To the Members of the Scientific Jury,

Appointed by Order No P-109-440/05.12.2024.

of the Rector of Medical University - Varna

for the announced competition for associate professor

State Gazette No. 85/08.10.2024

R E V I E W

from prof. Temenuga Zhekova Stoeva, MD, Dsc

Medical University - Varna

Department of Microbiology and Virology

on competition

for occupying the academic position "Associate Professor"

in the field of higher education 7. Health and Sport

professional field 7.4. Public Health

Speciality "Public Health Management (Clinical Microbiology)"

for the needs of the Department of Microbiology and Virology

Faculty of Medicine, Medical University, Varna

announced in SG No. 85/08.10.2024.

with candidate

Chief Assistant Professor Denis Sunay Niyazi, MD, PhD

Dr. Denis Niyazi graduated in medicine from the Medical University of Varna in 2018 with excellent grades. In 2018, he started working at the Department of Microbiology and Virology at MU-Varna as an assistant professor, and since 2023, he has been a chief assistant professor. In 2023, he obtained a specialization in "Clinical Microbiology." Between 2019 and 2022, he developed and successfully defended a dissertation to obtain a PhD degree in the scientific field of "Microbiology," with the dissertation title "A Study on Bacteremias and Invasive Mycotic Infections in Patients After Autologous and Allogeneic Hematopoietic Stem Cell Transplantation." In 2023, he earned a master's degree in "Public Administration with a specialization in Health Management." Between 2019 and 2024, he participated in 3 scientific

projects funded by the Science Fund of MU-Varna, in one of which he was the principal investigator.

Dr. D. Niyazi is a member of prestigious scientific organizations such as the Bulgarian Association of Microbiologists, the Bulgarian Medical Association of Hematologists, and the European Society of Clinical Microbiology and Infectious Diseases.

SCIENTIFIC-RESEARCH ACTIVITY

Scientific Production

The documentation presented by Dr. Denis Niyazi meets the requirements for participating in the competition for the academic position of Associate Professor. For this competition, Dr. D. Niyazi has submitted a total of 42 scientific works. They are distributed as follows:

1. Habilitation work – monograph - 1
2. Publications published in scientific journals that are refereed and indexed in world-renowned databases of scientific information (Scopus, Web of Science) - 20
3. Publications published in non-refereed peer-reviewed journals - 4
4. Participation in scientific forums - 17: international - 5; national with international participation - 12

In the competition, Dr. Niyazi is participating with his habilitation work (monograph) on the topic "Invasive Aspergillosis in Patients After Hematopoietic Stem Cell Transplantation" with a total volume of 225 pages.

Dr. D. Niyazi's scientific-research and publication activity is presented in three main areas, all directly related to current issues in contemporary clinical microbiology and medical practice. Key focuses of his scientific interests include microbial resistance and infectious complications in patients with oncological hematological diseases, including those after hematopoietic stem cell transplantation, as well as medically significant fungi. In all of these areas, significant contributions with original, confirmatory, and applied character have been made. Among the most notable are:

1. **Monograph:** Dr. D. Niyazi's monograph presents the current state of the problem of "Invasive Aspergillosis" in patients after hematopoietic stem cell transplantation, addressing all the important aspects of the disease. The author provides comprehensive scientific information both regarding the etiological agent and the epidemiology, clinical presentation, and risk factors for the disease in this high-risk group of patients, as well as diagnostic approaches, treatment, and prevention. The scientific information presented on the problem is based on over 500 reviewed literary sources, as well as the author's own clinical-laboratory experience.

Hematopoietic Stem Cell Transplantation is considered one of the revolutionary discoveries in the field of medicine, leading to the treatment of many previously incurable malignant and non-malignant diseases until the mid-20th century. Due to a number of specific characteristics, hematopoietic stem cell transplantation is often accompanied by the development of serious infectious complications associated with various types of bacteria, fungi, viruses, and parasites. Globally, systemic mycotic infections, particularly invasive aspergillosis, are among the most severe and critical infectious complications, associated with very high mortality in patients who have undergone hematopoietic stem cell transplantation. Understanding the risk factors, the specific features of the clinical course of the disease in this patient group, as well as knowledge and mastery of modern possibilities for rapid diagnosis followed by timely and appropriate antifungal therapy, is the correct approach to controlling the disease. Ultimately, this would result in a decrease in the morbidity and mortality from this invasive mycotic infection in patients with hematologic malignancies and those after hematopoietic stem cell transplantation.

Systemic mycotic infections, including invasive aspergillosis in severely immunosuppressed patients, are difficult to diagnose and pose a real challenge for clinical and laboratory specialists. The monograph discusses in detail the diagnostic possibilities in the context of a comprehensive approach, combining both classical and established methods in practice, as well as newer, modern, and innovative methods, commenting on their capabilities, sensitivity, specificity, limitations, and advantages.

The monograph “Invasive Aspergillosis in Patients After Hematopoietic Stem Cell Transplantation” is organized into 14 chapters: “History and Classification,” “Morphology and Structure,” “Ecology,” “Aspergillosis – Clinical Forms. Invasive Aspergillosis,” “Epidemiology and Risk Factors,” “Pathogenesis,” “Microbiological Diagnosis,” “Imaging Diagnosis,” “Antifungal Drugs,” “Antifungal susceptibility testing,” “Resistance of *Aspergillus* spp. to Antifungal Drugs,” “Recommendations for Diagnosis, Treatment, and Prevention of Invasive Aspergillosis,” “Nosocomial Aspergillosis,” and “Own Studies.”

In addition to the comprehensive presentation of the modern diagnostic approach for this invasive mycotic infection, I highly appreciate the sections where the author provides a very thorough overview of all groups of antifungal drugs (including newly developed), with information on microbial spectrum, mechanism of action, dosage regimens, drug interactions, as well as methods for antifungal susceptibility testing. The author also shares the most important and frequent practical difficulties and approaches for interpreting and solving them. Special attention is also given to the problem of resistance to the main antifungal drug groups, a phenomenon that is increasingly encountered in practice and poses a serious potential to compromise the treatment of this life-threatening infection.

From a practical point of view, a very valuable section is the one in which the recommendations for managing invasive aspergillosis (including diagnosis, treatment, and prevention) in adults and children with hematologic malignancies or who have undergone hematopoietic stem cell transplantation are presented. These recommendations are based on leading associations on the issue, such as EORTC/MSGERG, IDSA, ECIL-6, ASTCT, AGIHO 2018, and ESCMID-ECMM.

Dr. Niyazi's monograph answers many of the questions that arise in everyday clinical and laboratory practice concerning one of the most common invasive mycotic infections in patients with hematologic malignancies and after hematopoietic stem cell transplantation. It is a valuable resource for all clinical doctors, clinical microbiologists, and specialists whose professional activities are related to the diagnosis, therapy, and prevention of this life-threatening infection. It would also be of interest to medical interns and students.

2. Scientific Area: "Infectious Complications and Microbial Resistance in Patients with Hematologic Malignancies (HM) and Hematopoietic Stem Cell Transplantation (HSCT)

Blood Stream Infections in Patients with HM:

- A study covering a 6-year period (2015 - 2020), including 298 patients with HM and laboratory-confirmed blood stream infections, found that Gram-negative bacteria (54.7%) dominated as etiological agents, with leading species being *E. coli* (14.5%), *Enterobacter* spp. (12%), and *Klebsiella* spp. (10.1%). The relative proportion of extended-spectrum beta-lactamase producers was high among the isolates of *Enterobacter* spp. and *Klebsiella pneumoniae* (over 50%), and above 15% for *E. coli*. The results were compared to a previous study from 2011-2014, revealing a continuing trend of Gram-negative bacteria dominance in the etiological spectrum of the blood stream infections in patients with HM, with a consistently high level of ESBL producers among *Enterobacteriaceae* members and a high proportion of carbapenem-resistant *Acinetobacter baumannii*. The appearance of invasive carbapenem-resistant *Enterobacteriaceae* isolates was identified as a new negative trend during the 2015-2020 period.

Blood Stream Infections in Patients After HSCT:

- Dr. D. Niyazi conducted the first Bulgarian study on the frequency, risk factors, and outcomes of blood stream infections in patients after HSCT, involving 74 patients. A cumulative bacteremia rate of 35% was found in this group. The average time from transplantation to the onset of bacteremia was 8 days. The study identified intestinal colonization with multi-drug-resistant microorganisms and the occurrence of bacteremia

before transplantation as statistically significant risk factors for blood stream infections after HSCT. The 30-day mortality rate post-transplantation was 23%, while the four-month survival rate was 86.5%. The type of underlying disease (leukemia and lymphoma) and previous HSCT were identified as factors with a negative effect on survival.

- The species affiliation and antimicrobial susceptibility of staphylococci causing catheter-associated blood stream infections in patients after HSCT were studied. Coagulase-negative staphylococci (CoNS) were found to be the leading etiological agents (85.7%), with *Staphylococcus epidermidis* predominating (57.1%). The relative proportion of *Staphylococcus aureus* was 14.1%. All CoNS isolates were identified as methicillin-resistant, while *S. aureus* strains were found to be methicillin-susceptible (MSSA).
- In vitro activity of a new combined antibacterial agent (ceftazidime/avibactam, CZA) against isolates resistant to third generation cephalosporins and/or carbapenems, isolated from blood cultures and/or fecal samples from HSCT patients, was studied. Multi-drug-resistant bacteria carrying bla_{ESBL}, bla_{VIM}, bla_{OXA-23}, $bla_{OXA-24/40}$, and bla_{OXA-48} were found in 30.7% of the studied patients. All intestinal isolates producing ESBLs were susceptible to CZA. The excellent activity of CZA against ESBL isolates was confirmed, while no activity was observed against isolates carrying bla_{OXA} and bla_{MBL}.

3. Scientific Area: "SARS-CoV-2 and COVID-19"

- A large-scale hospital study was conducted on the dynamics of COVID-19 during the first year of the pandemic (May 2020 - April 2021) and on the role of certain demographic factors in the disease development. 40% of the tested samples were positive, with the most affected age group being 60-79 years. Male sex was confirmed as a risk factor in the 20-59 age group, while in the under-19 age group, female sex was identified as a predisposing factor for infection development.
- The relative proportion of SARS-CoV-2-positive samples from patients from Northeast Bulgaria over a two-year period (2020 - 2021), covering the first four waves of the pandemic, was 33.6%. The seasonal and regional spread of COVID-19 in Northeast Bulgaria was studied and compared with other European countries. The absence of seasonality was confirmed, as well as varying regional spread during the first two years of the pandemic. Differences in infection frequency between genders and by age during different periods were also established.
- The clinical significance of the "inconclusive" results when using the PCR method for COVID-19 diagnosis (detection of only one gene in the clinical sample) was assessed, and recommendations for their interpretation in relation to clinical symptoms and patient history data were made.
- The reliability of rapid immunochromatographic tests for diagnosing COVID-19 was studied, with results from over 2500 hospitalized patients being evaluated. A sensitivity of 60% and a specificity of 98% were found, confirming the place of this rapid method in the

diagnostic process, especially in conditions with a rapidly increasing number of patients and the need for specialized equipment and trained personnel for PCR testing.

- A study was conducted on carbapenem-resistant *Enterobacterales* isolated from clinical materials of patients hospitalized in the COVID-19 and intensive care units at "St. Marina" University Hospital - Varna during the first year of the pandemic (2020 - 2021). The study found a dominance of carbapenem-non-susceptible *Klebsiella* spp., with resistance mainly mediated by bla_{KPC}. The study also confirmed nosocomial dissemination of MDR *K. pneumoniae* and *Enterobacter cloacae* complex clones.

4. Scientific Area: "Mycotic Infections"

- Dr. D. Niyazi reports the first Bulgarian case of mucormycosis after COVID-19 in a 66-year-old male patient who presented with a rhino-orbito-cerebral form (ROC). The role of the viral infection and elevated blood glucose levels as risk factors for the development of ROC mucormycosis was confirmed, along with the need for rapid and adequate multidisciplinary diagnostic processes.
- The important role of the invasive mycotic infections (mucormycosis, aspergillosis, pneumocystosis) in the etiological spectrum of infectious complications in patients with HM and after HSCT was established.
- The role of HM and previous HSCT as significant risk factors for the development of invasive mycotic infections was confirmed.
- The effectiveness of molecular genetic techniques (PCR) in the diagnosis of invasive fungal infections and the importance of a multidisciplinary approach (microbiological, imaging, histological examinations) for their early diagnosis, considering the high disease burden associated with these infections, was demonstrated.
- The role of a combined therapeutic approach (etiological and surgical) for the rapid management of the infectious process accompanying the invasive mycotic infections (mucormycosis) in patients with HM was confirmed.
- The role of allogeneic transplantation as a factor in the reactivation of latent herpesvirus infections was confirmed.
- The aggravating role of the combined infectious complications (mycotic + viral) on the outcome of the disease in patients with HM and after HSCT was established.

Dr. D. Niyazi is the first author in 11 publications (52.4%), second author in 5 (23.8%), and third in 2 (9.5%), which proves his leading role and contribution. The total IF of his scientific publications is 17.57. His individual h-index is 4 (Google Scholar), and his scientific works have been cited 49 times, 16 of which are in scientific journals refereed and indexed in world-renowned databases with scientific information, providing evidence of the high scientific value of his publications.

EDUCATIONAL - TEACHING ACTIVITY

Dr. D. Niyazi is a university lecturer with a proven competence and over 5 years of teaching experience. His total lecture time for the last 5 academic years is 1308 hours, exceeding the prescribed norm. 60% of the hours are in the English-language program. He actively participates in conducting exercises and seminars in the specialty "Medical Microbiology" for students of Medicine, Dental Medicine, and Pharmacy, as well as in the Clinical Microbiology course. Since 2024, he has also participated in conducting courses for medical residents in Clinical Microbiology.

CONCLUSION

Dr. Denis Niyazi is a highly qualified specialist with excellent expertise in clinical microbiology and infectious complications in immunocompromised patients, as well as experience in teaching. The scientometric indicators, contributions of his scientific publications, and teaching activity fully meet and significantly exceed the national requirements of the Health Act and the requirements of MU-Varna for the position of Associate Professor. Based on all this, as a member of the scientific jury, I support his candidacy and recommend to the Scientific Jury to select Dr. Denis Niyazi for the academic position of Associate Professor in speciality “Public Health Management (Clinical Microbiology)” for the needs of the Department of Microbiology and Virology at the Medical University - Varna.

29.01.2025г. Signature:

/Prof. Temenuga Stoeva, MD, Dsc/