

**To
The Chairman of the Scientific Jury
determined by Order No. 616/11 Feb 2025
of the Rector of MU Plovdiv**

REVIEW

by Assoc. prof. Eduard Emil Tilkiyan, MD, PhD, II Department of Internal Medicine, Department of Nephrology of the MF of Medical University - Plovdiv

of a dissertation for awarding the educational and scientific degree 'DOCTOR'
professional field 7.1 "MEDICINE"

PhD program Pediatrics.

Code 03.01.50.

Author: Dr. Petya Petkova Markova

Topic: Monitoring of kidney function in children undergoing chemotherapy

Scientific Supervisors:

Prof. Maria Spasova, MD, PhD

Prof. Polina Miteva-Shumnalieva, MD, PhD

1. General Presentation of the Procedure and PhD Student

The presented materials are in accordance with the procedure for acquiring the degree of Doctor at MU – Plovdiv. Dr. Petya Markova is enrolled as a full-time PhD student.

2. CV

Dr. Petya Petkova Markova graduated in medicine from the Medical University of Plovdiv in 2006. with excellent grades. She worked consecutively at the Center for Emergency Medicine in Plovdiv from 02.10.2006 to 29.05.2008. Children's emergency room University Hospital "St. George" EAD Plovdiv – 29.05.2008 – 01.08.2008 Clinic of Pediatrics and Genetic Diseases; University Hospital "St. George" EAD Plovdiv 01.08.2008 – Department of Intensive Care and Resuscitation until 2016, then Department of Gastroenterology and Nephrology and until now. She is enrolled as a full-time PhD student at the Department of Pediatrics – Order N R-2374/17.12.2021.

She acquired a specialty in Pediatrics - December 01.01.2014. and Second Specialty Pediatric Nephrology and Hemodialysis - Medical University - Sofia 07.07.2016

Characteristics and evaluation of the dissertation

The dissertation is presented on 167 standard typewritten pages. It is illustrated very well with 63 figures and 29 tables. The dissertation is written in literary Bulgarian.

3. Topicality of the topic

Kidney damage in children with oncological diseases undergoing antitumor therapy is extremely important for the development of the disease process. The introduction of new drugs has significantly improved therapeutic outcomes in these patients, but has also led to an increase in the incidence of kidney damage, which can occur through various mechanisms. Good knowledge of the type of kidney damage and early diagnosis would allow for successful therapy with less pronounced side effects and improvement of the near and distant prognosis. Dr. Markova shows a very in-depth knowledge of the problem and excellent skills for conducting scientific research and interpreting the results obtained.

4. Literature review

The literature review, presented on 48 pages, is very detailed, and Dr. Markova describes in depth the different types of Acute Renal Injury, their pathogenesis and diagnosis. Modern methods for assessing renal function in the pediatric population are presented in detail, as well as the possibilities for early detection of AKI before clinical presentation. Dr. Markova also discusses in depth the mechanisms of renal injury in individual medications and types of damage (prerenal, direct nephrotoxic, immune). Modern views on the therapy and prevention of AKI in these patients are also considered separately. In conclusion of the literature review, Dr. Markova draws conclusions that justify the purpose of the presented dissertation.

5. Purpose and objectives

The purpose of the dissertation is clearly defined. To achieve it, Dr. Markova sets herself 6 tasks to solve.

6. Material and methods

The part is presented on 6 pages. In order to fulfill the set goals and objectives, the following studies have been conducted:

Retrospective study on hospitalized patients at the Clinic of Pediatrics at the University Hospital "St. George" for the period 2016-2020.

A cross-sectional study involving 40 children undergoing chemotherapy with nephrotoxic drugs and a prospective study on a group of 28 children who completed their treatment with nephrotoxic drugs at least one year ago for analysis and evaluation for the onset of chronic kidney disease. The methods used are clinical, standard laboratory and imaging tests, determination of NGAL levels in urine, functional tests. A statistical method of descriptive statistics was used. The statistical processing of the results was carried out with statistical software SPSS v.23.

The graphical presentation of the results is implemented with Microsoft Excel 2016.

The study was approved by the Ethics Committee at the Medical University of Plovdiv (Protocol No. 6/07.10.2021)

7. Results and discussion

The results and the discussion on the individual tasks are presented in great detail and reasoned on 68 pages. The results of each task are considered separately and the corresponding conclusions are drawn.

Particularly interesting are the conclusions that NGAL is not indicative as an early marker for the diagnosis of AKI, the result of drug nephrotoxicity, in particular nephrotoxic chemotherapeutics.

As a conclusion from task 3, it is recommended to use the Schwartz formula – adjusted for body surface area – when monitoring kidney function in pediatric oncology.

Task 4 shows that the main pathogenetic mechanism for drug nephrotoxicity resulting from drug nephrotoxicity is the occurrence of tubulopathy, as well as the possibility of using the markers for tubular damage - FeF % and Tmp/GFR (renal threshold for phosphates) for early diagnosis of drug nephrotoxicity in pediatric oncology.

The conclusions from task 5 are also important for practice:

The onset of tubulopathy is reversible in a large percentage of cases, but in a large part of children it remains chronic.

Follow-up is necessary for tubulopathy both during therapy, and after its completion.

NGAL is not indicative as a marker for diagnosing CKD in children with cancer who underwent chemotherapy.

An algorithm for monitoring the renal function of children conducted and conducting therapy with nephrotoxic drugs has been proposed.

8. Contributions and relevance of the development to science and practice

The conclusions are 10 and are based on the results of the study.

Dr. Markova's dissertation presents 5 contributions, of which 2 are original in relation to the child population in Bulgaria, 1 is of general and original character and 2 are of general and confirmatory character.

Of essential practical importance is the developed algorithm for monitoring the renal function of children undergoing chemotherapy with nephrotoxic drugs with included markers of tubular damage and the possibility of individual calculation of the doses of different drugs.

9. Publications in connection with the dissertation

The PhD student has attached 3 full-text publications related to the dissertation, refereed in an international database.

There are 3 announcements in national forums and one in international forums.

For the implementation of the dissertation, participation in 1 scientific project was presented.

10. Bibliography

247 literary sources are presented, 5 of which are in Cyrillic and 242 in Latin.

11. Abstract

The abstract is presented on 76 pages. It contains the most important components of the dissertation and gives clear data for the high level scientific work of the PhD student.

Conclusion

The dissertation contains scientific, scientifically applied and applied results that fully comply with the requirements of the Academic Staff Development Act in the Republic of Bulgaria (RASRB), the Regulations for the Implementation of the RASRB and the relevant Regulations of MU - Plovdiv.

The dissertation shows that the PhD student Dr. Petya Markova has in-depth theoretical knowledge and professional skills and I confidently vote positively and

recommend the other respected members of the scientific jury to vote for the award of the educational and scientific degree of “Doctor” to Dr. Petya Petkova Markova.

14.032025 Reviewer:
Залчено на основание
Чл.5 §1, 6. "В" Регламент (ЕС)2016/679

Ass. Prof. Eduard Tilkiari, MD, PhD