

University of Medicine and Pharmacy

“CAROL DAVILA“ Bucharest

Faculty of Medicine



HABILITATION THESIS

"TARGETED ANTIBIOTIC THERAPY IN INTENSIVE CARE , NEW  
PERSPECTIVES"

**CANDIDATE**

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## ABSTRACT

The habilitation thesis entitled "Targeted antibiotic therapy in intensive care , new perspectives " explores my professional evolution in the medical field and focuses primarily on my development as an anesthesiologist and intensive care physician, as well as my role as a university lecturer at the "Carol Davila" University of Medicine and Pharmacy. I would like to specify that the habilitation thesis is written in accordance with the recommendations of the National Council for Attesting Titles, Diplomas, and University Certificates (CNATDCU) and adheres to national legislation.

The first section of the habilitation thesis presents my professional development journey, starting from the beginning of my residency in the field of anesthesiology and intensive care, where I had the opportunity to learn from exceptional professors and doctors in the field and work with critically ill patients. Since the early stages of my medical career, my passion for intensive care has been fueled by the desire to provide patients with the highest quality of care. The residency period was a time of numerous challenges that exposed me to complex cases and helped me familiarize myself with the latest techniques and procedures in the field of anesthesia and intensive care. During the 5 years of residency, I participated in numerous conferences and symposiums with the desire to update and expand my medical knowledge and improve my communication and presentation skills. All of these experiences contributed to the consolidation of my medical knowledge and skills. At the end of the residency, I took the specialty examination and successfully passed the exam for a medical position, conducted at the Clinic of Plastic and Reconstructive Surgery and Burns. This was followed by a period of clinical activity combined with a professional training internship at Cochin Hospital in Paris, France, which I completed in 2003.

After a few years of working as an intensive care specialist, I took the primary examination in 2004. I continued my clinical activity at the Clinical Hospital of Emergency Plastic and Reconstructive Surgery and Burns, and from 2007 to 2009, I became the Coordinator Physician of the Anesthesia and Intensive Care Department. Subsequently, I held the position of General

Manager of the Clinical Hospital of Emergency Plastic and Reconstructive Surgery and Burns for approximately three years.

Later on, I held the position of Manager at Fundeni Clinical Institute, where I worked for 8 years. During the same period, I also served as the President of the Medical Council at Fundeni Clinical Institute. Throughout these years, I contributed to the development of Fundeni Clinical Institute and improved my managerial skills. Additionally, I continued to enhance my medical specialization by participating in scientific events

Since 2016, I have been working as a university lecturer at "Carol Davila" University of Medicine and Pharmacy. This role has provided me with the opportunity to actively engage in the process of knowledge transmission to students and residents. From October 2019 until the present, I have held the position of Chief of the Intensive Care Discipline at Bucharest Emergency University Hospital.

Thus, I have strived to ensure an adequate learning environment for both students and resident doctors to develop their clinical skills and strengthen their theoretical knowledge. I have been involved in organizing clinical rotations for resident doctors in various departments of the hospital, ensuring that each resident has the opportunity to be exposed to a wide range of clinical cases and improve their practical competencies. In Bucharest Emergency University Hospital, being a multidisciplinary hospital, we can provide comprehensive training for students and residents in anesthesia and intensive care. Residents are guided in the use of the latest invasive and non-invasive monitoring techniques, as well as advanced techniques for vital function support. In addition, I have organized sessions for the presentation of clinical cases, where resident doctors have the opportunity to present cases and share their experiences regarding diagnostic and treatment approaches. Weekly courses have been organized to cover the material included in the residency curriculum, especially to prepare for the specialty examination.

I also had the responsibility of teaching courses for 6th-year medical students at the Faculty of Medicine during their Anesthesiology and Intensive Care rotation. This educational activity is essential for their professional development as future doctors. I encouraged active student participation in practical work, providing them with access to the Intensive Care units to familiarize themselves with the monitoring of critically ill patients and the main therapeutic modalities available. Students had the opportunity to perform characteristic maneuvers in the

field of Intensive Care, such as oro-tracheal intubation, peripheral/central venous catheter placement, and advanced cardiopulmonary resuscitation techniques through hands-on practice on mannequins.

In 2013, I obtained the title of Doctor of Medical Sciences from "Carol Davila" University of Medicine and Pharmacy with a doctoral thesis titled "Adequate Antibiotic Therapy in Burn Patients with Various Forms of Sepsis," conducted under the guidance of Prof. Dr. Streinu-Cercel.

Throughout my professional career, I have contributed as a collaborator to the development of numerous chapters and specialized books published by recognized CNCSIS publishing houses

In the last 10 years, I have published two monographs as the first author, focusing specifically on intensive care concepts and the management of burn patients within the ICU setting. Additionally, I have published articles as the first author in ISI journals with impact factors, as follows:

1. Colita A† , Colita A† Horia Bumbea H† , Croitoru A† , **Orban C†**, et al. LEAM vs. BEAM vs. CLV Conditioning Regimen for Autologous Stem Cell Transplantation in Malignant Lymphomas. Retrospective Comparison of Toxicity and Efficacy on 222 Patients in the First 100 Days After Transplant, On Behalf of the Romanian Society for Bone Marrow Transplantation. *Front Oncol.* 2019; 9: 892. (†These authors have contributed equally to this work as first authors). *Impact factor: 4.137*
2. Iliescu L, Herlea V, Toma L, **Orban C.** Association between chronic HCV hepatitis, membranoproliferative glomerulopathy and cutaneous sarcoidosis. *J Gastrointestin Liver Dis.* 2015 Mar; 24(1):8. *Impact factor: 1.964. Times cited: 1*
3. Iliescu L, Ioanitiescu S, Toma L, **Orban C.** Spontaneous portohepatic venous shunt: ultrasonographic aspect *Ultrasound Q.* 2015 Jun;31(2):141-4. [doi: 10.1097/RUQ.0000000000000148](https://doi.org/10.1097/RUQ.0000000000000148). *Impact factor: 1.021, Times cited: 1*
4. Iliescu L, Toma L, Grasu M, Herlea V, **Orban C.** Neuroendocrine tumors-four case. *Acta Endo (Buc)* 2015 11: 116-123.[doi: 10.4183/aeb.2015.116](https://doi.org/10.4183/aeb.2015.116). *Impact factor: 0.411.*

5. Iliescu L, Toma L, Minzala G, **Orban C**. Acute Hepatitis after Methimazole. *Acta Endocrinologica* 2014 ISSN (print): 1841 – 0987; *Acta Endo (Buc)* 2014 10: 267-272 doi: 10.4183/aeb.2014.267. *Impact factor: 0.411*.
6. Orban H, Stan G, Gruionu L, **Orban C**. Stress distribution on a valgus knee prosthetic inclined interline - a finite element analysis. *Chirurgia (Bucur)* 2013 Jan-Feb; 108(1): 91–93, PMID: 23464776. *Impact factor: 0.777. Times cited: 2*.
7. **Orban C**, Tomescu D. The importance of early diagnosis of sepsis in severe burned patients: outcomes of 100 patients. *Chirurgia* 2013; 108(3):385-8. ISSN: 1221-9118, PMID: 23790789. *Impact factor: 0.777, Times cited:8*
8. Păun DL, Poiană C, Petriș R, Radian R, Dănciulescu R, Miulescu, Constantinescu G, **Orban C**. Multiple endocrine neoplasia type 2A: case report. *Chirurgia (Bucur)* 2013 Nov-Dec; 108(6): 900–903. *Impact factor: 0.777. Times Cited: 13*.
9. **Orban C**, Diagnostic criteria for sepsis in burn patients. *Chirurgia (Bucur)* 2012 Nov-Dec; 107(6): 697–700, PMID: 23294946. *Impact factor: 0.777. Times cited:10*
10. Orban H, Stan G, Gheorghiu N, Dragusanu M, Mares E, **Orban C**. 6 years follow-up of hip revision surgery. *Chirurgia (Bucur)*. 2012 Mar-Apr; 107(2):226-30. PMID: 22712353. *Impact factor: 0.777*.
11. Orban H, Adam R, **Orban C**. Arthroplasty risk after kidney or liver transplant. *Chirurgia (Bucur)*. 2012 Sep-Oct; 107(5):664-9. PMID: 23116844. *Impact factor: 0.777. Times Cited: 3*.

The second section of the habilitation thesis presents the strategic implementation of antibiotic therapy standards targeted at burn patients.

Burns represent a complex medical issue that affects millions of people globally. These traumatic injuries can have significant consequences on the physical, psychological, and social health of individuals, requiring a multidisciplinary approach in the diagnosis, treatment, and recovery of patients. Burn patients are at a higher risk of developing sepsis, multiple organ

failure, and ultimately death. After surpassing the acute phase of the disease, infections and its complications account for over 75% of the resulting deaths.[1]

One particular characteristic of burns is the immunosuppression of the patient.[2]Prolonged stays in intensive care units facilitate the transmission of infections from one patient to another[3] and invasive procedures, the use of medical devices, or invasive mechanical ventilation further increase susceptibility to nosocomial bacterial infections. [4] The involvement of a larger body surface area and the engagement of the lower respiratory tract are also risk factors that can contribute to microbial infection.

The increased prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) germ infections in intensive care units necessitates the empirical choice of antibiotics, even before bacteriological confirmation is available. Recent studies have demonstrated an increase in mortality and morbidity among these patients in the absence of early treatment initiated at the first signs of infection. Commonly encountered multidrug-resistant (MDR) and extensively drug-resistant (XDR) bacteria in burn intensive care units include *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, and methicillin-resistant *Staphylococcus aureus* (MRSA).[5] For instance, combinations such as ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam can be used for carbapenemase-producing *Klebsiella pneumoniae*. For other metallo-beta-lactamase-producing infections, ceftazidime-avibactam can be used in combination with aztreonam or cefiderocol as monotherapy.[6]

An important strategy in the management of severe infections is the appropriate use of antimicrobial therapy. The first step is early identification of the pathogen. Initially, empirical treatment is administered to reduce the mortality and morbidity rates in burn patients. After obtaining antibiotic susceptibility results through antibiogram testing, treatment de-escalation and targeted therapy based on the identified pathogen are recommended. The use of targeted antibiotics with a narrower spectrum plays an essential role in limiting the emergence of new MDR strains.

The study conducted on a group of burn and sepsis patients treated at the Bucharest Clinical Hospital of Plastic Surgery and Burns indicated that the first signs of sepsis appeared in 97% of patients within the first 14 days from the onset of injuries, and the most frequently implicated bacteria were *Pseudomonas aeruginosa* (28%), followed by *Acinetobacter* spp (25%), and MRSA (14%). The Enterobacteriaceae group was identified in 30% proportion. These results were consistent with other studies in the literature. [7] Therefore, considering the risk of mortality posed by infection in burn patients, it is important for empirical antibiotic treatment to be initiated as early as possible after obtaining cultures and susceptibility testing. It should be targeted to reduce the risk of selection of antibiotic-resistant strains.[8]

The third section of the habilitation thesis focuses on future projects. As the head of the discipline, I aim to encourage the formation of a research group that includes the definition of clear objectives and prioritization of areas of interest, such as healthcare-associated infections in the intensive care unit and the development of research protocols in compliance with ethical standards and best practices. I also aim to promote collaboration among physicians from various related specialties, both within and outside the hospital. I would like data to be collected using modern storage and management systems, with qualified personnel handling data analysis and extraction.

A future perspective in bacterial identification is next-generation metagenomic sequencing (mNGS). The metagenomic approach offers multiple advantages as it identifies all nucleic acids present in the analyzed sample, facilitating the analysis of the entire microbiome and the human genome from which the sample was collected. This ability to detect all potential pathogens in a sample (bacteria, viruses, fungi, parasites) and simultaneously analyze the host's immune response brings significant clinical benefits. With mNGS technology, diagnosis will be achieved in a shorter time, and the results, along with the antibiogram, will be correlated with the results obtained through MALDI-TOF in the Emergency University Hospital of Bucharest.

This will represent an innovative and promising approach to reducing the length of stay in intensive care units and reducing the risk of complications associated with prolonged hospitalization. In addition to precise and rapid diagnosis, mNGS will provide detailed information about microorganisms and antibiotic resistance, enabling personalized treatment. All

of these factors will lead to significant cost savings by reducing the use of antibiotics, avoiding ineffective treatment, and shortening the duration of stay in the intensive care unit. This can serve as the basis for the development of an artificial intelligence system in collaboration with the Politehnica University of Bucharest, which can develop algorithms for targeted use of antimicrobial therapy in infected patients.

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<sup>1</sup> **Orban C**, Antibioterapia adecvata la pacientii arsi cu diferite forme de sepsis 2013

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<sup>4</sup> Stuart Edwardson, Chris Cairns, Nosocomial infections in the ICU, Anaesthesia & Intensive Care Medicine, <https://doi.org/10.1016/j.mpaic.2018.11.004>.

<sup>5</sup> Anne M Lachiewicz, Christopher G Hauck, David J Weber, Bruce A Cairns, David van Duin, Bacterial Infections After Burn Injuries: Impact of Multidrug Resistance, *Clinical Infectious Diseases*, Volume 65, Issue 12, 15 December 2017, Pages 2130–2136, <https://doi.org/10.1093/cid/cix682>

<sup>6</sup> Pranita D. Tamma,<sup>1</sup> Samuel L. Aitken,<sup>2</sup> Robert A. Bonomo,<sup>3</sup> Amy J. Mathers,<sup>4</sup> David van Duin,<sup>5</sup> &

Cornelius J. Clancy<sup>6</sup> - Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended Spectrum  $\beta$ -lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant

Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTRP aeruginosa)

<sup>7</sup> Oncul O, Ulkur E, Acar A, Turhan V, Yeniz E, et al. Prospective analysis of nosocomial infections in a burn care unit, Turkey, The Indian journal of medical research. 2009; 130, 6:758-764.

<sup>8</sup> **Orban C**, Antibioterapia adecvata la pacientii arsi cu diferite forme de sepsis 2013