

MEDICAL UNIVERSITY OF SOFIA
MEDICAL FACULTY
DEPARTMENT OF INTERNAL DISEASES
Head: prof. Dr. B. Bogov, PhD
1431 Sofia, ul. "St. G. Sofiyski" 1, tel: 9230-227

OPINION

**from prof. Dr. Boris Iliev Bogov, PhD, Head of Internal Diseases Department at the
Medical faculty of Medical University - Sofia**

Appointed as a member of a Scientific jury with order № P-109-105 of Rector of MU - Varna and approved by protocol № 61/01.03.2022 on Faculty council for preparation of "Opinion" on the dissertation of Dr. Diana Dimcheva Nenova, on the topic "Adequacy of dialysis treatment and the relationship with achieved quality of life and survival in patients with stage V chronic kidney disease", for award of scientific and educational degree "Doctor", according to doctoral Nephrology program, in professional direction 7.1. Medicine in the field of high education 7. Health and sports

I. Presentation of the author.

Dr. Diana Dimcheva Nenova was born on 11.01.1987 in the city of Burgas. She graduated in 2006 in the High School "St. St. Cyril and Methodius" Karnobat. In 2012 she acquired a master's degree in "Medicine" at Medical University "Prof. Dr. Paraskev Stoyanov" Varna. In February 2013 she started working at the Clinic of dialysis of the University Hospital "St. Marina" EAD - Varna, and between 2014 - 2018 she was a resident in Nephrology at the clinic. In 2017, Dr. Nenova was elected for part-time assistant in nephrology at MU Varna, and from March 2018 is a full-time assistant in Nephrology at the second department of Internal diseases. In December 2018 she successfully acquired specialty in Nephrology.

As a regular doctoral student from 2019 she wrote a dissertation on the topic "Adequacy of dialysis treatment and the relationship with achieved quality of life and survival in patients with stage V chronic kidney disease", with scientific supervisor Assoc. prof. Dr. Alexandar Stoyanov, PhD, in order to acquire educational degree "Doctor".

Dr. Nenova has publications in Bulgarian editions and reports and posters at Bulgarian scientific forums. She is a member of The Bulgarian nephrological association and BMA. She is fluent in English, possesses good communication and presentation skills as well as the ability for effective teamwork.

II. The dissertation.

The presented dissertation consists of 200 standard pages and is illustrated with 24 tables, 43 figures and 1 appendix. Literary references include 379 literary sources, of which 10 in Cyrillic and 369 in Latin. It includes introduction - 2 pages, literary overview - 55 pages, with general and specific parts, purpose and tasks of the dissertation - 1 page, material and methods of the research - 10 pages, results - 53 pages, discussion - 36 pages, followed by conclusions and contributions - a total of 2 pages. The abstract is built according to requirements, as it presents all results and conclusions from conducted research.

1. Relevance of the topic and relevance of the set goals and objectives.

The topic of the dissertation "**Adequacy of dialysis treatment and the relationship with achieved quality of life and survival in patients with stage V chronic kidney disease**" is current and significant both in scientific and in pure practical aspects. Worldwide the spread of supporting hemodialysis continues to grow, most likely related to the growing morbidity from diabetes and cardiovascular diseases. Despite notable technological progress, unsatisfactory results in the population of patients on hemodialysis (HD) show that improved care for patients is not enough to increase survival rates. The current need for optimization of hemodialysis therapies is the subject of research and discussions for years. Adequacy of dialysis must include the totality of all measures that aim to increase survival of patients, to improve quality of life, to improve cardiovascular results, and other benefits to the patient.

The literary review on the topic is presented on 55 pages, and the bibliography contains 379 titles, from which 10 of Bulgarian authors. From presented literary reference, 39% of publications are after 2017, or in the last 5 years, which is indicative for topicality of the problem. In the introductory part of the literary review, Dr. Nenova presents the main factors that influence dialysis adequacy - multiplicity and duration of dialysis procedures, blood debit (respectively effectively functioning vascular access), speed of dialysate flow rate, permeability and area of dialyzer. She presents additional information of dialysis adequacy in the form of the logarithmic formulas of Daugirdas - $spKt/V$ and their modifications - eKt/V , $stdKt/V$, URR , which remains the gold standard for evaluation of dialysis dose. Represented are also developing new technologies that relate to quality dialysis, e.g., the introduction of high flux membranes, convective therapies, intensified therapy schemes with extended dialysis duration and frequency. In historical aspect she presents uremic syndrome and uremic toxicity related to the onset and progression of the CKD, as well as the main manifestations of uremia and opportunities for removal of harmful toxins. Dr. Nenova presents the three groups of uremic toxins according to their molecular weight, solubility, uremia toxicity and impact on the different organs and systems. Separately she presents as uremia toxins representatives of each of the three groups of toxins - as cause, but also as consequence in CKD stage V: low molecular weight water soluble toxins, middle-molecular, such as urea, guanidines, purines, phosphates and protein-connected uremic substances. Despite of their small molecular weight, less than 500 Da, the last are defined as difficult to remove through dialysis uremic toxins. The theory for the "middle molecules" is also represented, their participation in different ways in inflammatory processes, endothelial dysfunction, etc. The markers for dialysis adequacy and protein intake in HD patients, as well as basic transport mechanism on dialysis removal are important part of the literary review, giving clear idea for the whole process on dialysis such as artificial kidney, its dependance on different calculated clearances of urea, creatinine, vit. B12, different coefficients and membrane surfaces. The different mathematical formulas and calculations, as well as various coefficients relate to normalization of the dialysis dose to bodily surface. Subsequently the literary review presents different indicators that give opportunity for evaluation of nutritional status and protein intake in HD patients. Finally, the review specifies a few guidelines related to the dialysis process as well as unresolved problems and prospects. All this for determining the minimum volume of adequacy and implementing it in practice as criterion for optimal clinical result.

The set goal is accurate and clear, and the 9 tasks for performance are clearly formulated and specific for the achievement of the goal set. Based on the literary review and great literary

reference on the problem, the dissertation student aims to research effect of non-standardized dialysis dose $spKt/V \geq 1.5$, obtained through different dialysis techniques - conventional and convective, on the clinical outcome and to evaluate its significance for achieved survival and quality of life in patients with CKD-5D. The last of the tasks - developing of an algorithm for examination and treatment to increase survival and quality of life sets the purpose of the whole dissertation.

The methodological part is presented on 10 pages. The study includes retrospective part with review and evaluation of medical documentation for a five-year period (2017-2021) per 100 patients with CKD-5D conducting chroniodialysis treatment at the Clinic of nephrology and dialysis, at the University Hospital "Sveta Marina" Varna. The prospective part includes 50 patients with stage V CKD, for evaluation of the achieved quality of life. There are also 3 subgroups for researching the influence of vascular access on the indicators of adequacy, for researching the effect from attached convective therapies based on the received dose and for researching the relationship between the calculated through UKM indicators for adequacy through online monitoring.

Attached methods of research include documentary, laboratory, anthropometric, mathematical, sociological and statistical methods.

The statistical analysis is made with software statistical SPSS packages v. 20.0, EXCEL for Windows, with different kinds of analyzes used: Descriptive analysis, parametric methods for testing of hypotheses, Nonparametric methods for testing of hypotheses, Correlation analysis, Regression analysis, Survival analysis, Roc analysis, used critical level of significance is $\alpha = 0.05$. The corresponding zero hypothesis is rejected when the P - value is less than α .

The results from conducted studies are exposed on 53 pages, as all results are presented through 24 tables, 43 figures and 1 appendix, which gives clarity and better susceptibility on presented results.

Discussion is presented on 36 pages, where Dr. Nenova in detail analyzes received results. From analysis of own data and comparison with the literature it becomes clear that the received results are original and with practical focus. Dr. Nenova shows that the effects of high dialysis dose $spKt/V \geq 1.5$ on objective indicators for clinical result and achieved quality of life are obvious. The effect is remarkable on control of anemic syndrome. Achieving the purely clinical purpose of covering certain standards is not at the cost of reduced efficiency and self-confidence of the patient, to the contrary - therapy must provide necessary comfort. The dissertation student discusses and proves that received higher dialysis dose in patients with effective functioning AVF correlates positively with achieved better quality of life and survival, reduces significant cardiovascular risk, improves anemic syndrome, nutritional and immune status of patients, which significantly decreases the frequency of annuals hospitalization and lethality. AVF on forearm is superior to other types on permanent vascular access - by function, survival and lack on complications and should be discussed with all patients set for hemodialysis treatment. Finally in the discussion, Dr. Nenova discusses that the effect from high dialysis dose is durable, but for achieving it time is necessary, perseverance and precision control not only on indicators for adequacy, but also on all accompanying complications of

CKD-5D. This one complex approach in the therapeutic strategy will lead to improved clinical result at reduced financial cost for the community and improved quality of life and prognosis for the patient. Additionally, the discussion represents the question for psycho-emotional condition of patients. According to Dr. Nenova the main moments for improvement of the mental health of patients must include coaching them to communicate with doctors when feeling anxiety or fear to timely and adequately evaluate the problem and preparing a strategy for its resolution. Another successful approach would be organizing group therapy. This not only would improve self-esteem on patients, but would too, give them opportunity to feel they are not alone in the struggle with the disease and the burden of the dialysis treatment. In this case important roles have both the nephrologist and a qualified psychologists who can provide comfort to the patient, predispose them to "teamwork" and cooperation for the purpose overcoming the problem and preventing it from affecting everyday life and the desire to deal with the disease. Finally, Dr. Nenova offers original diagnostic and therapeutic algorithm for dialysis prescription aimed at improved clinical result, survival and quality on life in patients with CKD-5D.

The dissertation contributes in fundamental as well as purely practically aspects such as giving useful recommendations for the daily clinical work.

The conclusions summarized by Dr. Nenova are twelve, but more substantial and important among them are the durable effect from high dialysis dose $spKt/V \geq 1.5$ and its effect on the clinical result manifest up to the third year from intensification of treatment; the auspicious effect of high dialysis dose on nutritional status is undisputed in young and middle-age patients; high-dose dialysis therapy $spKt/V \geq 1.5$ is associated with improved survival, decreased risk from death HR 0.60; online HDF associates with better survival compared to patients on HD.

In the dissertation of Dr. Nenova **contributions** are separated into theoretical and scientifically-applied. Important theoretical contributions are that for the first time in our country it has been researched and evaluated the effect on convective therapies that are not applied routinely in the clinical practice on achieved dialysis dose, parameters of nutritional status and control of anemic syndrome, and that for the first time in our country it has been studied convective volume as indicator for dosing of OL-HDF and there has been established a threshold value for efficiency of therapy. The connection has been proven on high-volume OL-HDF with improved survival and significantly decreased risk from death to conventional HD, and the main predictors for death in both groups have been evaluated. For the first time in our country, it has been studied the ionic dialysis as method for evaluation of dialysis dose.

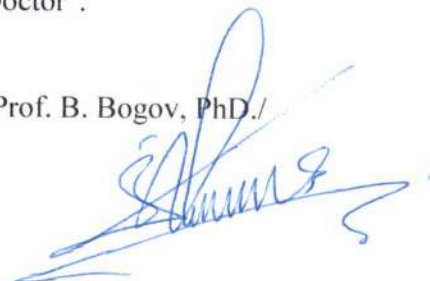
Practice-applied character have contributions proving the strong connection on high - dose HD $spKt/V \geq 1.5$ and OL-HDF with the achieved quality of life, high comparability and benefit on ionic dialysis to the classic indicators of UKM, as well as made original algorithm for therapeutically behavior and choice of dialysis mode in patients with CKD-5D - basis for complex and individualized approach in patients for improved quality of life and survival.

On the topic of the dissertation of Dr. Nenova there are 4 real publications, all in Bulgarian editions. In 3 of the publications Dr. Nenova is the first author.

In conclusion I can Yes state that the presented dissertation completely meets qualitative and quantitative criteria of the requirements of LDASRB, and of Annexes 3 and 4 of the RCPASDOAP of MU - Varna for awarding scientific and educational degree "Doctor" in the field of high education 7. "Health and Sports", by Professional direction 7.1. "Medicine" and science specialty "Nephrology" and I recommend to the respected Scientific jury to award Dr. Diana Dimcheva Nenova scientific and educational degree "Doctor".

Author:
14.03.2022

/ Prof. B. Bogov, PhD./

A handwritten signature in blue ink, appearing to read 'Bogov', with a long horizontal flourish extending to the right.