

To
the members of the Scientific Jury,
appointed by Order № P-109-469 / 05 Dec 2024
of the Rector of MU-Varna “Prof. Paraskev Stoyanov”, Varna

Statement of Opinion

by Assoc. Prof. Ivanka Gergova, MD, PhD

Head of Microbiology Laboratory at the Department of “Microbiology, Virology, Clinical
Laboratory and Immunology” of Military Medical Academy – Sofia,
an external member of the Scientific Jury

Subject: procedure for the defence of the dissertation work for awarding an educational and scientific degree "Doctor".

Field of higher education: 4. Natural Sciences, Mathematics and Informatics.

Professional field: 4.3. Biological Sciences.

Scientific speciality: ‘Microbiology’.

PhD program ‘Microbiology’.

Author: Viktoriya Snezhanova Snegarova-Toneva.

Thesis title: ‘Evaluation of the HB&L automated system for rapid diagnostics of urinary tract infections’.

Scientific adviser: Prof. Temenuga Stoeva, MD, PhD, DMs.

I. GENERAL PRESENTATION OF THE PROCEDURE

1. Procedure

The current opinion was prepared in accordance with Order № P-109-469 / 10 Dec 2024 by the Rector of MU-Varna “Prof. Paraskev Stoyanov”, Varna and with the decisions of the Scientific Jury appointed for the purpose. I was chosen as an external member of the Scientific Jury.

I declare I have no conflict of interest within the meaning of art. 4, para 5 of Law on Development of the Academic Staff of the Republic of Bulgaria. I have no publications in common with Dr. Viktoriya Snegarova.

The documents submitted under the procedure fully comply with the requirements of Law on Development of the Academic Staff of the Republic of Bulgaria (LDASRB) and the Implementing Regulations of the LDASRB of MU-Varna, for awarding the educational and scientific degree "Doctor" at MU-Varna.

2. Brief biographical and professional data for the author of the dissertation

In 2007 Dr. Viktoriya Snegarova graduated as Master of Medicine at MU-Varna.

She is a specialist in Clinical Microbiology (2014) and in Clinical Virology (2022). In 2013 she acquired a Master's degree in Health Management.

During the period from 2010 to 2022, Dr. Snegarova was an assistant professor at the Department of Microbiology and Virology, MU-Varna, and since 2013, she has been working as a clinical microbiologist at SMDL Laborexpress 2000, Varna, Bulgaria. She has been working in the fields of medical research and medical diagnostics since 2000.

She is fluent in English and French.

II. RELEVANCE OF THE TOPIC

Urinary tract infections (UTIs) are a significant health problem and the rapid establishment of a correct etiological diagnosis is a key point in their adequate therapeutic treatment.

Commonly applied first-line screening methods do not species-specifically identify the uropathogen and its resistance profile. From an epidemiological point of view, correct monitoring of the microbiological profile of uropathogens, both in terms of etiological structure and resistance to antimicrobials, cannot be performed. The accumulation of epidemiological data is the basis for making rational decisions when initiating antimicrobial therapy and for ensuring prevention and control of these infections.

Standard uroculture is the "gold standard" in the diagnostics of urinary tract infections. However, it is a relatively slow diagnostic method. For uncomplicated UTIs, the application of modern diagnostic platforms is sufficiently informative and improves the speed and accuracy of identification. In addition, rapid determination of antimicrobial susceptibility optimizes the therapy administered and is an element of prevention in the development of antimicrobial resistance.

The successful implementation and application of these advanced diagnostic methods has the potential to improve patient care and public health.

In recent years, no in-depth microbiological studies on the etiological spectrum and microbial resistance of the causative agents of urinary tract infections in outpatients have been conducted in Bulgaria, as well as on the clinical feasibility of new methods for rapid diagnosis of urinary tract infections. Clarifying the advantages and limitations of these modern methods would contribute to the improvement the quality of patient care and disease outcome, while promoting the appropriate use of antimicrobial drugs in the community.

In this aspect, I believe that the topic developed by Dr. Snegarova is relevant, for the health care system in the country, both in theoretical and applied aspects, mainly in outpatient practice.

III. STRUCTURE OF THE DISSERTATION WORK

The doctoral thesis contains 134 standard pages (including the appendices) and is optimally illustrated with eight figures, 19 tables and one appendix.

The title accurately represents the essence of the developed theme.

The dissertation is structured properly and includes a title page, abbreviations used, a table of contents, an introduction, a literature review, a clearly stated purpose and objectives, materials and methods, results and discussion, well-defined conclusions and scientific contributions, a list of publications and participation in scientific events related to the thesis, and bibliography.

The bibliographic reference contains 285 literature sources, of which 5 in Cyrillic and 280 in Latin; 162 of the sources presented (57%) are from the last 5 years, and 222 of the sources (78%) are from the last 10 years.

The Abstract is presented in a synthesized form, in 76 pages and corresponds adequately to the content of the dissertation work, and all the requirements of LDASRB were observed during its preparation.

IV. ADEQUACY OF THE FORMULATED PURPOSE AND OBJECTIVES

Dr. Snegarova aims to evaluate the HB&L Uroquattro automated system for rapid diagnostics of urinary tract infections.

The purpose is precisely and clearly formulated and the six objectives set logically result from it and fully represent the thesis topic.

V. GENERAL CHARACTERISTICS AND EVALUATION OF THE DISSERTATION

1. Literature review

The literature review is presented in a volume of 35 pages, and is well structured, balanced, informative, containing definitions and facts. Based on an impressive literature reference, the review is written competently and at a high scientific level.

It presents a comprehensive overview of the taxonomy, incidence and epidemiology of UTIs. Diagnostic and screening methods are described in detail. Both classical and modern methods, including molecular biology, are thoroughly reviewed. Furthermore, attention is focused on the determination of residual antimicrobial activity. The current status of antimicrobial drug resistance in the most common uropathogens is also reviewed.

The literature review is comprehensive and summarizes the contemporary status of the problem.

2. Materials and methods

The materials and methods are presented in detail in 15 pages.

The research on this topic is based on data from prospectively conducted studies in 842 outpatients, divided into several target groups: patients with clinical and ultrasonographic evidence of acute UTIs referred by a specialist; gravid women with a clinical picture of cystitis and probable bacteriuria; children with congenital abnormalities of the urinary system; outpatients with chronic diseases of the urinary tract; post-renal transplant patients undergoing periodic urine monitoring for bacterial growth; nursing home and hospice patients; and patients with indwelling catheters and nephrostomies.

The study design is described in detail, inclusion and exclusion criteria for patients and sample selection are formulated, and necessary definitions are introduced. For the purpose of the developed topic, a survey method was applied (Appendix containing the developed Questionnaire is presented). The sampling was completed over a 7-month period (October 2020 - April 2021).

The screening for microbial growth of urine samples (HB&L), routine culture of urocultures, methods for identification and determination of antimicrobial drug susceptibility, determination of residual antibiotic activity in urine samples, and statistical methods used to evaluate the results obtained are described in detail and with high precision.

The manner of presenting the forementioned techniques demonstrates the doctoral student's excellent methodological preparation.

A total of 1,600 urine samples were tested, 352 of which were clinically significant, non-duplicating microbial isolates from the samples of 352 patients.

3. Results and discussion

The results obtained from the conducted own research are reported and discussed within 46 pages and are well-illustrated with relevant tables and figures. They are highly informative and are presented in sections according to the logical sequence of the assigned objectives.

Dr. Snegarova analyzed the main demographic characteristics of the patients included in the studies on the topic, the etiological spectrum and the prevalence of the common uropathogens, according to the gender of the patients and the target group they belong to. The results obtained are discussed analytically and compared with national and international data (Europe, China and USA), separately for each of the target patient groups.

The comparative assessment of the accuracy of HB&L for the purpose of diagnostics of urinary tract infections is based on the analysis of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy (Accuracy) of the system. Testing of 1,600 urine samples revealed 97.4% sensitivity and 100% specificity, PPV and NPV of 100% and 99.3% for the automatic HB&L screening method. The results demonstrated the excellent performance of the HB&L system for rapid detection of microbial growth and optimal correlation with the results obtained with the classical culture method. Dr. Snegarova critically evaluates the benefits and limitations of the applied methods, and analyzes all possible sources of error.

The distribution of the frequency of resistance of isolates to the main groups of antimicrobials used for the treatment of urinary tract infections and the underlying resistance phenotypes of Gram-negative and Gram-positive bacteria were determined.

Dr. Snegarova established optimal categorical correlation (94.8%) between HB&L and standard disc diffusion testing and analyzed the frequency of confirmed major errors in the determination of susceptibility to individual antimicrobials, as well as the time to finalize the test.

Summarizing the findings of the performed study, Dr. Snegarova proposes a laboratory algorithm including urine sample screening, microscopy and antibiotic susceptibility testing directly from the clinical sample, the application of which dramatically shortens the diagnostic process by 24-48 hours. The rapidity of the HB&L AST method and its optimal correlation with the standard disc diffusion method confirm the large potential of the HB&L system for widespread application in routine laboratory practice.

Dr. Snegarova compared the results of antimicrobial drug susceptibility testing by the automated HB&L directly from a positive urine sample with those obtained by VITEK 2 testing, also directly from a positive sample, and found similar results of category agreement of the two approaches compared to the reference method.

In addition, the dissertant demonstrates that with the combined use of HB&L and VITEK 2, both rapid microbial identification and antibiotic susceptibility determination can be achieved within the day of receipt of clinical specimens for analysis in the laboratory by direct inoculation from a positive urine sample.

The determination of residual antibiotic activity (RAA) in urine samples is particularly important for the correct interpretation of microbiological test reports in cases where the patient has not reported antibiotic therapy, in order to avoid false negative results or inappropriate treatment. Dr. Snegarova found a high relative proportion of urine specimens with RAA (5.7%), as well as a high relative proportion of patients who had recently undergone antibiotic treatment. In the latter simultaneously found RAA and a positive culture finding (55.8%).

The dissertation has a completed form. The purpose and objectives posed have been fulfilled.

4. Conclusions and contributions.

On the basis of the literature review and the own research and experience, 10 conclusions were properly and logically drawn, which directly correspond to the stated purpose and objectives. The conclusions reached have theoretical and practical value and represent the core of the thesis.

Substantial contributions of original (four contributions), scientifically applied (three contributions) and confirmatory (three contributions) character were obtained. I accept the contributions indicated by Dr. Snegarova, which are adequately and realistically derived from the developed thesis.

5. Scientific publications and participation in scientific forums, related to the dissertation

The significance of the achieved results is demonstrated by the attached list with a total of four publications in reputable scientific journals.

Dr. Snegarova clearly has a leading role in the presented research articles, as evidenced by her position as the first author in the list of scientific publications.

The results of the conducted research were presented at three scientific forums, two of which international. In all of these contributions, Dr. Snegarova is the first author.

VI. ABSTRACT

The presented abstract corresponds to the requirements, completely representing the content of the thesis.

VII. CONCLUSION

The dissertation is a study on a relevant issue, with a solid theoretical basis, performed with a variety of routine and modern diagnostic methods.

The scientific value of this dissertation work originates from the in-depth research, conclusions and recommendations, and from the formulated contributions.

I consider the doctoral thesis to be complete, useful, analytical and precise in its conclusions. All this is the reason to consider it positive and to recommend it to the respective members of the Scientific Jury to unanimously grant Dr. Viktoriya Snezhanova Snegarova-Toneva the educational and scientific degree 'Doctor' in the scientific specialty 'Microbiology'.

25 Jan 2025

Sofia

Reviewer:

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

Assoc. Prof. Ivanka Gergova, MD, PhD