

**“CAROL DAVILA” UNIVERSITY OF MEDICINE AND  
PHARMACY  
BUCHAREST  
DOCTORAL STUDIES  
MEDICINE**

**Opportunistic Microorganisms and their Immunocompromised  
Hosts**

**ABSTRACT OF THE HABILITATION THESIS**

**CANDIDATE:**

**Ph.D. Valentina-Ruxandra Moroti-Constantinescu,  
Associate Professor  
Carol Davila University of Medicine and Pharmacy**

**2024**

The habilitation thesis with the topic "**Opportunistic Microorganisms and their Immunocompromised Hosts**" underlies the scientific, academic, and professional achievements I have attained after I completed my Ph.D. studies and depicts my academic career development proposals/ perspectives.

The thesis is structured into four chapters: the first three describe the scientific, academic, and professional achievements, the fourth describes the academic development proposals and the thesis ends with a reference section.

**Chapter 1 *Scientific Achievements*** describes my scientific work and attests my fulfilment of criteria for accreditation as a Ph.D. studies coordinator. I fulfilled the national standard of 10 articles published *in extenso* in ISI-rated journals as the main author: I wrote 11 original articles and reviews, and their cumulative impact factor (FCIAP) is 211.797. I published 17 papers in co-authorship (the national standard is five). My HIRSCH index in Web of Science Core Collection is 8 (the national standard is 6). In non-ISI journals, indexed by PubMed, I published six articles in extenso; in journals published in other BDI, non-PubMed, non-ISI – another 35 full articles.

I am the author of 10 specialized book chapters published in national and international publishing houses. Among these, a chapter on HIV Encephalopathy in an international publishing house and the translation of the Infectious Diseases Chapter of the Oxford Handbook of Clinical Medicine, Tenth Edition, 2019. In four treatises, four chapters are dedicated to students and residents.

I have over 150 communicated scientific abstracts, 58 published in ISI rated journals, 68 in non-ISI journals, with ISBN/ISSN, the rest being published in the conference book or on electronic media, and some without a published abstract.

**The themes** addressed with predilection in my work refer especially to the immunocompromised hosts and the relation between them and microbes, the microorganism-microorganisms interferences, and the microorganisms-microorganisms interferences. In this perspective, my scientific work refers to *invasive fungal infections*, *HIV-infection* with its opportunistic infections, and *neuro-infections* (the central nervous system is an anatomic site that is not so well immune-protected)

### ***Invasive fungal infections***

I have addressed all categories of invasive fungal infections – yeast infections – *Candida* spp., *Cryptococcus* spp., filamentous fungi infections – *Aspergillus* spp., *Fusarium* spp., *Mucor* spp., and infections with non-cultivable fungi – *Pneumocystis jirovecii*. I was able to document cases both in the clinic where I work (National Institute of Infectious Diseases Prof. Dr. Matei Balș, Bucharest) and in other clinics in Romania, where infectious diseases colleagues or specialists from other fields sought my advice and assistance. I have given oral presentations, as well as poster presentations, both locally, nationally, and internationally, covering all these types of infections, most of them illustrated with my own cases. I have presented and published my own and my colleagues' case reports on local, national, and international publications – on invasive infections with *Candida* spp., *Cryptococcus* spp., *Aspergillus* spp., *Mucor* spp., and *Fusarium* spp. These publications have appeared in both ISI-indexed journals and book chapters dedicated to clinical cases, aimed at the students and residents. As for dimorphic fungi, I have only theoretically addressed these types of infections, as this pathology is quasi-absent (or quasi-unrecognized? or underdiagnosed?) in our geographical area, and where there have been suspicions of cases, they have not been confirmed. I have covered dimorphic fungal pathology in postgraduate courses within the Travel Medicine Competence Certificate, as well as in courses dedicated to students and infectious diseases residents, where I documented cases from scientific literature, including clinical cases from my colleagues in the Netherlands. Abstracts of the main published articles are included in this section.

### ***HIV infection***

There are some main topics on which I concentrate my interest and my scientific research: One is *NeuroAIDS* including HIV encephalopathy, all central nervous system (CNS) opportunistic infections, and their challenging therapeutic options. I demonstrated the simultaneous presence of more than two (up to five!) opportunistic pathogens in the CNS of seropositive HIV patients. These pathogens exhibit complex interactions, including mutual exclusion or collaboration. For instance, *T. gondii* has a unique relationship with *Cryptococcus* spp., while *EBV* seems to hinder the entry of *Mycobacterium tuberculosis* into the CNS. There appears to be a “partnership” between *Mycobacterium tuberculosis* and *Cryptococcus* spp. Since 2009 I have published and given a large series of local, national, and international

presentations on this interesting topic. With two of my colleagues, I published in 2012 a book chapter in an international edition – dedicated to HIV encephalopathy and its differential diagnoses, encompassing all CNS opportunistic infections.

Another hot topic is the interrelation between *HIV and the host immune system* and the relationship among microorganisms that cohabitate in an immunosuppressed host, such as the one infected with HIV. I have had another series of presentations, communications, and publications throughout the decade 2013-2023, including the development of immune responses (IRIS among others); for example - an interesting national presentation (2022), that discussed the reactivation of hepatitis B virus secondary to persistent replicative SARS-CoV-2 presence in a therapeutically neglected HIV-infected patient. The concern for immune response against HIV and the peculiarities during primary infection have materialized through several publications and presentations – mentioning a presentation at the 12th European Workshop on HIV & Hepatitis, 2014, Barcelona, that highlighted the first case of recent infection following accidental non-medical occupational exposure to contaminated blood. An analysis of short-term evaluation of immediately treated patients with acute HIV infection, recently diagnosed in our Institute, was done in 2014, many years before the international guidelines stressed the necessity of rapid introduction of antiretroviral treatment (*ART*) in acute HIV infection. *ART* is a third important topic to me. I recently published one of my cases with HIV primary infection – in the section of ‘Clinical Images in Internal Medicine’ in the prestigious journal New England Journal of Medicine (December 2023), rapidly treated. I am preoccupied with *ART* and its rapid start, especially in acute HIV infection and I am among the group of specialists in my institution who prepared the local *ART* guidelines. I have given a lot of local and national presentations regarding *ART* (targeting drug-drug interactions, ABC in *ART*, etc.).

### ***Neuro-infections***

In the same thematic spectrum – infections in immunosuppressed individuals, with a focus on infections in less immune-protected sites – I have been concerned with central nervous system (CNS) infections in general. It all began with intriguing, rare, and fatal prion diseases, which I attempted to understand through literature (although I encountered very few suspected cases in my care). Continuing from there, I explored more accessible and frequent pathologies, such as pyogenic abscesses and empyemas in the CNS, bacterial pyogenic infections (including

recurrent pneumococcal cases) (summary of the most recent article published in an ISI journal below), as well as infections with clear cerebrospinal fluid (such as spirochetal infections). Tuberculosis of the CNS, which is common in Romania, occasionally presents with a surprising undulating course lasting months to years even without therapy. I also delved into viral meningitis and encephalitis, including epidemics caused by enteroviruses and West Nile virus, as well as herpes simplex virus encephalitis. During the COVID-19 pandemic, I explored CNS pathology related to SARS-CoV-2. Additionally, I investigated rarer CNS pathologies, such as infections with atypical pathogens (“intermediate” germs) and anthrax meningoencephalitis. All these topics constituted the focus of my research, which I disseminated through oral presentations, posters, full-length articles, and book chapters. The book chapters, particularly relevant for students, residents, and young specialists, cover *Coxiella* encephalitis and *Herpes simplex* encephalitis. Furthermore, I collaborated with infectious disease colleagues from approximately 20 countries on an article about the frequency and etiology of community-acquired CNS infections.

This chapter also included my *Research Projects*, *Memberships in Professional-Scientific Structures*, my involvement in *Scientific Event Organization Committees*, my *Editorial Board Membership* and involvement as a *reviewer in indexed articles*, and my *distinctions and awards*.

## **Chapter 2 Academic Achievements**

The chapter describes my Academic *curricula* from graduation (1993, the Faculty of General Medicine at the Carol Davila University of Medicine and Pharmacy in Bucharest) – through the Academic successive positions of Tutor (2002), Assistant Professor (2005), Lecturer (2014), and Associate Professor (2023) in Infectious Diseases. I pursued a Master’s course offered by the Department of Biophysics and Cellular Biotechnology (dissertation in 2006), then Ph.D. studies (title conferred in 2010), then postdoctoral studies (2010-2013). The workshops and other scientific meets or studies with my students and with my resident doctors, the supervisions (I supervised 50 License in Medicine Thesis), and the articles derived from working together. I listed my participation as a member of the examination committees for our students, our residents, specialists, and colleagues in ascending Academic positions.

### **Chapter 3 *Professional Achievements***

The chapter describes my professional curricula from graduation through two residencies, first in General Pediatrics and the second, in Infectious Diseases (ID), then ID specialist (2003) and Senior Physician (2008). There were listed the courses I attended, especially in HIV and mycology field, my competencies – in General Ultrasounds (2008 and 2014 a special course) and Travel Medicine. There were listed also my participation in exams committees. Along with these, I supervised the preparedness of one support hospital and two departments of another support hospital, for Covid19 pandemic and I promoted science and real facts about Covid19 among colleagues, my students, my patients, and in mass media.

### **Chapter 4 *Career Development Proposals/Directions***

Here I sketch my *Scientific Directions*: to publish my work in very visible journals and to achieve the position of Professor in Infectious Diseases. The *Academic Directions* are toward promoting knowledge and awareness in the emergent domains, such as infections in immunocompromised hosts (Invasive Fungal Infections, Opportunistic Infections in Immunosuppressed Hosts). In this regard, I have been initiating a course dedicated to invasive fungal infections for medical students at the Carol Davila University of Medicine and Pharmacy since 2014 (every year). In response to repeated national alerts and growing awareness among my colleagues, especially in the context of the post-COVID-19 surge (including alerts from the World Health Organization), a course specifically addressing these infections was introduced into the curriculum of our university – for the students in their VI years of study, during their stage in Infectious Diseases (starting in January 2024). *Professional Development* – I intend to deepen my knowledge in the already mentioned domains.

**20 February 2024**

**Associate Professor,**

**Valentina-Ruxandra Moroti-Constantinescu**