

STATEMENT OF OPINION

by Prof. Valeria Ignatova Kaleva, MD, PhD

on a Dissertation for the award of scientific degree "Doctor of Science"
in the Field of higher education 7. Healthcare and sports,
Professional direction 7.1. Medicine, Scientific specialty "Microbiology"

to Prof. Temenuga Zhekova Stoeva, MD, PhD

Department of Microbiology and Virology at MU - Varna

Thesis topic: Antimicrobial resistance of the most common causative agents of bacteremia and
the associated lethality

By order № P-109-388/28.08.2023 of the Rector of MU "Prof. Dr. Paraskev Stoyanov" Varna I am included in the scientific jury and after the decision of its first meeting on 04.09.2023 I am appointed to prepare an opinion for the above dissertation. The submitted documents comply with the Regulations for the Development of the Academic Staff of MU - Varna.

1. Biographical data and professional development

Prof. Temenuga Stoeva, MD, PhD graduated from the English Language School, Dobrich and with professional qualification "English teacher V-VII grade" in 1988. In 1994 she obtained a Master's degree in Medicine with excellent grades at the Medical University - Varna. She started her career in 1995 as a pediatrician in Ruse. Since 1998 she has been working as a paediatrician at the City Hospital - Varna, and since 1999 as a microbiologist at the Laboratory of Microbiology and Virology, RHI - Varna. After successfully passing the exams, she was assistant (2004-2006), senior assistant (2006-2009) and chief assistant (2009-2012) at the Laboratory of Microbiology of the University Hospital "St. Marina" - Varna and MU - Varna. In 2006 she obtained a medical specialty in Microbiology and in 2018 she graduated with a Master's degree in Health Management.

After successful defense of her dissertation thesis entitled: "Microbiological and molecular genetic studies on epidemiology and resistance to antimicrobial agents in clinical isolates of *Acinetobacter baumannii*", in 2009 she received her PhD in the scientific specialty of Microbiology. Since 2012 she has been an associate professor, and since 2018 she has held the academic position of "professor" in the specialty of "Microbiology" at the Department of Microbiology and Virology at MU - Varna. Since 2014 she is the Head of the Microbiology Laboratory at the University Hospital "St. Marina", Varna and since 2016 - the Head of the Department of Microbiology and Virology at Medical University, Varna.

Prof. Stoeva has participated in a number of trainings and postgraduate courses in microbiology and immunology in Bulgaria, Germany and Greece. Her research

interests are mainly in the field of modern molecular genetic methods for microbiological diagnosis, mechanisms of microbial resistance and surveillance of antibiotic resistance, healthcare associated infections and infections in immunocompromised, including transplanted patients. The majority of her scientific publications are in these areas, including the present thesis submitted for review.

Since 2011 prof. Stoeva has participated in 12 research projects - one international and 11 university projects under the Science Fund of MU - Varna. She is a scientific supervisor of 6 PhD students, four of them with successful defense. At MU - Varna she gives lectures in Bulgarian and English to students of 9 specialties, trainee doctors and postgraduate students. She is a member of the Expert Council on Microbiology at the Ministry of Health and of the Bulgarian and European Association of Microbiology and Infectious Diseases. She is fluent in English.

Prof. Stoeva is a specialist of national importance in the field of microbiology and infectious diseases in Bulgaria and a respected head of the diagnostic and academic structures she guides at the University Hospital "St. Marina", Varna. She has an established reputation in the Bulgarian and international scientific community as a scientist with capabilities based on excellent theoretical and practical training.

2. Relevance of the problem

Antibiotic resistance in bacterial pathogens is a major challenge worldwide, leading to high morbidity and mortality in clinical settings. The multi-resistant gram-positive and negative bacteria have led to infections that are difficult to treat and even incurable with conventional antimicrobials. Because early microbiological identification and antimicrobial susceptibility testing is lacking in many healthcare settings for patients with bacteremia and other serious infections, the empirical use of broad-spectrum antibiotics has been widely advocated and often unnecessary. This ubiquitous practice has caused a dramatic increase in antimicrobial resistance and, in an conditions of inadequate infectious disease control, has led to the widespread spread of resistant strains in both hospital settings and the environment. This problem is particularly relevant to oncology, oncohematology and transplant hospital settings due to the ever-increasing number of patients with malignancies associated with compromised immunity and high risk of lethality associated with infectious complications.

In the context of these alarming statistics, bloodstream infections caused by resistant microorganisms represent an extremely serious medical problem in search of a solution. The availability of up-to-date epidemiological data on antimicrobial resistance in common bacterial pathogens is of great importance and utility not only in the development and updating of empirical treatment strategies, but also in the establishment of effective antimicrobial infection prevention and control programs in hospital settings.

The present thesis is the first systematic study in Bulgaria on antibiotic resistance and associated mortality in immunocompromised and non-immunocompromised patients with bacteremia.

Comment: I appreciate the topic chosen by the dissertant as very topical.

3. Structure and content of the dissertation

The dissertation is 234 standard pages (excluding the bibliography and appendices). It is properly structured, containing the following parts: introduction; literature review; aim and objectives; material and methods; results and discussion; conclusions; contributions; list of publications and contributions to scientific forums related to the thesis; bibliography and appendices. The obtained data and the analyses are illustrated with 36 tables and 27 figures. The bibliographic reference contains 655 references, of which 5 in Bulgarian and 650 in Latin.

The introduction summarizes the scientific data and clearly motivates the need for research in the field of the dissertation.

The literature review is comprehensive, written in proper Bulgarian language and easy to understand narrative style. It gives a thorough analysis of the problem under consideration in the light of the latest research worldwide. Its content is entirely focused on the aim and objectives of the dissertation. Clearly and convincingly presents the need for local studies of antibiotic resistance in patients with bloodstream infection, which appears to be the main motive for the development of the dissertation.

Comment: The literature review demonstrates a very thorough knowledge and logical competence of the dissertant in the area under study.

The aim is clearly stated: to perform a microbiological and epidemiological study on the antibiotic resistance of the most common causative agents of bacteremia over a 10-year period and the lethality associated with them. From this, 5 specific and logical tasks directly related to the achievement of the stated objective follow logically and reasonably.

The Materials and Methods section is presented in 15 pages. The study has a retrospective descriptive design, analyzing the incidence of clinically significant bacteremias, their microbial causative agents, and risk factors for death in patients treated at St. Marina University Hospital for the period 1011 - 2020. Separately, all clinically significant episodes of bacteremia in patients with oncohematological diseases were studied for the period 2010-2020. In order to evaluate antibiotic resistance as a risk factor for lethality, a comparative analysis of 30-day lethality according to the type of bacterial causative agents - antibiotic-resistant and non-antibiotic-resistant - was performed in 798 patients. All definitions of the specific terminology used related to bloodstream infections and the microbiological and other methods used to identify them are presented in the section.

A wide range of reliable and state-of-the-art statistical analyses have been applied to process the data, ensuring the reliability of the results obtained and the conclusions drawn.

Comments: The material and methods used are described in detail and are adequate to the aim and objectives. They are presented in a way that allows the study to be extended and/or replicated by other independent researchers.

Results are presented in detail and appropriately illustrated in tables and figures.

During the study period, 27 650 bloodculture sets obtained from 15 602 hospitalised patients were examined. A total of 2727 microbial isolates associated with clinically significant episodes of bacteremia and fungaemia were isolated and identified in 2715 patients (17.4%). The relative proportion of positive bloodcultures interpreted as clinically significant was 9.9%.

The etiologic spectrum and microbiologic characteristics of bloodstream infections in hospitalized patients, particularly in patients with oncohematologic diseases, antibiotic resistance in the most common causative organisms of bacteremia, and 30-day lethality in patients with documented antibiotic-resistant and nonantibiotic-resistant organisms are presented in a consistent descriptive, tabular, and graphic format. The results were evaluated and interpreted epidemiologically and clinically, and are compared and discussed in detail with data available in the medical literature.

Comment: The results obtained are described in detail and in accordance with the objectives. The discussion is thorough. Prof. Stoeva demonstrates an impressive awareness and competence on the topic of the dissertation, which enable her to make an adequate comparison of her results with the published data in the literature.

The dissertation presents 16 conclusions that correctly summarize the main aspects of the dissertation and the results obtained.

The contributions presented stem directly from the conclusions drawn and are formulated in three categories: contributions of an original nature, contributions of a confirmatory nature and contributions of a scientifically applied nature. As main contributions I evaluate: (1) detailed analyses of the etiological spectrum of bacteremias and antibiotic resistance of ESKAPEEc pathogens in patients with oncohematological diseases, allowing to define recommendations for empirical antibiotic treatment in cases of febrile neutropenia or suspected infectious complications; (2) the study of 30-day lethality and associated risk factors for fatal outcome in bloodstream infections; and (3) the contribution to the expansion of available data on antibiotic resistance in Bulgaria and worldwide, enabling the establishment of policies for its containment and control at local and national level.

Comment: I accept the formulated contributions and assess them as extremely useful for medical science and practice and fully sufficient for the award of the degree of Doctor of Sciences.

In connection with the dissertation 18 articles have been submitted - 7 in Bulgarian and 11 in English. Twelve of them have been published in refereed and indexed in world-known scientific databases, 9 of them with impact factor. In 7 of the articles prof. Stoeva is the first author.

From the attached Academic reference from the library of MU - Varna it is evident that prof. Stoeva meets all the scientific metrics according to the requirements of the LDASRB for the scientific degree "Doctor of Science". The number of citations is 3671 (3408 after obtaining the AP "professor"), h-index - 12.

The abstract is written in 77 pages and faithfully and accurately presents the thesis.

4. Conclusion

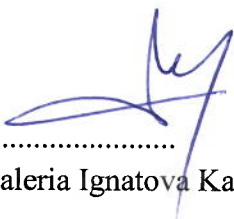
The dissertation of prof. Temenuga Stoeva is dedicated to an extremely topical medical problem. In recent years, antibiotic resistance has been recognized as one of the most important causes of death, and any local study in epidemiological and microbiological aspects is appreciated by the scientific community as an essential contribution to enrich knowledge on a global scale.

The volume of material studied and the analysis of the results obtained are impressive. I recommend that the formulated conclusions and contributions be used by clinicians and infection control professionals to create and/or update therapeutic algorithms and programs for the prevention of infections caused by multidrug-resistant bacteria and life-threatening infectious complications at local and national levels.

The dissertation fully meets the requirements for the degree of Doctor of Science as stipulated in the Law on the Development of the Academic Staff of Republic of Bulgaria and the Regulations for the Development of the Academic Staff of Medical University - Varna.

I confidently give my positive evaluation and recommend the esteemed members of the scientific jury to award to Prof. Dr. Temenuga Zhekova Stoeva, PhD, the scientific degree of Doctor of Sciences in the scientific specialty "Microbiology".

11.10.2023
Varna


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/Prof. Valeria Ignatova Kaleva, MD, PhD/

