

## OPINION

from

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Under the procedure for obtaining the educational and scientific degree "Doctor" in the scientific specialty "Nephrology" of Dr. Diana Dimcheva Nenova, according to the order of the Rector of MU - Varna № R-109-105 / 09.03.2022 and Protocol No. 61 / 01.03.2022, from the FC of a dissertation on the topic: "Adequacy of dialysis treatment and the relationship with the achieved quality of life and survival in patients with stage V chronic kidney disease "

The presented materials on the procedure meet the requirements of the Law for the development of the academic staff of the Republic of Bulgaria and the Regulations for the development of the academic staff of MU - Varna for awarding the scientific degree "Doctor".

### ***Biographical data and career development:***

Dr. Diana Dimcheva Nenova graduated from high school "St.St. Cyril and Methodius" - Karnobat in 2006. In 2012 she obtained a master's degree, majoring in Medicine at the Medical University - "Prof. Dr. Paraskev Stoyanov" - Varna. In 2013 she started working at the Dialysis Clinic of the University Hospital "St. Marina EAD", Varna, and in the period 2014-2018 she was a resident in Nephrology at the Clinic. In 2017 Dr. Nenova was hired as a part-time assistant in nephrology at MU Varna, and since March 2018 she is a full-time assistant in Nephrology at the Second Department of Internal Diseases. In December 2018 she successfully acquired specialty in Nephrology.

***Relevance of the developed topic:*** The dissertation of Dr. Diana Nenova is related to an important and current practical problem in the field of nephrology and renal replacement therapy: study of the effect of non-standardized high dialysis dose  $spKt / V \geq 1.5$ , obtained by different dialysis techniques - conventional and convective, on the clinical outcome and its importance for the achieved survival and quality of life in patients with CKD-5D. The important role has been confirmed of the obtained high non-standardized dialysis dose, leading to improved clinical outcome, survival and achieved quality of life in its two components - objective and subjective, as well as the reliability of ionic dialysis to assess the delivered dialysis dose at high benefit for the patient.

***The dissertation is written on 200 standard pages. It is illustrated with 43 figures and 24 tables and 1 appendix, using 379 literature sources - 10 in Cyrillic and 369 in Latin.***

***Literary awareness:*** The dissertation student made a detailed review, which presents basic literature data on the term "dialysis adequacy", which is most often associated with achieving a minimum acceptable indicator -  $Kt/V$  and largely does not consider other clinical indicators in patients with CKD-5D. Dialysis adequacy is a much broader concept and should be discussed: the dialysis methods used, water quality, volume and blood pressure control, treatment of anemic syndrome and bone-mineral disorders, as well as the recovery process and social rehabilitation of patients. Dialysis adequacy needs to include all the measures aimed at increasing patient survival, improving their quality of life, improving cardiovascular outcomes, and other patient-related benefits.



*It is considered in detail the role and importance of vascular access*, resp. blood flow ( $Q_b$ ) for the dialysis dose received and the clinical outcome, as well as the influence of different dialysis membranes and techniques on the dialysis dose delivered in patients undergoing OL-HDF and HD. Of interest is the analysis of the influence of the received dialysis dose and the different types of dialysis techniques on the annual survival and mortality of the studied population, as well as the evaluation of the received dialysis dose and its influence on nutritional status, serum hemoglobin levels and applied average weekly erythropoetin dose.

**In reviewing the literature**, Dr. Nenova analyzed the methods used by UKM and ionic dialysis to assess the received dialysis dose through the results of online monitoring and blood urea clearance in order to develop new therapeutic strategies. She formulates the basics for developing an algorithm for research and treatment with a view to increase survival and quality of life based on the assessment of the factors researched. The literary review ends with conclusions on the basis of which the purpose of the dissertation is clearly formulated.

**The dissertation student sets 9 main tasks, which she proves chronologically and systematically in her scientific work.**

A retrospective study was conducted of 100 patients on HD in the Clinic of Nephrology and Dialysis at the University Hospital "St. Marina" in Varna, divided into several subgroups with review and evaluation of the medical documentation for the period 2017-2021 and 50 patients for prospective assessment of the achieved individual quality of life.

Statistical analysis of the data was performed using SPSS v. 20.0.

**Evaluation of the results:** The author devotes a significant place in her work to the study of the relationship between survival, quality of life and different doses and techniques of dialysis treatment with a thorough review of the literature on the problem and the relationship of high dialysis dose  $spKt / V \geq 1.5$  with improved patient survival and reduced risk of death compared to the standard dialysis dose - a controversial statement in the world literature.

The benefit of ionic dialysis compared to the classical indicators of UKM is established and its routine implementation in clinical practice is proposed in view of improved clinical outcome and reduced cost of treatment. An original algorithm for therapeutic behavior and choice of dialysis regimen in patients with CKD-5D has been developed and proposed - a basis for a complex and individualized approach in patients for improved quality of life and survival.

Through her results, the dissertation student shows that despite advances in dialysis technologies with increased membrane biocompatibility and high clearance of uremic toxins, patients show a low score of physical and emotional component of HRQOL, which directly correlates with dialysis dose received and the type of dialysis therapy.

**In a discussion section, her results showed** that in elderly patients, high convective volumes were associated with hemodynamic instability, prolonged recovery time, and poor nutritional status with significantly lower nPCR and serum albumin values compared to the same age group performing conventional dialysis, which requires strict refinement of dialysis prescribing schemes.

Online HDF is associated with better survival than HD patients (87.7% vs. 57.2% at the end of the two-year period), with the latter being almost four times more likely to die (RR 3.59; CI 95% 1.25 - 10.24  $p < 0.001$ )



The use of a convective volume  $Q_{o} > 20$  l per session has been proven to be the main measure for dose and high efficiency of the performed OL-HDF. At volumes below the indicated value, the clinical effect is comparable to that of conventional dialysis. The high volume  $Q_{o} > 20$  l is not a universal dose for every patient, despite its higher efficiency, which is evidenced by the derived correlation dependencies after its adaptation. The beneficial effect of high dialysis dose on nutritional status is indisputable in young and middle-aged patients, but is unsatisfactory for elderly patients who, despite good rehabilitation, have age-related weight loss and malnutrition with high comorbidity. High-dose dialysis therapy  $spKt/V \geq 1.5$  is associated with improved survival, reduced risk of death HR 0.60 (CI 95% 0.35-1.02,  $p = 0.051$ ) and a significant increase in life expectancy compared to other groups, while the critical period for stabilization and survival is significantly shorter. In the conditions of the non-standardized high dialysis dose achieved by conventional (HD) or convective therapies (OL-HDF) the nutritional indices have a stronger predictive value for poor performance, as in OL-HDF the serum albumin is of special importance due to the expressed loss during the procedure. AVF significantly outperforms other types of vascular access in terms of dialysis dose and control of anemic syndrome, achieved survival with reduced risk of death.

Based on the obtained results, 12 main conclusions have been made, which are logically and correctly formulated, follow the data from the results and correspond to the set goals and objectives.

11 scientific contributions are determined - 7 with theoretical and original character and 4 with practical - applied character, which I fully accept and are the personal work of the author.

**Scientometric criteria:** The dissertation student applies a list of 4 publications related to the dissertation. The attached list fully meets the requirements for acquiring educational and scientific degree "Doctor".

The abstract is stylistically well illustrated and reflects the essence of the dissertation.

**In conclusion, I define the dissertation of Dr. Nenova as a topical scientific work of great practical importance.**

**Despite technological advances, unsatisfactory results in the hemodialysis (HD) patient population indicate that improved patient care is still insufficient to increase survival. The question of the need to improve hemodialysis therapies, which has been the subject of research and discussion for many years, remains relevant. Many studies have shown a significant correlation between hemodialysis dose, clinical outcome, and quality of life. It has been found that increasing the time and frequency of dialysis, blood flow rate, lack of recirculation and reducing intradialysis complications are associated with better adequacy of HD.**

Based on the presentation made, I suggest convincingly the members of the scientific jury to vote positively for the award of educational and scientific degree "Doctor" to Dr. Diana Nenova.

March 17, 2022

Prof. Dr. Svetla Staykova, PhD, DSc

