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PhD THESIS

THE SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2: NOVEL THERAPEUTICS AND SUPERINFECTION

A B S T R A C T

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TABLE OF CONTENTS

GENERAL PART

1. COVID-19

1.1. OVERVIEW

From the common cold to more deadly varieties like the severe acute respiratory syndrome (SARS), the middle east respiratory syndrome (MERS), and COVID-19, viruses can cause mild to fatal respiratory tract infections. The term "coronavirus" comes from the latin word "crown," which describes the distinctive appearance of virions under electron microscopy, which produces an image resembling the solar corona, or a halo.

The new disease first appeared in December 2019 in Wuhan, China, with early cases appearing to be linked to a local fish and live animal market. The cluster of patients exhibited respiratory features of pneumonia and acute respiratory distress syndrome, as seen in the SARS coronavirus of 2002-2003, leading scientists to suspect a zoonotic virus.

1.2. IMMUNE SYSTEM RESPONSE TO COVID-19

Infection with SARS-CoV-2 induces both innate and adaptive immune responses. The response time, target antigens, and mechanism of viral antigen recognition differ between innate and adaptive immune responses, and they offer the host with dynamic and broad protection.

1.3. PATHOPHYSIOLOGY

The inflammatory process is triggered by an interaction between the human ACE2 receptor and the spike protein on viral particles. A common cause of mortality is the development of SARS-CoV-2 pneumonia, which leads to acute respiratory distress syndrome (ARDS). ACE2 is specifically expressed in alveolar epithelial type II cells. When COVID-19 is severe, clotting factors are consumed and the coagulation process becomes fulminant. There is a high incidence of thrombotic complications in critically ill patients, including deep vein thrombosis, pulmonary embolism, and thrombotic arterial complications.

1.4. SEVERE COVID-19 IN THE INTENSIVE CARE UNIT

One week after the onset of symptoms, COVID-19 patients can rapidly deteriorate in 20% of cases, increasing the severity of the condition. Within 24 to 48 hours of the onset of symptoms, severe COVID-19 is indicated by worsening dyspnea, hypoxia, or lung infiltrates that are greater than 50% on imaging. The most frequent reason COVID-19 patients are admitted to the ICU is hypoxemic respiratory failure. Age, abnormal laboratory results, comorbidities (diabetes, hypertension, coronary artery disease, malignancy, chronic lung disease), and male sex have all been linked to a worsening of the disease. It has been reported that between 39 and 72% of patients who are admitted to the ICU die.

1.5. TREATMENT

Several classes of medications, many of which were created before the SARS-CoV-2 pandemic, are used to treat COVID-19 patients both in- and outside of hospitals.

1.5.1. Antivirals

The COVID-19 Treatment Guidelines Panel suggests the following anti-SARS-CoV-2 therapies as the top options for treating adults with COVID-19 outside of hospitals: Nirmatrelvir (Paxlovid) with ritonavir augmentation and Remdesivir are both highly recommended (moderate recommendation). When neither of the preferred therapies is available, practicable to use, or clinically appropriate, the Panel suggests molnupiravir as an alternative treatment (weak recommendation).

1.5.2. Immune modulators

Drugs known as immune modulators help to activate, enhance, or suppress immune function. The immune system may become overactive in the case of COVID-19 infection, which could worsen the condition. Immune regulators can aid in reducing this inflammation. For the treatment of COVID-19, the following immune modulators have been approved: tocilizumab, baricitinib, Anakinra, corticosteroids.

1.5.3. SARS-CoV-2 targeting monoclonal antibodies

Monoclonal antibodies made in a lab that specifically target SARS-COV-2 can support the immune system's fight against the virus. These monoclonal antibodies prevent the virus from entering human cells and neutralize it. Through an emergency use of

authorization, the following monoclonal antibodies that target SARS-COV-2 are permitted to be used: Bebtelovimab and tixagevimab co-packaged with cilgavimab.

1.5.4. Antithrombotic therapy

Increased levels of fibrin, fibrin degradation products, fibrinogen, and D-dimer have been linked to COVID-19 and inflammation as well as a prothrombotic state. Several organizations have released guidelines for the use of antithrombotic therapy in patients with COVID-19. According to the recommendations issued, hospitalized COVID-19 patients who are not pregnant should at the very least get a prophylactic dose of anticoagulation to stop venous thromboembolism. The Panel advises treating patients with COVID-19 who have a high likelihood of having thromboembolic disease with therapeutic anticoagulation when diagnostic imaging is not an option (strong evidence). The panel advises treating patients with antithrombotic therapy in accordance with the standard institutional protocols for those without COVID-19 in cases where they need ECMO, continuous renal replacement therapy, or have thrombosis related to catheters or extracorporeal filters

2. THERAPEUTIC PLASMA EXCHANGE (PLASMAPHERESIS)

2.1. INTRODUCTION

A therapeutic procedure called apheresis involves drawing blood from the body, purifying it of pathogens, and then reintroducing it into the body. However, plasma exchange can also replenish healthy substances. The most popular term for a specific therapeutic apheresis procedure in which the patient's plasma is removed and "exchanged" with a replacement solution is called "therapeutic plasma exchange" (TPE).

2.2. MECHANISMS OF ACTION

TPE exerts its beneficial effects via a number of mechanisms. Its main effects include the rapid depletion of specific disease-causing agents like antibodies, toxic factors, immune complexes, and thrombotic factors, or inflammatory agents like cytokines and complement, and replacement of specific plasma factors (clotting factors, immunoglobulins).

2.3. CLINICAL CONSIDERATIONS

The American Society for Apheresis has been working on categorizing relative indication groups for TPE and other therapeutic apheresis techniques since 1993. Disorders were categorized into four groups, from category I, where TPE is used as the primary treatment or as a first-line adjunct therapy to other available treatments, to category IV, where TPE has no therapeutic benefit and is not advised. TPE should be used for conditions where its efficacy is well established.

3. CONVALESCENT PLASMA

3.1. OVERVIEW

Convalescent plasma (CP), also known as immune plasma or hyperimmune plasma, is blood plasma donated by a patient who has recovered from a particular illness with the intention of giving a patient who is currently ill with that particular illness passive immunity. When CP is administered to a patient who is experiencing a particular illness for the first time, the convalescent plasma's antibodies bind to the disease-causing virus or bacteria and may reduce or stop the virus from entering and replicating in the patient's cells.

3.2. TREATMENT CONSIDERATIONS IN COVID-19

Humoral immunity, a crucial component of the human immune response to SARS-CoV-2, is variable and matures over the 2–6 weeks following infection. The idea behind using CP for the treatment of COVID-19 is that patients who have not yet produced their own antibody response may benefit from the passive administration of antibodies from a convalescent donor.

4. BACTERIAL AND/OR FUNGAL SUPERINFECTION IN COVID-19

4.1. THE CRITICALLY ILL PATIENT

Patients with COVID-19 who are admitted to the ICU run a high risk of contracting an infection for a variety of reasons. They first frequently experience multiple organ failure, necessitating the use of vasopressors, renal replacement therapy, and occasionally ECMO support. As a result, these patients typically have longer stays in the ICU (up to 49 days for ICU length of stay and up to 19 days for mechanical ventilation, respectively). Second, COVID-19 is linked to severe immune system dysfunction in the patient. Third, systemic corticosteroids are now routinely administered to all patients who need extra oxygen. Additionally, these patients frequently receive a variety of medications designed to reduce the immune system's reaction to the viral infection, such as cytokine inhibitors (tocilizumab, anakinra, sarilumab) or complement inhibitors (eculizumab).

4.2. VIRAL INFECTION AND BACTERIAL/FUNGAL SUPERINFECTION

Infections can be categorized into two groups: Co-infections are infections found at the time of the patient's admission to the healthcare facility, and superinfections, also known as healthcare associated infections (HAI), are infections found throughout the hospital stay.

Ventilator-associated pneumonia (VAP) and bloodstream infections (BSIs) are the most prevalent superinfections in COVID-19-infected critically ill patients. When a new pathogen is found in a biological specimen and the patient exhibits clinical symptoms and signs of infection, the diagnosis is made.

The presence of Clostridioides difficile infection should not be overlooked either. Although the full effects of the COVID-19 pandemic on CDI are still unknown, it was reported that during the pandemic there was a decline in C. difficile testing and an increase in the use of broad-spectrum antibiotics, which may contribute to the development of a CDI.

4.3. PRINCIPLES OF TREATMENT

In contrast to co-infections, which happen concurrently with the initial infection, superinfections are defined by the CDC as "an infection following a previous infection, especially when caused by microorganisms that are resistant or have become resistant to the antibiotics used earlier".

All patients on mechanical ventilation were to receive an empiric antibacterial medication, according to the initial Surviving Sepsis Campaign guidelines for the management of critically ill COVID-19 patients. Later data, however, revealed that SARS-CoV-2-infected patients rarely had concurrent bacterial infections at the time of ICU admission. Experts concur that prophylactic administration of empiric antibiotherapy in the absence of obvious signs of co-infection or of a secondary infection should be discouraged due to the high incidence of infectious complications brought on by multidrug-resistant (MDR) germs.

SPECIAL PART

5. MATERIAL AND METHOD

5.1. PURPOSE

Starting with early 2020, TPE and CP transfusion have been explored individually as potential treatments in the battle against severe and critical forms of COVID-19. Nevertheless, even though multiple case reports and case series emerged describing the potential benefits of these treatments individually, none of them explored the combination of sequential TPE followed by transfusion of CP from healthy donors. As such, the idea behind the current doctoral project was born – to explore the advantages of TPE followed by transfusion of CP in report to standard of care for patients with severe and critical forms of COVID-19. Furthermore, reasearch was continued to study superinfections in severe and critical COVID-19 patients hospitalized in the ICU, as national and global data was scarce and just starting to emerge.

5.2. OBJECTIVES

- determining whether combining TPE with transfusion of CP from healthy donors early during hospitalization in the ICU improves survival reported to standard of care treatment
- assessing the evolution of partial pressure of arterial oxygen to fractional inspired oxygen ratio (P/F ratio) before and after treatment

- assessing the evolution of CRP, lactate dehydrogenase (LDH) and ferritin levels before and after treatment
- determining the rate of bacterial/fungal superinfections in COVID-19 patients hospitalized in the ICU
- identifying risk factors associated with the development of bacterial/fungal superinfections
- discerning whether superinfections play a role in patients' outcome

5.3. GENERAL METHODOLOGY

This research project is structured in the form of a clinical trial and a case report in order to best apprehend the implications of TPE followed by CP transfusion in severe and critical forms of COVID-19 and a separate retrospective observational study to explore the implications of bacterial/fungal superinfections in COVID-19 patients hospitalized in the ICU.

The clinical trial was conducted according to the guidelines of the Declaration of Helsinki. Patients provided informed consent immediately after admission into the ICU. Where obtaining informed consent was not possible due to the patient's critical condition, a legal representative provided informed consent.

The first step was to design the trial. The intervention, consisting of TPE followed by transfusion of CP was applied to patients in a non-randomized way, as human and material respectively biological resources consisting of the convalescent plasma were scarce. After the patient's discharge from the ICU, relevant data was introduced into an electronic database (Microsoft Excel file) in order to allow statistical processing. Finally, data was statistically analized and a clear difference in mortality was observed between the intervention and the control group along with a few more interesting secondary endpoints.

For the observational study, data collection was carried out in accordance with the law, with the observance and protection of confidentiality being approved by the Ethics Commission of SCJUPBT, no. 206/7.09.2020. At the level of our university hospital, the informed consent is included in the consent given upon the admission of the patient with the possibility of using their data in any studies or research papers.

Firstly, the hospital records of 302 consecutive patients with SARS-CoV-2 pneumonia admitted to the COVID-19 ICU of SCJUPBT during the third wave of COVID-19, in Romania, were reviewed. Inclusion and exclusion criteria were established and relevant data was introduced into an electronic database (Microsoft Excel file). This study was performed using data of microorganisms isolated from clinical specimens in the Department of Microbiology of the Clinical Laboratory of SCJUPBT.

5.4. MICROBIOLOGICAL METHOD

The SCJUPBT Microbiology Laboratory's operating protocol was followed when performing microbiological diagnosis.

5.5. STATISTICAL ANALYSIS

The collected data were analyzed using IBM SPSS Statistics 20 (SPSS Inc., Chicago, IL). Category variables were characterized by value and percentage while continuous variables were characterized by median and interquartile range (IQR). The 95% confidence interval was measured for all variables. The Shapiro-Wilk tested the data distribution. Numerical variables were compared by Mann–Whitney U-test for comparison between two independents sub-samples. For nominal variables the chi2 test was used (Fisher exact test). The bivariate correlation was performed by applying the Pearson correlation. It was considered a risk factor in the case of an odds ratio (OR) / risk ratio(RR) > 1 (95% CI> 1), with statistical significance. Variables that met the statistical significance ($p \leq 0.05$) in univariate analysis were later investigated by logistic regression, the model being chosen according to the Nagelkerke R2 coefficient. The Hosmer-Lemeshow test assessed the deviation from the theoretical model. The avoidance of multicollinearity was achieved by linear regression, with the calculation of the variance inflation factor (VIF). The Kaplan-Meyer method with the log-rank (Mantel Cox) test was applied to evaluate the primary endpoint of the clinical trial. Cox regression was used to determine hazard ratio of the treatment group. All statistical tests were two-tailed and the statistical significance threshold p was set at 0.05.

6. STAGES OF THE RESEARCH

6.1. THERAPEUTIC PLASMA EXCHANGE FOLLOWED BY CONVALESCENT PLASMA TRANSFUSION IN SEVERE AND CRITICALLY ILL COVID-19 PATIENTS: A SINGLE CENTRE NON-RANDOMIZED CONTROLLED TRIAL

6.1.1. Introduction

As of June 7, 2021, the WHO had received reports of 173,005,553 confirmed COVID-19 cases worldwide, along with 3,727,605 deaths that were related to those cases. Even though mass vaccination programs began early in December 2020 and nearly 2 billion

vaccine doses have been given worldwide, the COVID-19 pandemic is about to enter its fourth wave. Few drugs have proven to be effective in treating COVID-19, despite the fact that the entire world's medical community has been working relentlessly to find the best cure.

6.1.2. Purpose/Objectives

The purpose of this study was to see if combining TPE (a specific therapeutic apheresis procedure performed to rapidly remove the patient's plasma and 'exchange' it with a replacement solution) with CP transfusion (CP therapy uses blood from people who have recovered from illness to help others recover) early during hospitalization improves survival among severe and critical COVID-19 patients. Secondary endpoints were to assess the effects of this combined treatment on other parameters like the P/F ratio, CRP, LDH and ferritin levels.

6.1.3. Material and method

The current single-center non-randomized controlled trial included 38 Caucasian patients. Patients who participated in the study were randomly assigned to one of two groups: a treatment group received sequential TPE and CP transfusions in addition to standard COVID-19 treatment, while a control group received only standard COVID-19 treatment (antiretrovirals, corticosteroids, anticoagulants, and antibiotics as needed) according to hospital protocols.

6.1.4. Results

There was a statistically significant difference in the survival rates between the two groups (log rank test: P=0.002). The treatment had a statistically significant positive impact on survival, according to the Cox regression analysis of outcome (HR 0.39; 95% confidence interval (CI), 0.16-0.91; P=0.007). Secondary outcomes showed an improvement in oxygenation, and a decrease in CRP, LDH and ferritin levels.

6.1.5. Discussions

The early initiation of TPE and transfusion of CP may play a crucial role in controlling dysregulated inflammation in severe forms of COVID-19 in patients needing ICU monitoring and therapy. Its benefits can be seen in enhancing oxygenation, decreasing inflammation, preventing cytokine storms, and eradicating viral load and autoantibodies, which rise in the later more severe stages of the infection. Our proposed therapeutic approach might as well shift the antigen-antibody ratio in favor of the latter.

6.1.6. Partial conclusions

The current study demonstrated that the early initiation of TPE, followed by the transfusion of CP, improved the survival rate in a small number of critically ill COVID-19 patients receiving intensive care treatment. Additionally, there was a decrease in inflammation and a nearly statistically significant increase in oxygenation.

6.2. THE SUCCESSFUL RECOVERY OF A CRITICALLY ILL COVID-19 PATIENT, FOLLOWING THE COMBINATION OF THERAPEUTIC PLASMA EXCHANGE AND CONVALESCENT PLASMA TRANSFUSION: A CASE REPORT

6.2.1. Introduction

The end of 2019 saw the emergence of a pandemic with a complex symptom pattern, including disseminated intravascular coagulopathy and thrombosis, systemic hyperinflammation, cytokine release syndrome, acute lung injury, and ARDS: COVID-19. Few studies have looked into the two procedures combined: transfusion of CP following the conclusion of the TPE session.

6.2.2. Case report

The current case report presents the recovery of a patient treated with TPE and subsequently transfusion of CP, from the group of the clinical trial mentioned above.

Timeline

Presentation	A 52-year-old man presented in the ER with malaise, fever, severe cough, tachypnea, tachycardia, and dyspnea, which started 2 days before the presentation. Upon rapid assessment, the patient had low oxygen saturation and showed signs of respiratory failure. The decision was made to transfer the patient to the ICU after preliminary radiological examination.
Initial treatment	Upon ICU admission, the patient was immediately started on high flow nasal oxygenation (60 L/min, FiO_2 = 100%) combined with a non-rebreathing oxygen mask (oxygen flow rate 15 L/min). Antiviral therapy with remdesivir, high dose corticosteroid pulse therapy with methylprednisolone, and therapeutic anticoagulation with nadroparine were started, according to hospital and national guildelines.
Day 1	Patient's respiratory status worsened, requiring escalation to non-invasive ventilation with CPAP facemask and, 3 h later, after rapid assessment, intubation and mechanical ventilation were considered vital. A dual lumen 14 French dialysis catheter was placed in the right femoral vein under echographic guidance and a single TPE session was performed using 40 mL/kg FFP as substitute. Upon completion of the TPE session, the patient was transfused with 500 mL ABO compatible CP under careful monitorization. (The procedures were performed on day 3 after the onset of symptoms).
Day 9	Sedation and neuromuscular blockade were ceased and respiratory weaning from mechanical ventilation was started by switching the ventilation mode to spontaneous (CPAP).
Day 11	Extubation was performed.
Day 12	Uncontrollable hypercapnia leading to neurologic status aggravation determined intubation and the start of mechanical ventilation and continuous sedation.
Day 15	Patient was weaned off mechanical ventilation and extubated. RT-PCR test resulted negative and the patient was transferred to the non-COVID-19 ICU.
Day 23	Lung CT was performed for pulmonary re-evaluation.
Day 24	The patient was discharged home.

6.2.3. Discussions

In order to reduce inflammation, prevent cytokine storms, improve oxygenation, and eliminate viral load and autoantibodies by tipping the antigen-antibody ratio in favor of the latter, the dysregulated inflammation syndrome in severe forms of COVID-19 may be managed by the early initiation of TPE followed by the transfusion of CP. This case report has the significant benefit of presenting a rescue treatment option that has not received much attention but has the potential to be very effective in treating critically ill patients with severe COVID-19 and may also be useful in treating other diseases.

6.2.4. Partial conclusions

The current case report demonstrated that early TPE administration followed by CP transfusion improved our patient's overall prognosis by lowering inflammatory markers and improving oxygenation. It is challenging to determine how much corticosteroids and antivirals influenced the result.

6.3. BACTERIAL AND FUNGAL SUPERINFECTIONS IN COVID-19 PATIENTS HOSPITALIZED IN AN INTENSIVE CARE UNIT FROM TIMISOARA, ROMANIA

6.3.1. Introduction

Data on bacterial and mycotic superinfections in COVID-19 patients in Romania are scarce and still developing. The dynamics of bacterial and fungal infection in severely and critically ill COVID-19 patients, however, are still poorly understood.

6.3.2. Purpose

In the COVID-19 ICU of the largest university hospital in Western Romania, we conducted a study to ascertain the hospital acquired infection rate in patients with COVID-19 pneumonia, risk factors related to the emergence of bacterial and fungal superinfections, and prognostic risk factors for mortality in the aforementioned patient population.

6.3.3. Material and method

In a retrospective cohort, non-interventional, single center study, the medical files of 302 patients with SARS-COV-2 pneumonia who were admitted to the COVID-19 ICU of SCJUPBT between October 2020 and May 2021, were examined.

Two independent reviewers went over the hospital records of all the enrolled patients. The following groups of variables were created: demographic information, comorbidities, clinical information (including COVID-19-relevant biological variables obtained at ICU admission), microbiological information, antibiotic use, length of stay, and patient

discharge status. A database created for this study was used to collect the data after it was anonymized.

Patients were split into two groups: those who had unfavorable outcomes (died or became worse during hospitalization) were in group 1, and those who had favorable outcomes (improved status upon discharge) were in group 2. The same patients were divided into groups 3 and 4 based on whether they had a bacterial/fungal infection during their ICU hospitalization (group 3) or not (group 4).

6.3.4. Results

A study group of 236 patients was formed during the 8 months of surveillance, with a median age of 66.50 years, a male gender predominance of 58.90% versus a female gender predominance of 41.10%, and a median number of days spent in the ICU of 9.00 days. The majority of the patients (64.41%) had severe forms of the disease, 33.47% were in critical condition, and 2.12% had moderate forms of COVID-19 but with severe underlying pathology.

Case fatality rate was 74.58%; patients with bacterial/fungal superinfections had a similar rate (73.11%) compared to non-infected patients (76.07%).

Superinfection didn't come up as an independent risk factor for unfavourable outcomes. It is important to note that only 13 patients (11.11%) with COVID-19 who were free of bacterial or fungal infections underwent hospitalization without receiving antibiotic chemotherapy.

6.3.5. Discussions

In the study carried out at our institution, we discovered a rate of bacterial or fungal superinfection of 50.42%, with a significant number of MDR and XDR strains isolated from the biological specimens. The long duration of CVC maintenance and prior corticosteroid therapy were two predictors of bacterial or fungal superinfection that the regression model identified. However, not even the univariate analysis model identified the bacterial or fungal superinfections as a risk factor for unfavorable outcome of patients. The case fatality rate was comparable in the subsamples of superinfected and uninfected patients, confirming that superinfection did not significantly affect patient outcomes in our study population.

6.3.6. Partial conclusions

During the third wave of the pandemic, a population of COVID-19 patients hospitalized in our ICU had a high rate of superinfection (50.42%). Considering that some clinical (particularly fever, cough, dyspnea, diaphoresis, etc.) and paraclinical (radiological signs of pneumonia, high inflammation, etc.) findings in viral infections, only a small

percentage of COVID-19 patients who did not develop bacterial or fungal superinfections were not prescribed antibiotics over the course of their hospitalization, there are serious concerns regarding the prudent prescribing of antibiotics in viral infections. Superinfection didn't play a major role regarding clinical outcomes in our study population.

7. GENERAL CONCLUSIONS

There are few rescue therapies reserved for severe and/or critical forms of COVID-19 pneumonia who require ICU hospitalization. Two methods have been individually described through a large number of case reports and small case series, even a few larger studies, TPE and transfusion of CP. A statistically significant increase in the survival rate at 30 days was noticed in the group which underwent this treatment. Inflammation was decreased through the reduction of markers such as CRP, LDH and ferritin. An improvement in oxygenation was also noticed in the treatment group. These promising results advocate for the need to continue the study of this exploratory therapy through more powerful randomized controlled trials in order to determine the characteristics of patients who would benefit the most from this treatment.

Bacterial and/or fungal superinfections in COVID-19 patients hospitalized in intensive care units present with great variations around the globe, which can be explained by local specific epidemiology and medical practice and also depends on the strength of the antibiotic stewardship program. It has not yet been agreed upon, whether superinfection increases mortality in this specific population. In our study group, superinfection did not come up as a risk factor for unfavorable outcomes of patients with severe or critical forms of COVID-19, and fatality rates were similar between patients with superinfections and uninfected patients. The high superinfection rates described in this thesis, along with the high incidence of MDR bacteria and the overuse of empiric antibiotic chemotherapy should raise concerns and improve collective efforts to strengthen local antimicrobial stewardship programs, which would result in relieving the burden of antibiotic resistance, improving antibiotic prescribing patterns and reducing hospitalization costs.

Our reasearch has reached our proposed objectives and presents original data of actuality for current clinical practice.

8. ORIGINALITY OF THE THESIS

Our project's originality mainly consists of exploring a novel treatment, consisting of the sequential early use of TPE, followed by transfusion of CP from healthy donors in patients presenting with severe and critical forms of COVID-19 pneumonia. Data on this treatment is currently scarce in international literature, and the promising results we have observed may lead to further study of its application in COVID-19 and possibly other existing diseases, or in diseases that have yet to emerge.

New local data is also brought to light to complete the national and international databases with regard to bacterial and/or fungal superinfections in patients hospitalized with COVID-19 pneumonia in the ICU of the largest universitary hospital in western Romania.

Thereby, through the reasearch conducted, this thesis lays base for further study of COVID-19 in the years to come.