

UNIVERSITY OF MEDICINE AND PHARMACY "CAROL DAVILA" BUCHAREST

**Escalating antibiotics' collateral damages: antimicrobial resistance and
Clostridium difficile infections; the role of antimicrobial stewardship as a
control strategy**

SUMMARY OF HABILITATION THESIS

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Antibiotics are relatively new drugs – less than 80 years of usage, but they were considered probably the most important medical discovery of XXth century. Along with immunizations, better sanitation and socioeconomic development, the antibiotics use allowed an unprecedented increase of life expectancy, lowering the mortality rate due to infections; likewise, antibiotics contributed to a shortened duration of bacterial infections and to prevention of countless postoperative infections. It is easy to understand that we hope to maintain the power of antibiotics for the next generations. However, the use of antibiotics could undermine their efficacy: selection of germs with increasing resistance to antibiotics and emergence of post-antibiotic diseases such as *Clostridium difficile* infections (CDI) or *Candida* infections. Antimicrobial resistance is otherwise considered one of the major problems of public health globally, being included among the threats to the Human Race in post-antibiotic era.

The habilitation thesis **”Escalating antibiotics’ collateral damages: antimicrobial resistance and *Clostridium difficile* infections; the role of antimicrobial stewardship as a control strategy”** includes my most relevant achievements in research, academic and medical areas during the past 18 years, the period of time after I obtained my PhD in Medicine. The thesis was prepared in accordance with the recommendations of the Order issued by the Ministry of Education and Scientific Research 3121/27.01.2015 and consists of four sections.

The first section includes a description of recent evolutions in Infectious Diseases specialty explaining the major interest for antibiotics, especially focusing on antimicrobial resistance. The Infectious Diseases field is a very challenging one and generates the most severe threats to public health. My main interest area was the use of antibiotics and its collateral issues, including CDI; other interest areas were severe infections and HBV-HDV hepatitis. The **presence of infectious diseases specialists as close as possible to patients with infections**, in different hospitals, as an essential medical team member, has become a necessity in the era of emerging antimicrobial resistance, being helpful for a better diagnosis of infections and for a better use of antibiotics. I came to realize this in our medical system, where Infectious Diseases was and is still largely separate specialty, in dedicated hospitals; I tried to educate the medical students, residents and junior doctors to adopt a similar approach. In research area the main principle that I have followed was **the applicative research**

addressing major issues in clinical management of patients with infectious diseases.

There is an interconnection between research and the improvement of clinical activity, for me and for my students.

The scientific impact of my research achievements could be expressed by means of Hirsch index, calculated to be 8, 14 and 11 for ISI Web of Science Core Collection, Academic Google and Scopus Elsevier, respectively.

The second section covers my professional, educational and scientific activities in my main area of interest, the prudent use of antibiotics, the control of collateral damages of antibiotics, i.e. antimicrobial resistance and CDI and healthcare-associated infections.

I have dedicated the most of my professional and research time to antimicrobial resistance problem and its containment. A milestone for me was the involvement as national coordinator in the public funded project „**Multicenter monitoring of antimicrobial resistance – use in the improvement of antibiotic treatment guidelines**”, conducted during 2007-2010. This study was the first one of this scale, involving the analysis of more than 8500 bacterial isolates from four hospitals located in different region of Romania and it generated a more credible picture of antimicrobial resistance in our country. The results were published in several journals, including a paper in an ISI indexed journal; the resistance data allowed to update the antimicrobial use recommendations as included in the 3rd edition of *Angelescu Guideline of Antibiotics* and were the background for the antimicrobial stewardship program performed in National Institute of Infectious Diseases Matei Bals during 2010-2012. The antimicrobial resistance and treatment option for infection with resistant germs were the topics for other 11 papers published in ISI Web of Science indexed journals. Especially during last 15 years, I have done many presentations on antimicrobial resistance in medical conferences; I was invited speaker for many clinical trainings and workshops.

Antibiotic consumption is a driving force for the emergence of antimicrobial resistance, but the prudent use of antibiotics could curb this evolution. The good results obtained with the antimicrobial stewardship program that I have coordinated during 2010-2012 indicated the possibility to deploy in Romanian hospitals such successful programs. I have spoken many times about the necessity of antimicrobial stewardship, the difficulties to initiate such a

program and the major strategies to be followed. I represented Romania as an expert in ESAC project (2008-2009), a project analyzing antimicrobial consumption in Europe and lately, since 2013, I was Romanian National Focal Point for antimicrobial consumption. My activity in this area recommended me to be included in the working group for the project *Forgotten antibiotics* (2016) conducted by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID). The results of these studies generated several papers published in high ranked journals, Journal of Antimicrobial Chemotherapy and International Journal of Antimicrobial Agents respectively, with 10 to 160 citations in ISI Web of Science indexed journals alone. The experience acquired in antimicrobial use during clinical activity was the ground for co-authoring *The Angelescu Guideline of Antibiotics* (four editions since 2004) and the monography *Antimicrobial resistance and the use of antibiotics*, published in 2011.

My commitment for a better knowledge of prudent use of antibiotics was materialized in several academic and research activities: elective course for the students of Carol Davila University of Medicine and Pharmacy (2016-2017), courses for the infectious diseases residents and for other residents during Infectious Diseases rotation, participation as coordinator for the Bucharest in the multi-center European study analyzing the self-assessed knowledge of antimicrobial use and antimicrobial resistance of last year medical students, **PREscriber Perspectives on Antibiotic use and Resistance Education (PREPARE-Student)**, conducted during 2015. Starting with 2012, I participated to writing and I coordinated the publication of annual reports AC&ARHAI (in Romanian, **CARMIN**), that means Antimicrobial Consumption, Antimicrobial Resistance and Healthcare Associated Infections. The reports contain the analysis of the data collected in our country and are posted on website of National Public Health Institute.

The rise of incidence and severity of *Clostridium difficile* infection were reported in Romania since 2011. I was concerned about this collateral damage of antibiotics use before 2011, and I have written many papers about global evolution of CDI related to the emergence of the ribotype 027. Since 2011, I have managed hundreds of patients with CDI, I have organized and I have been a speaker in several educational programs about CDI, for physicians and nurses. Starting from the first years of CDI emergence in Romania I have set

up cooperation among NIID and Austrian Institute for Public Health (AGES); with AGES help we succeeded to prove that the emergence of CDI in Romania was related to increased circulation of *Clostridium difficile* 027 ribotype in our country. During the next years, 2013-2014, I was the scientific coordinator for a study involving hospitals from six academic centers in Romania; we confirmed the dominant involvement of ribotype 027 in all these hospitals. The results of my involvement in CDI field generated five papers published in ISI journals; one of them has already 9 citations. In a close related area, I participated in a multicenter study concerning the etiology of severe community-acquired diarrhea (EUCODI) which involved 10 European countries. Romania was the only country where the prominent etiology for these cases was *Clostridium difficile*. The paper with EUCODI results was published in *Clinical Microbiology and Infection* (IF = 4. 575) and already has 62 citations in other ISI Web of Science journals.

The healthcare-associated infections (HAI) are more frequently produced by germs with antimicrobial resistance and could be related to excessive use of antibiotics. The interest for HAI increased in the last few years in Romania, due to HAI severity and the gaps in their prevention; however, the HAI remain largely underdiagnosed and underreported in Romania with a suboptimal control of infection in hospitals. In this field I have developed many workshops with physicians from many hospitals and I have performed several lectures in medical conferences.

The third section presents activities in other areas of Infectious Diseases field. The infective endocarditis was the topic of my PhD thesis and it remained an interesting one due to its challenging diagnosis and outcome risks; the lethality rate is higher in Romania than in developed countries because of difficult access to cardiovascular surgery. I have continued to be involved in endocarditis clinical management and I have contributed to several papers; two of them were realized in cooperation with colleagues from Germany and France and their importance was confirmed by 18 and 8 citations, respectively, in ISI indexed journals.

The highlighting of the involvement of highly resistant and/or virulent bacteria in the etiology of infections was another area connected with antimicrobial use; a couple of published papers in ISI journals described such type of cases. A special interest was assigned to the presence of *Klebsiella pneumoniae* liver abscess syndrome in Romania.

Another topic addressed in my scientific work was the HBV-HDV infection. In the past three decades Romania was one of the very few European countries with a high prevalence of this infection with very limited therapeutic resources. I conducted a study having as objectives to update the HBV-HDV epidemiology and to obtain a better definition of patient subgroups with different therapeutic approaches; this project was sustained with public funds obtained in the competition CEEEX 2005. The study results were presented in medical conferences and in a paper which was published in an ISI indexed journal (IF = 2.37) with 11 citation in ISI indexed journals.

The fourth section includes information about my academic and professional activities, other than those described in the previous sections. I described the steps of my academic career and the main activities carried out with medical students, residents, postgraduate physicians and nurses; a section was dedicated to my contribution to increase the general audience awareness concerning antimicrobial resistance and antibiotic prudent use.

After a short description of my professional achievements, I discussed my involvement as a clinician in the management of hospitalised patients from my department, but also as consultant for patients admitted in several other hospitals, especially from intensive care, cardiology and oncology. I pointed out about my efforts to improve the cooperation with colleagues from microbiology and infection control, but also with colleagues from many other medical specialities for better outcomes in patients with infection.

The fifth section presents the development directions of my professional, academic and research activities. I propose two major directions of these activities hoping for the growing interest of younger physicians in these domains.

The antimicrobial stewardship is at its very beginnings in Romanian hospitals. I will continue to promote and to support the initiation of antimicrobial stewardship programs. In the research area I intent to perform studies to evaluate the efficacy of different interventions in reducing the consumption of second line or last-line antibiotics; moreover, I would evaluate the extent of differences among real-life antibiotic use and recommended use, as background for improvements of infectious syndromes management.

The better use of diagnosis tests (**the diagnosis stewardship**) in order to improve anti-infective treatment will be a second major interest area ("classical" microbiological tests, rapid diagnostic tests, molecular diagnosis tests); an improvement in this area needs a good cooperation between Infectious Diseases and Medical Microbiology and I would like to promote some changes in order to have a real clinical microbiology, as in several European countries (i.e. United Kingdom).

I think that my past activity proves my capacity to guide younger physicians in order to achieve more than my generation did in the antimicrobial use and antimicrobial resistance fields. Some arguments in this direction are the coordination of 36 M.D. theses and my informal cooperation to define the theme and to realize the study design for three PhD thesis; I have contributed to the training of infectious diseases specialists who are now well appreciated in different countries (USA, UK, France); as project manager I have coordinated teams of several dozens of researchers; I have organized and coordinated educational programs and medical conferences. But these results were not possible without a team work and without interactivity with my younger and my older colleagues. In this respect, the Nicolae Iorga's words could not be more trustworthy:" The good school it is where the student also teaches the teacher".