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OPINION

By Prof. Yana Dimitrova Bocheva, MD, Ph.D
Head of the Department of Clinical Laboratory
at the Faculty of Medicine
at the Medical University "Prof. P. Stoyanov” – Varna

Regarding the dissertation of Dr. Adriana Dimitrova Hadzhjieva-Hristova, PhD student in the full-time form of study in the PhD program “Pediatrics”, held at the Department of Pediatrics, Faculty of Medicine, Medical University “Prof. Dr. Paraskev Stoyanov” - Varna, for obtaining PhD in the field of higher education 7. Health and Sport, professional field 7.1. Medicine, specialty “Paediatrics”, with scientific supervisors Prof. Dr. Violeta Mihova Yotova, MD, PhD, DSc. and Prof. Dr. Temenuga Zhekova Stoeva, MD, PhD, DSc

On the basis of the Order No. P-109-147/13.03.2025 of the Rector of the Medical University “Prof. Dr. Paraskev Stoyanov”, Sofia. Varna prof. Raikov, Ph.D. and by decision of the Scientific Jury on the basis of Protocol No. 1/24.03.2025. I have been appointed to prepare an opinion on the procedure for the acquisition of PhD with candidate Dr. Adriana Dimitrova Hadzhjieva-Hristova on the dissertation entitled “Septic and critical conditions in children treated in intensive care unit: clinical profile, early diagnosis and prognosis”

The opinion has been prepared according to the requirements of the Law for the Development of Academic Staff in the Republic of Bulgaria (LADRB) and the Regulations for the Development of Academic Staff at Medical University "Prof. Dr. Paraskev Stoyanov - Varna.

Topic Relevance

The topic of the submitted dissertation has been carefully selected according to the personal clinical interests of the dissertant and the accumulated expertise and direction of the supervisors. Modern clinical medical disciplines today with their scientific projections have focused their efforts on the validation of new laboratory, genetic and molecular markers as well as in the search for new projections of known parameters.

Sepsis continues to be a leading cause of morbidity and mortality, particularly in the pediatric population. Although the introduction of different criteria in the definitions of sepsis over the years has led to better diagnosis in adults, uncertainties still exist in children due to differences in age-related physiology, the lack of specific diagnostic markers, and the limitations of uniform criteria.

Early recognition of sepsis and an appropriate therapeutic response are critical to achieving a more favorable prognosis in children. Developments in

high-tech microbiological diagnostic methods such as MALDI-TOF-MS show potential for more rapid identification of the infectious agent, but are inaccessible tools for mainstream clinical practice. Biochemical laboratory indicators used in routine practice (CRP, procalcitonin), on the other hand, demonstrate some weaknesses but are relatively generally available and easy to use. There is evidence in the world literature of attempts by multiple teams to validate different markers for more accurate diagnosis, prognosis and monitoring of complications and therapy. Novel markers such as presepsin (sCD14-ST) and soluble mannose receptor (sMR; sCD206) represent promising predictors for timely detection of septic process, but have analytical and methodological limitations. These diagnostic shortcomings clearly contribute to some difficulties and imperfections in therapeutic strategies, leading to adverse prognosis and outcome in patients. Despite the multidirectional searches of different author teams and the numerous publications on the subject, there is a lack of focused studies and implemented publications on the subject in our country.

In view of the critical need to optimize diagnostic and therapeutic strategies in children, and as a logical outcome of this information vacuum in our country, the current research interest of the dissertation and her supervisors is motivated.

In this context, I consider the conceptual design of this dissertation, submitted to me for evaluation, to be relevant as a conception, prospective as publication results and at the same time classical as methodological execution.

Characteristics, scope, structure and content of the thesis

The dissertation is presented in 164 pages, including: Introduction- 1 p., Literature review- 50 p., Aim and objectives- 1 p., Materials and methods- 14 p. Results- 33 p., Discussion- 18 p., Conclusions- 1 p., Contributions- 1 p., Conclusion- 2 p., Publications- 1 p., Bibliography- 19 p., Appendices- 23 p. The illustration consists of 15 tables and 35 figures. The bibliography contains 262 sources, of which 16 are in Cyrillic. The latter includes contemporary sources, 80% of which are from the last 10 years and 47 from the last 5 years.

The structure of the dissertation conforms to contemporary formulations for the internal proportion of the parts of a dissertation with a bias towards theorizing and extensive justification in the introduction and literature review and with emphasis on results, interpretation and analysis. A clear style is demonstrated, with an excellent knowledge of highly specialised terminology.

The literature review is logical and well-structured, consistently defining the clinical problem, its epidemiological characteristics and going through the etiological and pathophysiological mechanisms, clinical presentations and assessment scales, comments on microbiological identification and discusses established and investigational biochemical markers of inflammation, followed by data on treatment, prevention and prognosis

The aim is clearly stated and is a logical consequence of the summary of the literature review. It is consistent with the title and is further refined by the text of the dissertation tasks.

The dissertation is designed with the formulation of five specific **tasks**, justified by the highlights of the literature review.

Materials and Methods

Dr. Hadzhieva's study was a single-center, prospective study. It included 80 children aged 7 days to 18 years, selected according to predefined criteria and hospitalized in the First Children's Clinic with Intensive care department in St. Marina Hospital- Varna. The patients were divided into 3 patient groups:

1)Septic children with systemic inflammatory response syndrome (SIRS) caused by confirmed or suspected infection

2)Critical children with SIRS of non-infectious origin

3)Control group children without history and clinical evidence of infectious syndrome or SIRS.

The study was approved by the Scientific Ethics Committee of MU-Varna with the decision № P-115/31.03.2022. The laboratory tests were performed in the Clinical Laboratory and Microbiology Laboratory of University Hospital "St. Marina", Burgas. Varna. The laboratory methods used were standardized, automatic, ELISA methods, hematological and biochemical analyses, which comply with the Rules of Good Medical Practice and are precisely described.

Results

In a total of 33 pages, Dr. Hadzhieva describes in detail and in sequence the implementation of each of the set tasks leading to the fulfillment of the formulated goal of her scientific work. There are 15 tables and 35 figures, accompanied by analyzing and explanatory text. The applied statistical methods of analysis are properly selected and correctly interpreted.

On task 1, the author systematizes the etiological structure of diseases in children with septic and critical conditions hospitalized in the Intensive care department, visualizes the etiological spectrum of microbiologically confirmed infections and describes the typical complications.

Tasks 2 and 3 summarize the examined clinical characteristics and rates of patients with/without complications, present the prognostic reliability of the scales for predicting the risk of developing complications, and evaluate and beautifully visualize the discrimination and calibration of the four prognostic scales.

For Tasks 4 and 5, the results of the studied laboratory parameters in the three groups are presented as medians, direct comparisons, correlations and diagnostic reliability. An attempt is made to derive reference values of presepsin and sMR, which I consider to be insufficient. The diagnostic performance and reliability of biomarkers of inflammation in distinguishing septic patients from controls by ROC analysis is discussed and presented in the text. A combined biomarker analysis with multiple logistic regression of a combination of two and three biomarkers is performed.

In the “**Discussion**” section of the dissertation, Dr. Adriana Hadzhieva provides an objective analysis of her results, comparing them with those of other research teams, respecting the order of the results presented, the logic of

her presentation, and keeping the guiding line of the stated aim and objectives. It is in this chapter of the dissertation that the good level of preparation of the dissertant is evident, which demonstrates the knowledge of the Bulgarian and world literature on the problem under consideration, as well as the ethical and critical attitude of the young scientist considering her own results.

I fully agree with the defined 6 **conclusions** that reflect the results obtained. They are clearly and specifically formulated. They have the support and evidence in the Results chapter of the thesis.

The dissertation concludes by defining 6 **contributions**.

Publications on the topic

A list of 2 full-text publications in Bulgarian journals- Journal of Paediatrics and Scripta Scientifica Medica, where the dissertation is the first author and co-authored with the supervisors is presented.

The abstract (56 pages) is developed and structured according to the requirements, and its content fully corresponds to the dissertation.

Conclusion

The dissertation of the PhD student Dr. Adriana Dimitrova Hadzhjieva-Hristova is essentially a thorough scientific work with practical orientation. The topic is interesting and challenging. The applied methods are adequate to achieve the set goals and objectives, the results are meaningful, and the conclusions are logical and correctly drawn.

The dissertation work of Dr. Adriana Dimitrova Khadzhieva-Hristova on "Septic and critical conditions in children treated in intensive care unit: clinical profile, early diagnosis and prognosis" complies with the requirements of the Law on Medical Education and Research, the Regulations for its implementation and the relevant regulations of the Medical University "Prof. P. Stoyanov - Varna.

On the basis of the foregoing I give a positive evaluation of the dissertation and recommend the Honourable Jury to award Dr. Adriana Dimitrova Hadzhjieva-Hristova the educational and scientific degree "DOCTOR" in the field of higher education 7. Health and Sport, professional field 7.1. Medicine, specialty "Paediatrics".

26th April 2025 Prof. Yana Dimitrova Bocheva, MD, Ph.D
Varna, Bulgaria