To the Chair of the Scientific Committee, as designated by Order No. R 2970/12.10.2023
by the Rector of the Medical University of Plovdiv

REVIEW

By **Prof. Dr. Penka Ilieva Perenovska, M.D., PhD**
Pediatrics Clinic, University Multiprofile Hospital for Active Treatment "Alexandrovska" EAD - Sofia...

of a dissertation for the award of the educational and scientific degree of 'Doctor'
in the professional field of Medicine, Specialization: Pediatrics 03.01.50, doctoral program: Pediatrics

Author: Dr. Boris Petrov Angelov

Type of Doctorate: regular/independent study
Department: Assistant at the Faculty of Organizational Sciences and Health Care Management, University "Prof. Dr. Assen Zlatarov" - Burgas.
Doctoral Student at the Department of Pediatrics and Medical Genetics "Prof. Ivan Andreev," Medical University, Faculty of Medicine - Plovdiv

Topic: "Therapeutic Possibilities in Acute Bronchiolitis in Children Under 2 Years of Age"

Academic Advisors: Prof. Dr. Miroslava Bosheva, M.D., PhD and Assoc. Prof. Dr. Delyan Penev Delev, M.D., PhD, Medical University – Plovdiv

General Presentation of the Procedure and the Doctoral Candidate

The presented set of materials in electronic format is in accordance with Article 70(1) of Part I, "Acquisition of the Educational and Scientific Degree of DOCTOR" and the scientific degree of "DOCTOR OF SCIENCES" at the Medical University of Plovdiv; Regulation of the Medical University of Plovdiv dated January 28, 2021, and includes the following documents:

- A letter to the Rector of the Medical University of Plovdiv requesting the initiation of the dissertation defense procedure.
- Curriculum vitae in European format with the doctoral candidate's signature.
- Notarized copy of the diploma for higher education.
- Orders related to enrollment in the doctoral program, interruptions in education (due to maternity), and resumption of education, as well as orders for dismissal with the right to defend.

- Orders for conducting an examination from the individual study plan and the corresponding protocol for passing the examination or doctoral minimum in the specialty.
- Protocol from the departmental council meeting for the preliminary discussion of the dissertation and decisions made regarding the initiation of the procedure and the composition of the scientific jury.
- The doctoral dissertation.
- An abstract.
- A list of scientific publications on the subject of the dissertation.
- Copies of the scientific publications.
- A list of participation in scientific forums.
- A declaration of the authenticity and accuracy of the attached documents.

The doctoral candidate has submitted a total of 4 publications related to the dissertation, with publications in which Dr. Angelov is the first author in 3 of them. Additionally, the candidate has participated in 2 scientific forums. The submitted set of materials and documents by Dr. Angelov complies with the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria and its implementing regulations. It includes all the required documents according to the established rules. The research work comprises 115 pages, 64 figures, and 12 tables. The sections are structured in accordance with the rules: introduction, literature review, objectives, materials and methods, original research, discussion, conclusions, contributions, and bibliography. The individual sections are well-balanced. The bibliography includes 253 sources, 9 of which are in Cyrillic, and ¼ of them are from the last 10 years. The literary sources are sufficient for the dissertation and demonstrate a good understanding of the subject. The abstract reflects the main data presented in the dissertation, which is written in a clear, competent, and in-depth manner.

2. Brief Biographical Information about the Doctoral Candidate

Dr. Boris Angelov graduated from the Medical University of Varna in 1995.
He worked as a physician at the Central Emergency in Burgas for 2 years.
Since 1997, he has been specializing in pediatrics at the Municipal Hospital for Active Treatment - Burgas, subsequently becoming a pediatrician in the hospital's first pediatric department, which he has been heading since 2013.
In 2020, after a competition, he was selected as an assistant professor in pediatrics at the Faculty of Medicine at the University "Prof. Dr. Asen Zlatarov" in Burgas, where he also trains medical specialists.
He is a member of the Bulgarian Doctors Society and the Bulgarian Pediatric Association. He is proficient in English and Russian.
In 2022, he was enrolled as a doctoral candidate for independent study at the Department of Pediatrics and Medical Genetics at the Medical University of Plovdiv.

3. Relevance of the Topic and Appropriateness of the Objectives and Tasks

I find the topic "Therapeutic Possibilities in Acute Bronchiolitis in Children Under 2 Years of Age" to be contemporary, even though pediatricians have been familiar with the disease for

80 years. Bronchiolitis, most commonly caused by Respiratory Syncytial Virus, is a seasonal infection characterized by global epidemics every one or two years. Its frequency reaches up to 162 per 1000, with a male-to-female ratio of 1.5:1. Approximately 80% of those affected are under the age of 1, with the peak occurring between 2 and 6 months of age. More than 40% of those affected require hospitalization for at least 24 hours. Despite the high prevalence of the disease, pharmacological therapy is still debated. The question of defining the disease remains unanswered, as does the question of developing a vaccine against RSV.

Acute bronchiolitis is among the most common respiratory diseases, especially in children under the age of 2, and it should be well understood by every pediatrician. For these reasons, the topic of the doctoral thesis is interesting and relevant. The literature review presents the characteristics of the disease, diagnostic methods, and contemporary therapeutic and preventive approaches. Risk factors for more severe cases have been clearly outlined, but the methods for determining the severity of the disease are still an open question. Over the years, the use of epinephrine, inhalation therapy with Ventolin, the need for antibiotics, and corticosteroids have been proposed and contested. Recently, the literature has discussed the use of hypertonic saline solution 3% in the treatment of acute bronchiolitis, especially in cases of mild and moderate severity, both in hospitalized patients and in outpatient settings. Bronchodilators are the most controversial therapeutic intervention, particularly in the age group under 2 years. The influence of widely used inhaled budesonide on the clinical course of acute bronchiolitis, depending on the child's age, remains unexplored.

On August 9, 2021, the NICE (National Institute for Health and Care Excellence) published an instruction on Bronchiolitis in children: diagnosis and management, and on October 10, 2021, the AAP (American Academy of Pediatrics) published a protocol titled "Clinical Practice Guideline: The Diagnosis, Management, and Prevention of Bronchiolitis (0-23 months)," which does not recommend pharmacological treatment. There have been few studies with a small number of patients that have focused on a precise analysis of the clinical picture of the disease in children, especially in those under 2 years of age, and considering objective indicators. Studies on specific age groups in children under 2 years are lacking. There is still no clear strategy and precise algorithm for the treatment of this often life-threatening condition. In view of the above, Dr. Angelov's doctoral thesis topic is interesting, relevant, and related to practical aspects of a pediatrician's approach to children with acute bronchiolitis.

4. Understanding of the Problem

The doctoral dissertation is evidence that Dr. Boris Angelov has a deep understanding of the problem. The doctoral candidate presents a comprehensive literature review that provides a clear picture of his knowledge of the issue, as well as his ability to interpret the available literature. The literature review is contemporary, in-depth, and written in an academic style. The conclusions and unresolved and debatable questions mentioned at the end of the review provide sufficient grounds for the doctoral candidate to formulate clear and precise OBJECTIVE OF THE STUDY: Development of a therapeutic strategy for acute bronchiolitis in children under 2 years of age.

To achieve this objective, the following TASKS have been defined:

1. Analyze the socio-demographic characteristics, clinical profiles of patients, and their complications.
2. Analyze the results of the treatment administered according to age groups: 0-3 months, 4-6 months, 7-12 months, 13-24 months, and derive a therapy that influences vital signs in acute bronchiolitis in children aged 0-24 months, depending on age: 0-3 months, 4-6 months, 7-12 months, 13-24 months.
3. Analyze the effects of administered pharmacological treatment according to age: 0-3 months, 4-6 months, 7-12 months, 13-24 months, with a focus on side effects.
4. Develop a behavior algorithm for children with acute bronchiolitis under 2 years of age, depending on their age.

5. Research Methodology

The proposed research design has been wisely chosen. The technical unit selected is the 1st Pediatric Department of UMBAL Burgas, AD. The logical unit of observation is each child hospitalized with a diagnosis of acute bronchiolitis for the first time, aged from 0 to 24 months, in the 1st Pediatric Department of UMBAL Burgas, AD from June 2017 to December 2019. The study covers 90 patients, divided into 4 age groups: 0-3 months, 4-6 months, 7-12 months, and 13-24 months, on whom 817 therapeutic interventions were performed. Inclusion and exclusion criteria have been specified. The material is sufficient for obtaining reliable results and drawing specific conclusions. The research setup, stages of the study, and research methods used are well-described. The methods are appropriate for the topic. The effects of 5 therapeutic possibilities have been evaluated: parenteral methylprednisolone, inhalation with Ventolin, inhalation with pulmicort, methylprednisolone + inhalation with Ventolin, and inhalation with pulmicort followed by inhalation with Ventolin. The clinical symptoms of the disease, respiratory and heart rate, the need for oxygen therapy, and the dynamics of these indicators have been tracked. I appreciate the effort put in by Dr. Angelov in collecting and processing the material for the study.

The processing of the collected primary information is done using well-selected statistical methods

6. Description and Evaluation of the Doctoral Thesis

Following the introduction, the doctoral candidate presents a comprehensive literature review that demonstrates his in-depth knowledge of the problem. The results of the study are presented in 64 figures and 12 tables, which are both sufficient in number and well-organized. After presenting the results of each task, there is a discussion and drawing of conclusions. Regarding *Task 1:* The author analyzes the average age and age distribution of the patients, their distribution by gender, the duration of the disease before the development of bronchiolitis, and the frequency of observed symptoms. After analyzing the results, Dr. Angelov concludes that the course of the disease in Bulgaria is not significantly different from that described in the literature, except for a lower percentage of complications such as otitis and diarrhea. Data from the statistical analysis of vital signs - heart rate, respiratory rate, oxygen saturation, and blood pressure before therapeutic intervention, at 30 and 60 minutes after

therapy - are presented. The discussion of the results of *Task 2* concludes with four important findings. A favorable effect of inhaled Ventolin becomes evident after 6 months of age in isolated cases and nearly all children after 1 year. Based on the results, Dr. Angelov establishes that in all examined age groups, the use of pulmicort, either alone or in combination with inhaled Ventolin, does not reduce tachypnea and does not increase oxygen saturation. According to the results, the use of methylprednisolone has a therapeutic effect, primarily in children up to 6 months of age. To address *Task 3*, an analysis of the effects of pharmacological treatment was performed, focusing on heart rate. Summarizing the results from the *four tasks*, Dr. Angelov offers specific conclusions, some of which are of significant importance for clinical practice: chest X-rays of the lung fields should be undertaken in children with acute bronchiolitis based on the indications; antibiotic treatment should begin in the case of worsening of the condition, prematurity, and comorbidity of the patient. A proposal is made to eliminate $SpO2 \leq 90\%$ as a condition for hospitalization for children over 1 year. In conclusion, Dr. Angelov presents an algorithm for the management of children with acute bronchiolitis under the age of 2. The recommendations for the drugs used, their dosage, and application intervals are clear and easy to implement. The doctoral candidate has taken into account critical feedback and has presented the algorithm graphically in a colorful appendix.

7 - Contributions and Significance of the Research for Science and Practice:

1. An innovative study on children up to 2 years of age with acute bronchiolitis, with a focus on the clinical course, complications, and therapeutic possibilities, has been conducted in the country.
2. Effective therapeutic options have been derived based on the analysis of vital indicators of patients with acute bronchiolitis, depending on the age groups of patients: 0-3 months, 4-6 months, 7-12 months, and 13-24 months.
3. A protocol/algorithm for managing children with acute bronchiolitis has been proposed, taking into account their age.

8. Evaluation of Publications in the Dissertation Work:

In connection with the dissertation work, four publications have been presented. Two of these publications are in foreign-language journals, and there have been two participations in scientific forums - one international congress and one practical conference, which meet the minimum requirements for the "Doctor" degree, as per the regulations of the University of Plovdiv.

9. Personal Involvement of the Doctoral Candidate:

The dissertation work is the sole work of the doctoral candidate. I believe that the academic advisors have been well chosen - highly qualified individuals with extensive scientific, clinical, and teaching experience.

10. Abstract:

The presented abstract meets the requirements and reflects the main data from the dissertation work.

11. Critical Remarks and Recommendations:

1. The author could condense the literature review in all of its parts.
2. The bibliographic reference would benefit from citing more Bulgarian authors.
3. I recommend that the doctoral candidate increases the number of publications and their participation in regional and national scientific forums, including presenting the results and conclusions of their dissertation work.

CONCLUSION

Dr. Boris Angelov's dissertation work contains scientific, scientifically applicable, and practical results that represent an original contribution to science and meet the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria, the Implementation Regulation of the law, and the relevant Regulation of the University of Plovdiv. The materials and dissertation results presented fully comply with the specific requirements of the University of Plovdiv.

The dissertation work demonstrates that the doctoral candidate, Dr. Boris Angelov, possesses in-depth theoretical knowledge and professional skills in the scientific field of pediatrics, showcasing qualities and abilities for independent scientific research. Dr. Angelov's dissertation work is logically written and contains results from which correct conclusions have been drawn.

Based on the above, I confidently provide my positive evaluation for the conducted research presented in the reviewed dissertation work, abstract, achieved results, and contributions. I recommend to the esteemed academic jury to confer the educational and scientific degree of 'Doctor' upon Dr. Boris Petrov Angelov in the field of pediatrics.

October 24, 2023

Reviewer:

Prof. Penka Perenovska, MD, Ph.D.