”VICTOR BABEŞ” UNIVERSITY OF
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DOCTORAL SCHOOL
MEDICINE

HABILITATION THESIS

MODERN RESEARCH IN SARS-COV-2 PATHOLOGY AND OTHER RELATED DATA

A B S T R A C T

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ABSTRACT

The **purpose** of the empowerment thesis entitled **MODERN RESEARCH IN SARS-COV-2 PATHOLOGY AND OTHER RELATED DATA** is to present the most important personal academic and scientific achievements, as well as the future plans for the development of the professional career. The empowerment thesis is drafted according to the recommendations of CNATDCU and the Regulation of the "Victor Babeș" University of Medicine and Pharmacy Timisoara and is structured in five parts.

The **first part** of the thesis is focused around CARS-CoV-2 infection, with the special follow-up of cardiopulmonary and cutaneous changes in post-COVID-19 acutely, both from an electronophysiological and clinical point of view.

The first section of the research activity is dedicated to the persistent alteration of the function of the left ventricle in the context of SARS-C0V-2 and we have found correlation between the number of weeks that have passed since the onset of COVID-19 disease, the PCFS score and the RVD characterized by RV-GLS; which together explain 87.6% of outstanding symptoms. At first the symptoms were associated only with the sequelae of pulmonary damage, but similar manifestations have been described in the absence of COVID-19 pneumonia, with some authors acknowledging that there is probably a per-se syndrome responsible for these dysfunctions, with multi-organic impairment, especially the lungs, heart and brain: post-acute COVID-19 syndrome.

The second section addresses the association between the severity of post-acute COVID-19 syndrome and echocardiographic changes. This syndrome includes residual heart changes or mental disorders that seem to be correlated with the initial severity of the infection and the time elapsed since the acute infection, impacting the functional status and quality of life of the patients.

The third section highlights the presence of pulmonary hypertension post SARS-CoV-2 infection, which occurs even in cases with moderate pneumonia and lasts longer than initially estimated and seems to be correlated with the severity of the initial lung damage and inflammatory response.

The fourth section evaluates the factors that influence the evolution of pulmonary hypertension in subjects who recover from SARS-CoV-2 infection. The increase in pressure in the pulmonary artery suggests pulmonary hypertension associated with dysfunction of the right ventricle in patients recovering from COVID-19, partially explaining the symptoms that persist and that gradually improve after 3-6 months after the initial infection. The recovery is proportional to the initial severity of complications and lung damage, but also to viral pathogenesis.

The fifth section assesses respiratory complications in COVID-19 patients: spontaneous pneumomediastinum, pneumothorax, pneumopericard and subcutaneous emphysema, with a prevalence of 0.66%, similar to 1% reported in the medical literature. Pneumothorax was most commonly diagnosed 72.72%, followed by pneumomediastinum associated with subcutaneous emphysema (63.63%), and pneumoperitoneum was identified in a single case. Mortality was 72.72%, despite intensive care measures, including ECMO in one case.

The sixth section identifies cutaneous manifestations in infection with SARS-CoV-2, a new clinical element as the only clinical expression and may suggest a moment of resurgence in the evolution of the disease, the patients being classified in moderate forms of the disease. These skin manifestations have been classified into maculopapular eruptions, urticarial lesions, rosacea-like rashes and erythema multiforme lesions.

The second part contains data of epidemiology, pathogenesis and treatment in clostridium difficile infection, an infection constantly increasing in number, severity/mortality and increased costs. The first and second sections establish correlations between ribotype and clinical form, in two distinct studies over one year and two years respectively: strain 027 again demonstrates the importance of ribotyping, even in mild initial forms of disease. The first treatment option is oral vancomycin. The ATLAS score must be correlated with other risk factors in order to obtain mathematical models as accurate as possible in evolutionary predictions. 3% of patients with IDUs will progress to fulminant colitis, which is associated with a mortality rate of 80%.

The third section analyzes patients with COVID-19 and clostridium difficile, in which 80% of the subjects recognized hospital services 48h before the first digestive symptoms, 95% of the patients being at the first episode of IDUs. The most widely used antibiotic was azithromycin,in outpatient patients. The most common comorbidities were cardiovascular disease or diabetes. For optimal management of

COVID-19 patients, we need to implement antibiotic guidelines and guidelines related to specific protective equipment.

The third part contains relevant data about the new natural anti-inflammatory and antitumor components (bedulin, triterpenoid, eugenol) and silver nanoparticles obtained by biosynthesis from natural compounds. These antitumor compounds have been investigated using drug delivery systems, nanostructures called polyurethane carriers and the results show that polyurethane nanostructures have good values for their size and stability. Bedulin, a natural compound in birch bark, can be used by an interfacial polyaddition technique in obtaining a polymeric drug delivery system that allows use on human skin. Polyurethane structures with and without eugenol were sintetised using a polyaddition process combined with simultaneous emulsification. The bio-evaluation of the product, based on different methods on the skin of mice, suggests that these products are safe in the use of oral therapies. Silver nanoparticles obtained by biosynthesis are also an area of interest in approaching biofilm. They were obtained from rosemary leaf extract and analyzed spectrophotometrically as activity against S.aureus, E.coli, P. aeruginosa and C. albicans. The most pronounced action has been identified against E. coli and the viability of healthy gum cells is significantly influenced only at concentrations higher than 10 microgram/ml. Silver nanoparticles obtained by green synthesis, using plant extracts, are optimal candidates, which must be exhibited to the maximum in the prevention and control of antimicrobial biofilm.

In the fourth part I present the development of my career over the years and the most important scientific advances. This part contains my early career and subsequent evolution, research activity, managerial activity as well as merits and publishing activity. The appetite for knowledge and information, one of my basic traits, began in 1997, when I became a resident physician in the infectious diseases specialty. The development on the medical level continued with obtaining the title of specialist doctor and then senior physician of infectious diseases.

The first important step in my academic career was made in 2004, once I obtained the title of Doctor of Medicine with the thesis 'Clinical, evolutionary and therapeutic correlations in HIV infection in children' Subsequently, in May 2005, I obtained competences in general ultrasound. His academic career began in 1997,

and since 2019 I am an Associate Professor in Infectious diseases at "Victor Babes" University of Medicine and Pharmacy Timisoara. As a result of all the experiences throughout my career, I have gained an important knowledge package, harnessed by publishing numerous books, guides and articles.

In the last part of this paper I present strategies, specific to each of the three important areas: didactic activity, research activity and clinical activity. The steps of my professional development will follow the previous trend of my career, that of constantly updating the knowledge in the medical field in which I work. For my short, medium and long-term plans, I intend to continue the projects started and initiate new projects that will be the subject of my active participation in the competitions organized to obtain funding for medical research, both locally, as well as at national or even international level. The main future directions of research continue the activity of the postdoctoral period. One of my priorities will be related to SARS-CoV-2 infection, including long-COVID and post-acute COVID components, with the identification of phenotypes/ resistance mutations for a personalized therapy. Another project will include modern therapy and molecular diagnosis of HIV/AIDS. Another topic proposed as a future research project, includes the detection of risk factors involved in the emergence of resistance to anti-infective therapy in Romania, in terms of local adaptive genetic changes. Last but not least, the next topic proposed is to continue the research in the field of anti-inflammatory and antitumor nanotechnology, as well as to combat microbial infections.

In conclusion, in this empowerment thesis, I have tried to summarize the main achievements and perspectives of my professional, academic and research development, trying to make arguments in favor of accepting me as a competent coordinator.

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