REVIEW

By Prof. Boryana Varbanova, MD, PhD

Medical University "Prof. Paraskev Stoyanov" Varna

Department of Pediatrics

Regarding the dissertation submitted for the awarding of the educational and scientific degree of Doctor (PhD) in the specialty of Pediatrics, code 03.01.50, within the professional field 7.1 Medicine, under the higher education area 7. Healthcare and Sports.

Author: Adriana Dimitrova Hadzhieva-Hristova, MD

Form of doctoral study: full-time in the Doctoral Program in Pediatrics.

Department: Department of Pediatrics, Medical University "Prof. Paraskev Stoyanov" Varna

Topic: Septic and critical conditions in children admitted to the intensive care unit: clinical profile, early diagnosis, and prognosis

Scientific supervisors: Prof. Violeta Mihova Iotova, MD, PhD, DSc and Prof. Temenuga Zhekova Stoeva, MD, PhD, DSc

Defense procedure:

The dissertation documentation has been prepared in compliance with the regulatory requirements for awarding the educational and scientific degree of "Doctor." The procedure has been approved by the Department of Pediatrics and the Faculty Council of the Medical University of Varna, as recorded in Protocol No. 36/10.03.2025. This review has been prepared in accordance with the Law on the Development of Academic Staff in the Republic of Bulgaria, the Regulations for the Implementation of the Law on the Development of Academic Staff, and the Regulations on the Conditions and Procedures for Acquiring Academic Degrees and Holding Academic Positions at the Medical University of Varna. The scientific jury for the public defense of the dissertation was appointed by Order of the Rector of the Medical University of Varna, No. P-109-147/13.03.2025.

General presentation of the doctoral student and the procedure:

Dr. Adriana Dimitrova Hadzhieva-Hristova was born in 1991 in Kavarna, Bulgaria. She completed her secondary education at the Yoan Exarch Foreign Language High School in Varna in 2010. In 2017, she obtained her master's degree in medicine from the Medical University of Sofia. In 2018, she began her residency in Pediatrics at the Medical University of Varna, which she is expected to complete in 2022. In 2020, Dr. Hadzhieva-Hristova was appointed to the Pediatric Intensive

Care Unit at St. Marina University Hospital, Varna. In the same year, she joined the Department of Pediatrics at the Medical University of Varna as an assistant professor. She has participated in postgraduate training courses in Pediatrics and Intensive Care Medicine. Dr. Hadzhieva-Hristova is proficient in English and French.

The dissertation materials have been prepared in accordance with the regulatory framework governing the award of the educational and scientific degree "Doctor," and in compliance with the Regulations of the Medical University "Prof. Paraskev Stoyanov" – Varna.

Relevance of the topic:

Septic conditions in children remain a significant contributor to morbidity and mortality in contemporary medicine. Early diagnosis and timely therapeutic intervention are critical for achieving improved patient outcomes. This dissertation presents a comprehensive review and analysis of established practices and emerging approaches for the recognition and assessment of sepsis in early childhood. Special emphasis is placed on contemporary methods for the stratification and evaluation of septic states, utilizing various clinical scoring systems, as well as microbiological and biological markers.

Knowledge of the problem:

The literature review presented in the dissertation not only demonstrates a thorough understanding of the problem but also reflects the author's in-depth engagement with the scientific literature and evidences a high level of scientific maturity. It provides an important foundation for the subsequent intelligent analysis and evaluation of the author's own research findings and the conclusions drawn from them. The development of the concept of microbiological identification of pathogens across different historical periods is outlined in a coherent historical and chronological framework. The review addresses the contemporary interpretation of critical and septic conditions, various scales for the assessment of septic states, as well as conventional and innovative diagnostic and prognostic biomarkers. It further examines the predictive value of these indicators for potential complications, therapeutic response, and inflammatory assessment. The epidemiology of septic conditions across different age groups, countries, genders, races, and other demographic and nosological factors is presented competently and systematically. In addition, the dissertation offers a detailed overview of the pathophysiology of septic conditions, leading clinical manifestations, and modern microbiological and laboratory diagnostic methods. The advantages and limitations of various clinical scales used for the assessment of children with septic and critical conditions are critically analyzed.

Characteristics and evaluation of the dissertation and contributions:

The dissertation is well-structured and represents the original work of the author. It is presented over 170 pages and includes 15 tables, 35 figures, and 10 appendices. A total of 269 sources are cited, of which 16 are in Bulgarian and 253 are in English. The content of the dissertation is proportionally organized into the following sections: Introduction, Literature Review, Aim and

Objectives, Materials and Methods, Results and Discussion, Conclusions, Contributions, Publications and Presentations, Bibliography, and Appendices.

The aim of the dissertation is clearly formulated, and the five objectives are logically structured and comprehensive.

The study material includes 80 children aged from 7 days to 18 years, hospitalized at the First Clinic of Pediatrics and PICU at St. Marina University Hospital, Varna, during the period from June 1, 2022, to January 31, 2024. The patients were selected based on predefined inclusion criteria and were divided into three main groups: septic, critical, and control. The study is prospective in design, approved by the Ethics Committee, and supported by funding from the Fund "Science" at the Medical University of Varna.

Diagnostic **methods** employed include clinical examination, microbiological methods (blood culture testing and microbial identification using mass spectrometry with MALDI-TOF Sirius and MALDI-TOF-MS Sepsityper, PCR), laboratory testing of routine inflammatory markers, procalcitonin, and innovative inflammatory biomarkers such as presepsin and soluble mannose receptor (sMR).

Statistical analysis was performed using the SPSS statistical software package.

The results are organized into three main sections: (1) the etiological structure of diseases in children in septic and critical conditions hospitalized in the Pediatric Intensive Care Unit; (2) scales for the assessment of clinical condition; and (3) laboratory markers of inflammation. **The first section** presents the demographic characteristics of the patients, the presence of fever, prior antibiotic treatment, underlying diseases, the use of oxygen therapy and intensive care measures, and the disease outcomes. A detailed analysis is provided of the disease structure, the microbiological identification of pathogens, and the complications that developed in 53 children with septic and critical conditions.

In the section on **Assessment Scales**, Dr. Hadzhieva-Hristova analyzes the prognostic reliability of various scoring systems for predicting the risk of complications in pediatric patients. The PRISM III and PELOD-2 scales demonstrated comparable accuracy in identifying patients who developed complications, with predictive values of 47.8% and 43.5%, respectively. The pSOFA score exhibited high reliability in patients without complications, achieving an accuracy of 88.0%. The Phoenix Sepsis Score (PSS) showed the highest predictive value for identifying septic patients who developed complications during hospitalization (70.6%). Overall, the PSS demonstrated the highest predictive accuracy across the study population (76.2%), with good performance in both the septic and critically ill patient groups.

The section on **Laboratory Markers of Inflammation** compares the results of surrogate markers of inflammation—leukocyte count, C-reactive protein (CRP), procalcitonin—and the innovative biomarkers soluble mannose receptor (sMR) and presepsin among children in the three clinical groups. The study demonstrates the diagnostic effectiveness and reliability of these indicators in patients with septic and critical conditions compared to the control group. Using multiple logistic regression analysis, the diagnostic value of various combinations of biomarkers was evaluated. Among the analyzed models incorporating three laboratory parameters, the combination of **sMR**

+ CRP + procalcitonin showed the highest diagnostic effectiveness for distinguishing sepsis, offering the best discriminatory capacity among the assessed combinations. Particularly noteworthy is the analysis of septic conditions in children under two months of age, which, in addition to the typical Gram-negative pathogens, reflects the impact of the COVID-19 pandemic. The study also highlights risk factors for the development of antibiotic resistance, stemming from inappropriate empirical antibacterial therapy.

The Discussion section of the dissertation skillfully interprets and contextualizes the findings within a comprehensive review of contemporary scientific literature. The author demonstrates extensive knowledge and an impressive ability to critically analyze and integrate data from their own research in relation to global trends. The creative approach is further evidenced by the attempt to improve the discriminatory capacity of the Phoenix Sepsis Score through recalibration, positioning it as superior to other assessment scales. The dissertation emphasizes the critical importance of early recognition and identification of septic conditions for achieving favorable patient outcomes, reducing complications, and minimizing the burden on the healthcare system and society.

The conclusions drawn in the dissertation are logical, well-founded, and align closely with the analyzed results, namely:

1. Septic conditions are observed predominantly in infections of the lower respiratory tract, gastrointestinal tract, and nervous system.
2. A high relative proportion of microbiologically confirmed infections in septic conditions is demonstrated, with bacterial pathogens predominating. The most identified organisms are *Escherichia coli*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*, which is consistent with published literature data.
3. Among the assessment scales studied, the Phoenix Sepsis Score exhibited the highest overall predictive value and the greatest reliability in predicting complications in children with septic and critical conditions.
4. The biomarkers soluble mannose receptor (sMR) and presepsin demonstrated significant variability, underscoring the need for further validation through future studies.
5. Procalcitonin and C-reactive protein (CRP) proved to be the most reliable biomarkers for sepsis diagnosis, while sMR and presepsin may serve as valuable supplementary markers.
6. The simultaneous measurement of sMR, CRP, and procalcitonin is a useful diagnostic strategy for the clinical assessment of patients with sepsis.

The contributions of the dissertation are objective, adequate, and clearly articulated. I acknowledge all the contributions listed by the author, namely:

- The study is among the few in the contemporary literature that provides a detailed analysis of the etiology of septic and critical conditions in children hospitalized in intensive care units.
- The role of modern microbiological methods in the timely identification of microbial causative agents, facilitating appropriate etiological treatment, has been confirmed.
- For the first time, a comparative assessment of four international scoring systems for critical and septic conditions in children admitted to intensive care units has been conducted.

- New predictive biomarkers for the diagnosis of sepsis in children have been evaluated.
- The significance of the combined use of CRP and procalcitonin as a reliable laboratory approach for the diagnosis of sepsis in children has been confirmed.
- The results of the study provide a foundation for the development of an effective model for the diagnosis and management of septic conditions in pediatric patients.

The abstract is well-structured and accurately reflects the content of the dissertation. Two full-text publications in Bulgarian scientific journals related to the dissertation have been presented.

Assessment of the dissertation:

The presented dissertation addresses a topical and significant subject, and it is characterized by both innovation and substantial informational value. It represents an excellent integration of the doctoral student's profound knowledge of the problem, the application of appropriate research methods, skillful academic guidance, and competent analytical interpretation. The conclusions are well-founded and logically derived from the results obtained. Dr. Hadzhieva-Hristova's dissertation constitutes a valuable scientific contribution to the study of septic and critical conditions in children admitted to intensive care units in our country. Its advancements are significant from both theoretical and practical perspectives.

Conclusion

The dissertation presented by Dr. Adriana Dimitrova Hadzhieva-Hristova on the topic "*Septic and critical conditions in children admitted to the intensive care unit: clinical profile, early diagnosis, and prognosis*" possesses the necessary qualities of an independent, relevant, and significant scientific work, fully meeting the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria, the Regulations for its Implementation, and the Regulations on the Conditions and Procedures for Acquiring Academic Degrees and Holding Academic Positions at the Medical University "Prof. Paraskev Stoyanov" – Varna. In view of the above, I confidently recommend that the distinguished members of the Scientific Jury award Dr. Adriana Dimitrova Hadzhieva-Hristova the educational and scientific degree of "**Doctor**."

23.04.2025

Reviewer:

Prof. Boryana Varbanova, MD, PhD