

TO
The Chairman of the Scientific Jury,
determined by order No. R-109-147/13.03.2025
of the Rector of the Medical University, Varna

OPINION

From Prof. Dr. Gergana Petrova Stoyanova, MD, PhD

Department of Pediatrics of the Faculty of Medicine at the Medical University of Sofia

External member of the scientific jury for the Medical University of Varna "Prof. Dr. Paraskev Stoyanov"

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MEMBER OF THE SCIENTIFIC JURY, ACCORDING TO ORDER No. R-106-147/13.03.25g according to art. 24, para. 6 and art. 30 para. 2 reglement for academic advancement, art. 68, para. 1 of the Regulations for the Development of the Academic Staff at MU-Varna, at the proposal of the Head of the Department of Pediatrics, entry No. 102-629/04.03.2025, approved by a decision of the Faculty Council of the Faculty of Medicine MU-Varna - protocol No. 36/10.03.25, and a report of the Dean with entry No. 103-1349/12.03.2025.

Regarding: Procedure for the defence of a dissertation thesis by Dr. Adriana Dimitrova Hadzhieva-Hristova in the program "Pediatrics" in the field of higher education 7. "Healthcare and Sports", professional direction 7.1. "Medicine", full-time doctoral student at the Department of Pediatrics, MU-Varna

All documents for the procedure have been submitted in accordance with the requirements of the regulations, with the necessary evidentiary material.

Professional Development

Dr. Adriana Dimitrova Hadzhieva-Hristova has been a full-time PhD-student at the Department of Pediatrics at MU-Varna since January 2020. She graduated from MU-Sofia in 2017. After that, she began her residency in pediatrics at the MC "Euromedica - Kavarna", University Hospital "St. Marina" Varna. Since March 2020, after a competition, she has also been appointed as an assistant at the Department of Pediatrics, MU-Varna. In May 2022, she successfully passed the national board exam and is a specialist in pediatrics. According to her brief biography, Dr. Hadzhieva-Hristova has an affinity for pediatric pneumology. She has not provided data on memberships in scientific societies. She has participated in two specialized courses (one in Bulgaria and one abroad).

Thesis analysis

Dr. Hadzhieva-Hristova presents a dissertation on the topic "SEPTIC AND CRITICAL CONDITIONS IN CHILDREN TREATED IN THE INTENSIVE UNIT: CLINICAL PROFILE, EARLY DIAGNOSIS AND PROGNOSIS"

The dissertation is written on 170 standard typewriter pages. The text contains 15 tables, 35 figures and 10 appendices. The bibliography includes 269 titles - 16 in Cyrillic and 253 in Latin. The work is structured as follows: introduction and literature review 51 pages, aim and

objectives 1 page, materials and methods 14 pages, results 33 pages, discussion 17 pages, conclusions 1 page, contributions 1 page, conclusion -2 pages, publications and other scientific contributions 1 page, bibliography 21 pages, appendices 23 pages. It is striking that the review takes up almost as many pages as the results and discussion all together. One critical recommendation is to shorten part of the review or to transfer the analysed data in it to the discussion. Another large section is the appendices, which are almost as long as the results. Moreover, some of the appendices are related to the review, and not to the thesis research work. Specific examples are appendices 5,6 and 7. Appendices 1, 2,3 and 4 are assessment score systems, on the basis of which the children's assessment was carried out and can remain as such. In my opinion, the appendix for the survey information, informed consent and the decision of the ethics committee are mandatory.

Regardless of these remarks, the presented dissertation reflects the scientific work of Dr. Hadzhieva-Hristova and is in accordance with the requirements for such a dissertation of MU-Varna.

The relevance of the chosen topic - the topic is also indicated by the bibliographic reference in which 65.79% of the literary sources are from the last 10 years. I have no remarks on the bibliographic reference.

In her dissertation, Dr. Hadzhieva-Hristova aims to study the clinical profile and outcome in children with septic and critical conditions in a pediatric intensive care unit and to evaluate the approaches for their early diagnosis.

Sepsis continues to be a leading cause of morbidity and mortality, especially in the pediatric population. Early recognition of sepsis and appropriate therapeutic response are crucial for achieving a more favorable prognosis. In view of the critical need to optimize diagnostic and therapeutic strategies in children, Dr. Hadzhieva-Hristova focuses on a systematic review of established and innovative approaches to recognizing and assessing sepsis in early childhood. This topic not only reflects the current scientific interest in the multidisciplinary management of the disease, but also draws attention to poorly filled gaps in clinical practice in our country, the overcoming of which would contribute to improving survival and quality of life in children.

The literature review is written extensively, informatively and up-to-date, focusing on the various assessment scales and markers for diagnosis and behavior in sepsis. Part of the review very clearly and accurately shows a historical overview of the related medical terminology and clearly emphasizes the need for its refinement. The candidate's diligence is commendable, all figures adapted from foreign sources are translated into Bulgarian, which is a plus for the dissertation work. There are several typographical errors in the analysis - e.g. in Table 2 - *physiolochni* should be *physiological* (p. 41).

Based on this detailed review, the dissertation author very precisely and clearly defines seven conclusions, the most important in my opinion are that there are no unified diagnostic criteria for sepsis in children, PEWS and scoring systems such as Phoenix Sepsis Score and PELOD-2 have the potential to improve early diagnosis and prognosis in sepsis, they are not routinely applied and are not adapted to all clinical contexts, there is uncertainty in the diagnostic reliability of the biomarkers used and there is a need to improve antibiotic policy.

In an attempt to find a partial solution to the above problems, Dr. Hadzhieva-Hristova is developing the present dissertation. To achieve the goal - To study the clinical profile and

outcome in children with septic and critical conditions in a pediatric intensive care unit and to evaluate the approaches to their early diagnosis, 5 specific and clear tasks have been formulated.

Materials and methods. The study is prospective and includes 80 children aged 7 days to 18 years, selected according to predefined criteria and hospitalized in the First Children's Clinic with DOIL of the University Hospital "St. Marina".. The study has permission from the ethics committee of MU-Varna attached to the dissertation work, as well as informed consents from the parents of the patients.

In methodological terms, for the purposes of her dissertation work, Dr. Hadzhieva-Hristova divides the patients into three groups - septic, critical and controls. The doctoral student indicates the research methods in great detail and clearly and accurately describes the statistical methods used. All analyses were performed with an appropriate statistical apparatus that allows for accurate analysis and derivation of reliable results and conclusions.

I have a critical remark that the discussion is relatively short as a separate chapter and for completeness I will analyze it together with the obtained results, where the doctoral student also has elements of discussion.

The results and discussion are well illustrated and thoroughly discussed and compared with international data. According to the known physiological characteristics of children under 5 years of age, the highest relative proportion of hospitalized patients in the age group 13–48 months is expected and confirmed in the dissertation work. The main pathology in septic patients in this group are respiratory system infections. One critical patient was diagnosed with acute laryngotracheitis (Table 4), which is a little surprising in the results. This child probably had another underlying pathology. In Table 4 it is a little unclear what the numbers in the subscript mean, I assume the number of patients and it would be nice to clarify this in the table legend. Additionally, the formula of potassium permanganate is KMnO_4 , not KnMnO_4 as written in the table and in the legend (probably a technical error). It is extremely important to emphasize the problem of intoxications, which are the leading cause of hospitalization in children with non-infectious SIRS. According to these results, it is possible to emphasize this problem more in the future in the training of emergency conditions in pediatrics.

Another result of the dissertation is the relatively high relative share of microbiologically confirmed infections (over 40%), which indicates the use of modern and timely diagnostic tests. In this regard, I recommend that the names of the pathogens in Fig. 8 be in italics, as they are correctly indicated in the text of the dissertation. Knowledge of the microbial spectrum of the causative agents of sepsis allows for the implementation of etiologically directed antibiotic therapy, which is more effective than the empirical approach and reduces the risk of antibiotic resistance.

The most important achievement of the study, in my opinion, is the comparative analysis of the point scales for assessing septic conditions in children. The results show that the Phoenix Sepsis Score outperforms the established PRISM III, PELOD-2 and pSOFA scales in terms of sensitivity and specificity for predicting the septic process and its associated complications. As well as the established model that the combined use of soluble mannose receptor (sMR), C-reactive protein and procalcitonin have the highest diagnostic efficiency for differentiating sepsis.

The combination of laboratory markers and methods can significantly improve the diagnosis and treatment of severe septic conditions in infancy and childhood, as well as potentially reduce associated mortality.

Dr. Hadzhieva-Hristova defines very accurately and clearly **six conclusions** of the work as follows:

- 1. Infections of the lower respiratory tract, gastrointestinal tract and nervous system were the leading causes of sepsis in the study group.*
- 2. A high relative proportion of microbiologically confirmed infections in septic conditions was demonstrated, with a predominance of bacterial causative agents. The most frequently documented pathogens were E. coli, S. pneumoniae, and S. aureus, which correlates with global data on the etiology of sepsis in children.*
- 3. Among the four clinical scales studied, the Phoenix Sepsis Score showed the best overall predictive value and the highest reliability in predicting complications in children with septic and critical conditions.*
- 4. The sMR and presepsin show considerable variability, highlighting the need for further validation in larger cohorts to confirm their diagnostic and prognostic value.*
- 5. procalcitonin and CRP are confirmed as the most reliable biomarkers for sepsis, while sMR and presepsin may be useful as additional markers to aid diagnosis.*
- 6. Simultaneous testing of sMR, CRP and procalcitonin is a useful diagnostic approach in the clinical evaluation of patients with sepsis.*

Dr. Hadjieva-Hristova also identifies six contributions from her dissertation, which I fully accept. In connection with the dissertation, Dr. Hadjieva-Hristova has made 2 full-text publications.

In conclusion, based on everything said, I believe that the proposed dissertation work of Dr. Adriana Dimitrova Hristova-Hadjieva " SEPTIC AND CRITICAL CONDITIONS IN CHILDREN ADMITTED TO THE INTENSIVE CARE UNIT: CLINICAL PROFILE, EARLY DIAGNOSIS, AND PROGNOSIS " meets the requirements of the Regalement for academic advancement in MU-Varna, by voting positively and recommending to the esteemed Scientific Jury to vote for the acquisition of the scientific degree "Doctor" in the field of higher education 7. "Health and Sports", in the professional field 7.1. "Medicine" and the scientific specialty "Pediatrics".

Заличено на основание чл. 5,
§1, б. „В“ от Регламент (ЕС)
2016/679

19.04.2025
Sofia

Prof. G. Petrova, MD, PhD