To the Chairman of the Scientific Jury,
Appointed by order 109-147/13.03.2025
Of the Rector of MU-Varna

REVIEW

by Prof. Rumyana Donkova Markovska-Davidkova, MD, PhD
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Regarding a dissertation on the topic: "Septic and critical conditions in children treated in the intensive care unit: clinical profile, early diagnosis and prognosis" by Dr. Adriana Dimitrova Hadzhieva-Hristova , submitted for the acquisition of the educational and scientific degree "Doctor", **in the doctoral program "Paediatrics"** in the field of higher education 7.0 Health and sports, professional field 7.1 Medicine

The submitted documents under the procedure have been prepared correctly, according with the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria and the rules for its implementation at the University of Varna.

Biography

Dr. Hadjieva obtained a Master's degree in Medicine in 2017. She has a specialty in Pediatrics since 2022. Since 2020 she has been a PhD student and assistant professor at the Department of Pediatrics, MU-Varna.

Relevance and significance of the selected scientific problem

Dr. Hadzhieva's dissertation is dedicated to an extremely actual problem for medical practice - septic conditions in childhood. Despite the extremely great progress of medicine in recent decades, blood infections continue to be among the significant problems related to public health and a leading cause of morbidity and mortality. This type of infections is also common in children and is among the leading causes of childhood mortality. Among the main causes of sepsis are microorganisms from the ESKAPE group (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter* spp), which are a paradigm for therapeutic response, mainly based on high levels of

resistance. Several studies have demonstrated a persistent trend towards a rapid increase in the incidence of infections caused by the ESKAPE group, and these infections are often associated with prolonged hospital stays, increased economic costs, and worse outcomes due to inadequate and delayed antimicrobial therapy due to antibiotic resistance of the causative agents. Carbapenem resistant Enterobacterales, *Acinetobacter baumannii, Pseudomonas aeruginosa*) are on the list of the World Health Organization (WHO), which are of "critical" priority for research and creation of new, effective antibiotics. Given this trend, early and accurate diagnosis of septic conditions in childhood is even more important, which would improve the choice of therapy and prognosis.

Structure of the dissertation

The PhD thesis is written on 169 pages, and is structured according to the generally accepted scheme: Abbreviations used - 2 pages; Introduction - 1 pages, Literature review - 51 pages, Aim and tasks - 1 page, Materials and methods - 14 pages, Results – 33 pages and Discussion - 18 pages, Conclusions and contributions - 4 pages. The dissertation work is illustrated with 15 tables and 35 figures and 10 applicationя. Two sixty nine references were used, of which 5 in Cyrillic and 264 in English.

Evaluation of the qualities of the literature review

The literature review is written correctly. The definitions of sepsis and septic shock in children are given in detail, as well as their development in recent years, the epidemiology of septic and critical conditions in children is studied, and data on morbidity and mortality are presented. The risk factors, etiological spectrum, pathophysiology and clinical manifestations of sepsis are examined. The various scales for assessing septic conditions in children, such as PRISM III, pSOFA, Phoenix Sepsis Score, etc., are presented in great detail. Dr. Hadzhieva has examined in detail the biochemical markers of inflammation, presenting both established markers such as CRP, procalcitonin and leukocytes, and innovative markers such as preserpin and the soluble mannose receptor sMR. Their advantages and disadvantages are correctly described. The review and appropriately cited applications describe the algorithms for the treatment of critical and septic conditions. The literature review ends with a conclusion, which logically justifies the need to develop a dissertation on such a topic.

Aim and tasks

The aim is clearly formulated, and the tasks (5 in total) correspond to the main aim and lead to its fulfillment.

Section "Materials and methods"

The section includes the methods used and a description of the material base, the study period (1 year and 8 months) and the included patients – 80 children from the University Hospital "St. Marina" - Varna. The study is prospective and the criteria for inclusion or exclusion in the study are clearly described. The methodology for admission and assessment of the condition of the patients, the laboratory indicators studied, as well as the scoring systems used and the methods for studying innovative biomarkers of inflammation are presented in detail. The microbiological part shows in detail the examination of blood culture, microbial identification and determination of sensitivity. The use of molecular genetic methods for identification makes a good impression. The statistical methods used are appropriate and determine the effectiveness and reliability in predicting the outcome for patients, as well as validate the reliability of the conclusions. The study has received approval from the Research Ethics Committee (REC) at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

Section "Results" and section "Discussion"

The "Results" section is structured into three subsections that cover the five tasks. The first subsection presented the etiological structure of diseases in children with septic and critical conditions hospitalized in the Department of Pediatrics. The doctoral student presents data for 53 children, 42 with septic and 11 with critical condition. There is a difference with the data from Materials and Methods, where 80 children included in the study are reported, probably from them the 53 children meeting the criteria were selected. Information is presented on gender and ethnicity, on the presence of underlying chronic diseases in 24.5% of the children, mainly those from the septic group. According to the data presented by the PhD student, 42 of the patients had an infectious etiology, with 27/50.9%/ of the children having respiratory system infections (mainly pneumonia), with microbiologically confirmed causative agents Streptococcus pneumoniae, Mycobacterium tuberculosis and SARS-CoV-2. Six children had gastrointestinal infections, with *Rotavirus, Salmonella* Group D and *Clostridioides difficile* among the identified pathogens, and five had nervous system infections. There were only a few children with skin and

soft tissue infections and nephritis. Among children with SIRS of non-infectious origin, the largest relative share was occupied by intoxications (n=4) and diseases related to endocrine and metabolic disorders - insulin-dependent diabetes mellitus with initial diabetic ketoacidosis (n=2). Respiratory and neurological complications were among the most common in the studied cohort of patients, 18.8% and 9.4%, respectively. In the "Discussion" section, Dr. Hadzhieva compares the obtained data with the world data and the data from the "Bulstar" system. It is interesting to note that in over 40% of the diseases of infectious genesis included in the dissertation work, a specific causative agent was identified, data corresponding to the world data. Accurate identification of the infectious agent is essential for adequate treatment and patient prognosis. Among the most frequently isolated etiological agents in septic patients are *Escherichia coli*, *Streptococcus pneumoniae* and *Staphylococcus aureus*, which is consistent with global trends. The second main subsection in the "Results" and "Discussion" sections includes an assessment of the prognostic value of different scales for assessing the condition, which covers the next two tasks. Timely identification of a child with sepsis among numerous febrile patients is a serious challenge. The results of the PhD thesis show that the PRISM III (Pediatric Risk of Mortality) scale has a better predictive value compared to the PELOD-2 (Pediatric Logistic Organ Dysfunction) in children with septic and critical conditions (62.3% vs 58.5%), but both scales showed a similar number of false negative cases in identifying patients with complications, which can delay therapy. Dr. Hadzhieva shows that over 50% of patients with real complications are missed by the pSOFA model (Pediatric Scale for Organ Failure Assessment), which indicates low sensitivity in identifying high-risk cases with sepsis. In contrast, the doctoral student finds that the PSS demonstrates better efficiency, managing to identify a significantly larger proportion of patients with complications. The doctoral student compares the obtained data with the world data, according to her data, the PRISM III system gives a similar prognostic value to the world data (AUC 0.701), which makes it a reliable predictor in different populations, although the results show moderate discriminatory ability. pSOFA has high specificity (over 80%), which is useful in identifying patients without complications, but the low sensitivity indicates that the model misses a significant proportion of patients with real developed organ dysfunction. As a result of the dissertation work, Dr. Hadzhieva makes a main conclusion that the Phoenix Sepsis Score is the most effective prognostic scale for identifying septic patients with complications with sensitivity values of 80.0% and AUC 0.736. The third subsection of

"Results" and "Discussion" corresponds to the last two tasks, the results obtained for established and innovative markers of inflammation are considered. Dr. Hadzhieva establishes extremely high diagnostic efficiency for Procalcitonin and leukocytes (100%). Lower sensitivity is demonstrated for sMR (80%), presepsin (75%) and CRP (73%). The doctoral student reports high specificity (≥ 88%) for all biomarkers, with the lowest frequency of false positive results recorded for sMR (96%), procalcitonin (96%) and leukocytes (93%). The highest PPV is reported for procalcitonin (100%) and sMR (89%). Dr. Hadzhieva concludes that 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.

As a result of the presented work, Dr. Hadzhieva formulated 6 main conclusions that meet the aim and objectives.

Evaluation of the contributions of the PhD thesis

From the results obtained and conclusions drawn, Dr. Hadzhieva formulates 6 contributions, which I fully accept. The most important contributions are: - Among the four clinical scales studied, the Phoenix Sepsis Score shows the best overall predictive value and the highest reliability in predicting complications in children with septic and critical conditions. - Procalcitonin and CRP are confirmed as the most reliable biomarkers for sepsis, while sMR and presepsin may be useful as additional markers supporting the diagnosis. - Simultaneous examination of sMR, CRP and procalcitonin is a useful diagnostic approach in the clinical evaluation of patients with sepsis.

Scientific indicators

Dr. Hadzhieva has submitted 2 full-text publications in non-refereed journals in connection with her dissertation. A separation protocol has been submitted for one of the publications, and thus the total number of points for the publications is 31.5, which meets the national requirements and those of MU-Varna. It is particularly impressive that she is the first author in all of them.

Abstract

The attached abstract critically presents the dissertation work and its results, contributions and conclusions. The requirements of the regulations have been met.

In conclusion, the presented PhD thesis by Dr. Hadzhieva in terms of structure, content and volume meets the criteria in the ZRASRB and the Regulations of MU-Varna for acquiring

the educational and scientific degree "doctor". The topic is actual, the selected methods are appropriate, Dr. Hadzhieva shows thoroughness and precision in presentation, statistical processing and analysis of the results. I am pleased to give my positive assessment and recommend to the members of the Scientific Jury to vote for awarding the educational and scientific degree "doctor" in the scientific specialty "Pediatrics" in the field of higher education 7.1 Health and Sports, professional field 7.1 Medicine to Dr. Adriana Dimitrova Hadzhieva-Hristova.

28.04.2025г. **Prepared the review:**

/ Prof. Rumyana Donkova Markovska-Davidkova, MD, PhD /