively prevent acute rejection (8). While acute rejection is the main obstacle to the short-term success of transplantation, suboptimal long-term survival after kidney transplantation is due to numerous immunological and non-immune factors (9). The main causes of kidney graft loss, on which our model to improve post-transplant outcomes is based, is shown in the Figure.

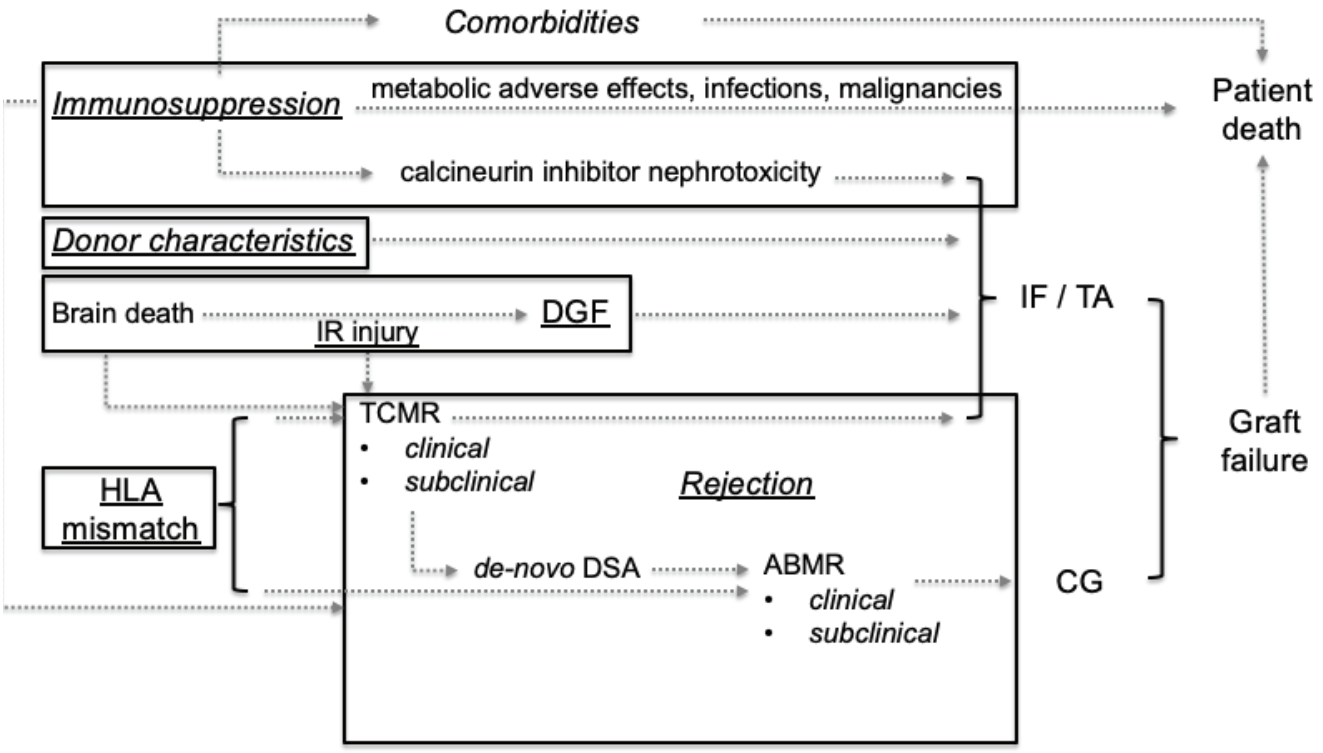

Figure. Causes of kidney graft failure and patient death after transplantation. The frameworks show main strategies where we can improve post-transplant outcomes.

Abbreviations: HLA, human leukocyte antigens; IR injury, ischemia-reperfusion injury; DGF, delayed graft function; TCMR, T cell-mediated rejection; DSA, donor-specific antibodies; ABMR, antibody-mediated rejection; IF / TA, interstitial fibrosis / tubular atrophy; CG, chronic glomerulopathy.

Living donor kidney transplantation

The average age of deceased organ donors in Eurotransplant is steadily growing. Kidney donors are the eldest and their median age was 54 years in 2017 (10). Today we are frequently transplanting kidneys from the donors older than 70 years. Elderly donors often have associated comorbidities (e.g., arterial hypertension, diabetes) that reduce the survival of transplanted kidneys.

Due to the increase in age and the lower quality of deceased donors, the number of kidney transplants from living donors is increasing in most of the member states of Eurotransplant (10). The main advantage of living donor kidney transplantation is superior long-term graft and patient survival. Thus, five years after transplantation, about one-tenth of the transplanted kidneys from living donors are still functioning when compared with the kidneys transplanted from deceased donors (11). In addition to a better kidney quality and a shorter cold ischemia time, an important advantage of living donor kidney transplantation is a possibility of planned pre-emptive transplantation just before the start of dialysis treatment. In the Centre for Kidney Transplantation at the UMC Ljubljana, living donor kidney transplantations were mainly performed during the period prior to joining Eurotransplant in 2000. After this period, the program of transplantation from living donors almost stopped completely. In 2016 we have revived it and in the past two years we have performed 6 such transplants.

According to our legislation, we may perform living related or living unrelated kidney transplantations. We mainly encourage living donor kidney transplantations in younger end-stage kidney disease patients, as they will have

to live with a transplanted kidney for a longer period, therefore it is important that they get the highest quality kidney. We do not encourage live kidney donations from children or young adults to their parents or grandparents or donations from donors with associated diseases that may adversely affect the remaining kidney in the long run (e.g., high blood pressure or diabetes).

Ameliorating kidney ischemia reperfusion injury

The longer the cold ischemia time, that is, the longer the kidney is not perfused, the shorter is the survival of the graft and recipient (12). Cold ischemia causes ischemic-reperfusion injury, which is a major risk factor for delayed graft function (DGF). When the new kidney does not start functioning immediately after transplantation, patient needs one or more dialysis. In the long term, DGF is associated with poorer graft function and shorter graft survival. In some vulnerable groups of patients (especially elderly and those with increased cardiovascular risk), DGF may be associated with early graft failure and mortality. Lastly, DGF increases costs of kidney transplantation due to the need for dialysis, graft biopsy, increased risk of rejection, and consequently longer hospital treatment. It is therefore necessary to transplant the kidney as soon as possible after retrieval form the donor, and at the latest within 36 hours. After Slovenia joined Eurotransplant, in 90% of transplantations the cold ischemia time was longer than 12 hours and in 20% of transplantations longer than 24 hours.

In order to reduce the adverse effects of cold ischemia and the risk of developing DGF, many developed transplant centers in the world use machine perfusion instead of hypothermic static cold storage of kidneys. During machine perfusion, the kidney is placed in a special transporter, where it is continuously perfused with a perfusion pump and a special preservative solution at a constant temperature (2-5 °C) and at a certain perfusion pressure. Machine perfusion has been shown to reduce the frequency and the detrimental effects of DGF. Already in 2009, a prospective randomized trial compared hypothermic machine perfusion and static cold storage. The results showed that machine perfusion reduces the frequency and duration of DGF and improves the survival of transplanted kidneys (13).

In 2018, our kidney transplant center purchased two LifePort kidney transporters for the perfusion of kidneys retrieved from deceased donors. The first machine perfusion was performed in September 2018. By the end of 2018, machine perfusion was used in 10 deceased donor kidney transplantations. There were no complications associated with the installation of the kidneys in the transporting system. Only one kidney transplant (10%) developed DGF.

HLA matching

Due to the lack of organs, the degree of HLA matching between the donor and the recipient decreased over the years, which often leads to the development of donor-specific anti-HLA antibodies (14). *De-novo* DSA are the major risk factor for the development of chronic antibody-mediated rejection, which is the most common cause of long-term kidney graft failure (15).

In Slovenia, due to a good donor program, we do not transplant kidneys to recipients that are completely mismatched in the HLA with their potential donor. At least one matching in the HLA-DR is also required in kidney transplants for older recipients within the Eurotransplant Senior Program. Eurotransplant acceptable mismatch (AM) program also allows for the transplantation of highly sensitized recipients with numerous anti-HLA antibodies. By avoiding unacceptable HLA, we prevent early antibody-mediated rejection and thus an early failure of the transplanted kidney.

Avoiding, minimization and optimization of immunosuppression

Optimization of immunosuppressive therapy is one of the biggest challenges in modern transplant medicine. In addition to nephrotoxicity, long-term immunosuppressive treatment also causes other adverse effects, as patients tend to be more prone to infections, the development of malignant diseases and cardiovascular complications. Immunosuppression is the most powerful in the early period, especially during the first 3 months after transplantation. In a later period, doses of immunosuppressive drugs are often reduced, and individual medications are also discontinued. This reduces the toxicity of treatment, which may prolong the survival of the patient and the graft. On the other hand, a reduction in immunosuppression can lead to the formation of *de-novo* DSA, which increases the risk of chronic rejection (15).

In the Centre for Kidney Transplantation in recent years patients with favorable early postoperative course and good functioning of the transplanted kidney have undergone rapid steroid withdrawal. Our results show that rapid steroid withdrawal in the first week after transplant does not impair kidney graft function and does not increase the risk of early rejection or the formation of *de-novo* DSA in the first year following transplantation. In addition, after rapid steroid withdrawal, patients had a lower incidence of new-onset diabetes after transplantation, osteoporosis and some opportunistic infections (16).

The problem faced by all transplant centers around the world is that patients are insufficiently involved in the treatment and do not take into account consistent instructions on the administration of immunosuppressive drug medications and their doses are frequently reduced or sometimes even discontinued. Patient nonadherence has recently been recognized as one of the main risk factors for the emergence of *de-novo* DSA and chronic antibody-mediated rejection (17). In Slovenia, with only one national transplant center we may cope with this problem better than other countries with numerous transplant centers who may also refer their patients to nephrologists or general practitioners.

During the last decade cyclosporine was replaced for tacrolimus in the majority of transplant centers as tacrolimus-based immunosuppression has been associated with less acute rejections, better graft function, and also reduced *de-novo* DSA formation (18). Our center switched from cyclosporine to tacrolimus-based immunosuppression in 2013. Nowadays we mainly use tacrolimus-prolonged release, which additionally simplifies treatment because it has prolonged action and can be administered only once daily in the morning. With less daily doses there is less chance for patients to miss the dose, and more consistent use of medication increases treatment adherence, which reduces the risk of *de-novo* DSA formation and chronic rejection (19).

Using mammalian target of rapamycin (mTOR) inhibitors we can safely reduce the dose of calcineurin inhibitor, which may reduce the adverse effects of immunosuppressive treatment. The results of a recent multicenter Transform study in which our transplant center also participated demonstrated that the efficacy of everolimus and the decreased dose of calcineurin inhibitor versus mycophenolate mofetil and the standard dose of calcineurin inhibitor is similar but associated with a significantly lower incidence of opportunistic infections with the Polioma BK virus and cytomegalovirus (20).

A new immunosuppressive drug called belatacept was recently introduced, which can substitute the calcineurin inhibitor. Belatacept is a fusion protein that selectively inhibits the activation of T lymphocytes by blocking the costimulatory signaling pathway. In 2016, the 7-year BENEFIT study results showed that a relative risk of death or graft failure was 47% lower in patients treated with belatacept compared with cyclosporine therapy (21). In the belatacept treatment arm, the function of transplanted kidneys has improved over time, while treatment with cyclosporin has been associated with a decrease in graft function. Last but not least, treatment with belatacept was associated with a lower incidence of *de-novo* DSA formation and less cardiovascular events. Some of our transplanted patients already receive this drug. Unfortunately, its prescription is limited, because the drug is expensive and the demand for it is so high that the manufacturer cannot produce enough medication.

Early detection of kidney graft injury

In our transplant center DSA monitoring and surveillance kidney biopsies are regularly performed within the first year after transplant. Surveillance biopsies have been performed as an outpatient procedure since 2014. With a surveillance biopsy, we aim to identify early rejection or other subclinical injury phenotypes that can be successfully treated in the early post-transplant period. Nevertheless, repeated surveillance biopsies pose challenges, including invasiveness, feasibility and cost.

Several investigators have recently attempted to identify molecular biomarkers of immune function in blood, urine, and the graft itself, to distinguish between rejection and other injury phenotypes, as well as to detect these adverse events before they can reduce kidney function. In addition, these biomarkers may identify patients receiving insufficient or excessive immunosuppression, which can lead to adverse events associated with under- or over-immunosuppression leading to transplant failure or patient death (22). Unfortunately, the determination of molecular biomarkers is costly and requires sophisticated laboratory equipment that is often not accessible in routine clinical medicine. Last but not least, we need to ensure standardized collection of blood, urine and tissue to identify injury to the graft using biomarkers, and to ensure proper storage of biological samples for the future. Since we will find it difficult to provide this kind of biobank ourselves, in 2019 we established cooperation with the Institute of Biochemistry at the Medical Faculty of the University of Ljubljana. We will develop a standardized information system for the management of biological samples in biobank. We have also established a cooperation with the Alberta Transplant Applied Genomic Centre (ATAGC) in Canada for molecular analysis of kidney biopsy samples (MMDx, Molecular Microscope Diagnostic System), which enables a more precise diagnosis and prognosis of kidney graft injury phenotype. We hope this will in the future enable new discoveries in the field of early detection of kidney graft injury, more effective treatment, and thus improved long-term transplant outcomes.

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" *Transplantation is based on trust in medicine and doctors. We haven't and will not jeopardize this trust.*

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