**OVIDIUS UNIVERSITY OF CONSTANTA**

**DOCTORAL SCHOOL OF MEDICINE**

**MEDICINE FIELD**

**DOCTORAL THESIS**

# THE IMPACT OF PATHOGENIC GERMS ON THE EVOLUTION OF PATIENTS ASSISTED IN THE INTENSIVE CARE UNIT

**-SUMMARY-**

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# I. GENERAL PART

## INTRODUCTION

Assessment of hospital bacterial strains is central to effective patient management. With the help of this data, doctors decide on empiric antibiotic therapy for patients, which is often life-saving. Determining the difference between bacterial colonization and infection is essential for determining antibiotic treatment, particularly if a backup antibiotic is used. Unfortunately, due to multiple factors, bacterial colonization and infections in hospitals are not assessed, leading to the transmission of bacteria from one patient to another. Thus, the transmission of antimicrobial resistance from one bacterium to another is present in hospitals, being one of the causes of healthcare-associated infections in hospitals. Regarding bacterial colonization, bacterial infection, and the associated resistance mechanisms, it is important to know and differentiate between them in order to initiate the correct treatment and decrease the risk of acquiring infections associated with the medical act.

Regarding antibiotic resistance, there are multiple resistance mechanisms, among which methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamases (ESBL), and carbapenem-resistant Enterobacterales (CRE) are detected by specific microbiological methods.

Patients who have acquired infection with MRSA bacteria, ESBL, especially CRE, carbapenemase-producing CRE (CP-CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenemase-producing Acinetobacter baumannii (CP-CRAB), *Pseudomonas aeruginosa* carbapenem-resistant carbapenemase-producing (CP-CRPA) and vancomycin-resistant *Enterococcus* (VRE) usually have limited therapeutic alternatives, requiring new antibiotics or the invention of other antibiotics to neutralize these bacteria [1.2.3.4].

There ample discussion on decolonization in at-risk patients, and studies are in favor of decolonizing patients to decrease the risk of acquiring and transmitting infections. Clinical data overwhelmingly support the fact that bacteria pass their resistance genes to other bacteria, and decolonization is an effective method to decrease the risk of passing bacterial resistance to other patients.

The role of bacteriological screening consists in detecting patients colonized with multi-resistant bacteria (MDRB) before admission in order to:

– Ensure an optimal framework from an epidemiological point of view for their isolation and for the prevention of the spread of the infection in an intra-hospital environment;

– Adapt preoperative antibiotic prophylaxis depending on the particular germs detected to ensure extra anti-infective security for patients;

– Reduce the risk of infectious septic complications associated with the medical act;

– Ensure the protection of medical personnel by acknowledging patients colonized with MDRB and taking the necessary precautions, described below:

- Notify the entourage of the patient colonized with MDRB and inform them of the necessary decolonization measures, where this is possible and useful:

- Protect immunosuppressed patients (oncological, surgical wards, patients of advanced age) via knowledge of the infectious particularities and estimating the potential risks associated with the applied treatments, which allows the timely approach of necessary preventive measures [5].

The paper includes a batch of 320 patients and 3 main studies, adding up a total of 47 tables, 34 figures, and a bibliography consisting of 110 references.

## II. SPECIAL PART

## PERSONAL CONTRIBUTION

### Chapter 1. Research Purpose, Working Hypothesis, and Study Objectives

#### 1.1. Research Purpose and Working Hypothesis

This research topic was chosen based on the desire to bring effective methods to hospitals to reduce the infections associated with the medical act. Thus, the first chosen topic was the knowledge of the circulation of germs in the intensive care unit, which has an essential role in establishing an antimicrobial stewardship plan. We started from the premise that if we knew what we were up against, we had a chance to win through prophylaxis or choosing the right treatment, in a situation where the enemy is invisible and dangerous.

Antimicrobial resistance is a growing pandemic, which is difficult to manage. In a context of knowing the nature of the bacterial colonization, bacterial infections, resistance mechanisms, and the risk factors for acquiring them from high-risk wards, effective means exist to combat microbial resistance through the formation of antimicrobial stewardship programs.

Since the establishment of the intensive care unit of the Constanța Clinical Hospital for Infectious Diseases (September 2017), until March 2020, when the first patient with SARS-CoV-2 infection was admitted to the ward, 320 patients underwent bacteriological screening at admission or during hospitalization in the intensive care unit. During the 2 1/2 years, we expected there to be an increased population of bacterial strains that evince resistance mechanisms, as the patients who were admitted to the intensive care unit were at increased risk of acquiring resistant bacteria.

### 1.2. Main Objectives

The main objectives of the studies are:

- Decreasing the number of infections associated with the medical act by assessment of the circulation of germs, the risk factors of colonization, and of bacterial infections;
- Evaluating the mortality rate and the risk factors associated with death.

### 1.3. Secondary Objectives

- Establishing the statistical basis necessary for the creation of a local guide (antimicrobial stewardship) specific to the intensive care unit of the Constanta Clinical Hospital for Infectious Diseases according to the existing microbial flora and the mechanisms of resistance to antibiotics;
- Making recommendations for testing strains with MRSA, ESBL, carbapenemases, and VRE in wards at risk of colonization or bacterial infections with resistance mechanisms.

## Chapter 2. General Research Methodology.

### 2.1. Study Design, Inclusion, and Exclusion Criteria

For the completion of the doctoral thesis, approval was obtained for the processing of patient data from the intensive care unit of Constanța Clinical Hospital for Infectious Diseases, from September 2017 to March 2020. The first study was a retrospective, observational study, covering a period of two and a half years, from the establishment of the intensive care unit in the Constanța Clinical Hospital for Infectious Diseases (September 2017) until March 2020, when patients with severe acute respiratory syndrome 2 (SARS-CoV-2) infection were admitted. Studies 2 and 3 were retrospective, case-control studies, and included the same group of patients as the first study.

From the screening data performed at admission, 7 days after admission, and from other microbiological samples collected, the following criteria were used:

**2.1.1. Inclusion Criteria of the Two Categories of Samples:**

– Patients hospitalized in the intensive care unit between September 2017 and March 2020 who underwent bacteriological screening, regardless of admission pathology, with epidemiological, clinical, paraclinical, and imaging data collected on admission**.**

**2.1.2. Exclusion Criteria of the Two Categories of Samples:**

– Patients who were hospitalized in the intensive care unit of the Constanța Clinical Hospital for Infectious Diseases for less than 24 hours;

– Patients who were not bacteriologically screened in the intensive care unit.

**The data used in the study were the following:**

– Year of admission;

– Sex;

– Provenance;

– Age and age range;

– Condition on admission in the intensive care unit (neurological, pneumatological, cardiological, digestive, urological/nephrological cause, human immunodeficiency virus (HIV), and other causes);

– Type of infection upon admission (bacterial, viral, infection of unknown cause);

– Microbiological strain as a cause of admission to the intensive care unit;

– Previous hospitalization/transfer in the last six months and the hospitals where they were previously hospitalized;

– Pre-hospital antibiotic therapy in the last 6 months;

– Duration of hospitalization in the intensive care unit;

– Charlson and Carmeli scores;

– Use of invasive medical devices such as orotracheal intubation (IOT);

– Bacterial colonization detected on admission or discharge in/from the intensive care unit;

– Bacterial infections detected on admission or discharge, or during hospitalization in the intensive care unit (without them being the cause of admission to the intensive care unit);

– Type of bacterial strain detected;

- Site of colonization/infection (nasal, pharyngeal, pulmonary, digestive, blood, and urinary);
- Mechanism of microbial resistance (MRSA, ESBL, carbapenemases, and VRE);
- Antibiotic treatment administered according to the classes of antibiotics selected and the reserve antibiotics;
- Administration of antiviral treatment;
- Administration of antifungal treatment;
- Cortisone treatment;
- Patients' comorbidities;
- Evolution of patients.

### 2.2. Microbiological Detection Methods

The microbiological laboratory tests used to perform bacteriological screening in the intensive care unit were performed using phenotypic methods of bacterial identification. Chromogenic agar medium, the double disc synergy test, the modified Hodge tests, and the Rosco disc tests were used.

From rectal swabs, ESBL-producing gram-negative bacilli (GNB) were detected on chromium ESBL agar in selective culture media (CHROMID ESBL, bioMrieux). ESBL production was confirmed using a double-disc synergy assay. Escherichia coli ATCC 35218, Klebsiella spp. ATCC 700603 and ATCC BAA-2814 were used for quality control purposes.

Detection of carbapenem-resistant Enterobacteriaceae (CRE) and carbapenem-resistant Acinetobacter baumannii (CRAB) isolated from rectal swabs was performed using carbapenemase-producing Enterobacteriaceae chromogenic agar medium (CHROMID CARBA) and confirmed using the modified Hodge test (MHT) or Rosco disk (ROSCO Diagnostica) as CPE.

Vancomycin-resistant Enterococcus faecalis and Enterococcus faecium (VRE) were detected in rectal swabs using a selective chromogenic medium (CHROMID VRE).

To detect MRSA in nasal or pharyngeal exudates, Chrom MRSA or CHROMagar chromogenic media (CHROMID MRSA) were used. Isolates were confirmed by a diffusion disk using a cefoxitin disk or oxacillin disk. The Staphylococcus aureus ATCC 29213c quality disc was used for quality control.

Bacterial strains were identified using VITEK 2-Compact 15 and MALDI-TOF MS 1000, according to the European Committee for Antimicrobial Susceptibility Testing (EUCAST) guidelines.

All microbiological investigations were performed in the Constanta Clinical Hospital for Infectious Diseases.

This research project was not financed by external sources and microbiological investigations of the patients were paid for by the Constanta Clinical Hospital for Infectious Diseases.

### 2.3. Clinical and Paraclinical Data

Data were collected from electronic medical records. An infectious disease specialist determined the difference between infection and colonization of strains detected from microbiological products based on significant clinical and biological evidence for infection. Evidence for the symptoms and signs of infection was based on organ-specific diseases (e.g., urinary tract infection, pneumonia, and invasive bloodstream infection). UTI biologics were urine culture ≥ 103 colony forming units (CFU)/mL associated with urinary symptomatology. For pneumonia, the biological data were the detection of good-quality sputum strains (> 25 polymorphonuclear leukocytes and <10 epithelial cells), while for invasive bloodstream infections, they consisted in the detection of strains without commensal growth. These data were associated with suggestive paraclinical data such as increased levels of inflammatory markers.

### 2.4. Statistical Data Analysis

Statistical analyzes were performed using Microsoft Excel 2019 (Microsoft Corporation, USA) and Statistical Package for the Social Sciences (SPSS). Descriptive statistics were performed using Microsoft Excel 2019 software. Statistical results were organized in tables and graphical representations using Microsoft Excel 2019, and statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) program. We used the Chi-Square test for categorical variables to compare differences between groups. Univariate analysis identified factors associated with the risk of developing bacterial colonization or bacterial infection with resistance mechanisms. The odds ratios (OR) for these patients were also determined. Multivariate analysis was performed using binary logistic regression (LR) to identify independent risk factors. Time-dependent covariance was performed on the duration of hospitalization in the intensive care unit in patients who had bacterial colonization or bacterial

infection with detected resistance mechanisms to determine whether days of hospitalization were associated with an increased risk of death.

Statistical significance was set at $P \leq 0.05$. All the reported p-values were two-tailed. The statistical results were organized into tables and graphical representations using Microsoft Excel 2019.

## Chapter 3. Study I. Results

### 3.1. Study I. Circulation of Germs in the Intensive Care Unit: September 2017- March 2020

#### 3.1.1. Objectives

- Identification of the circulation of germs in the intensive care unit and resistance mechanisms;
- Assessing the importance of the study of resistance mechanisms in the intensive care unit, thus demonstrating the need to implement bacteriological screening and understanding the spread of germs in other medical university centers or wards that are at risk.

#### 3.1.2. Study I. Materials and method

##### 3.1.2.1. The Studied Cohort

Between September 2017 and March 2020, bacteriological screening was performed on 320 patients admitted to the intensive care unit of the Constanța Clinical Hospital for Infectious Diseases, and 60 bacterial colonizations that had resistance mechanisms were detected. From the 320 bacteriologically screened patients, microbiological samples that caused secondary infections were collected, which were caused by a different germ from that of the admission diagnosis. 65 bacterial strains caused secondary infections, of which 24 evinced resistance mechanisms. All patients included in the study were hospitalized for at least 24 hours in the intensive care unit and underwent at least one bacteriological screening in the intensive care unit.

#### 3.1.3. Results of Hospital Germs Spread

##### 3.1.3.1. Bacterial Strains Detected

In Figure 1 it can be observed that, from the total of 320 patients included in the study, 105 (33%) patients presented bacterial strains secondary to the cause of admission to the intensive care unit, and 215 (67%) did not present secondary bacterial strains detected. In 65 (20%) patients, bacterial strains were detected that produced infections secondary to the cause of admission to the intensive care unit, of which only 24 (37%) of them were cases with strains with

resistance mechanisms (ESBL, carbapenemases, MRSA, VRE) and in 41 (63%) no bacterial strains with resistance mechanisms were detected. Regarding bacterial colonization in the intensive care unit, the bacteriological screening revealed 60 (19%) patients who had bacterial strains with resistance mechanisms. In total, only five (5%) patients acquired infection and colonization with the same bacterial strain and the same resistance mechanism, and in 15 (14%) patients different bacterial strains were detected that caused both bacterial colonization and infection (Figure 3.1).

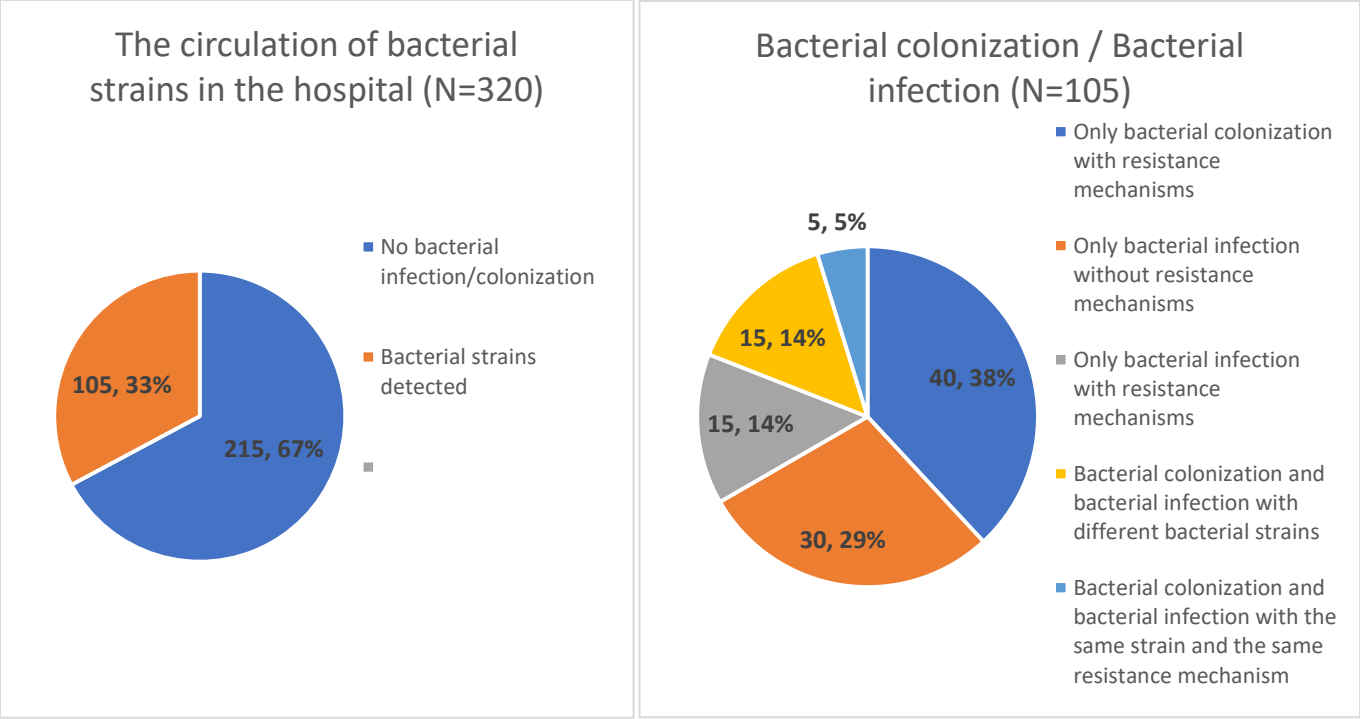


Figure. 3.1. Germ circulation in the intensive care unit, between September 2017 and March 2020.

### 3.1.3.2. Resistance Mechanisms of Bacterial Colonization or Bacterial Infection

Regarding resistance mechanisms, the data has been illustrated in Figures 3.2-3.4. The most common resistance mechanism detected in patients who had bacterial colonization was ESBL-production, with 45 cases (75%), of which 25 (41.7%) with the ESBL-producing strain as the only mechanism of resistance detected. Seventeen (28.3%) carbapenemases, 12 (20%) strains with MRSA, and 13 (21.7%) strains with VRE were detected (Figure 3.2).

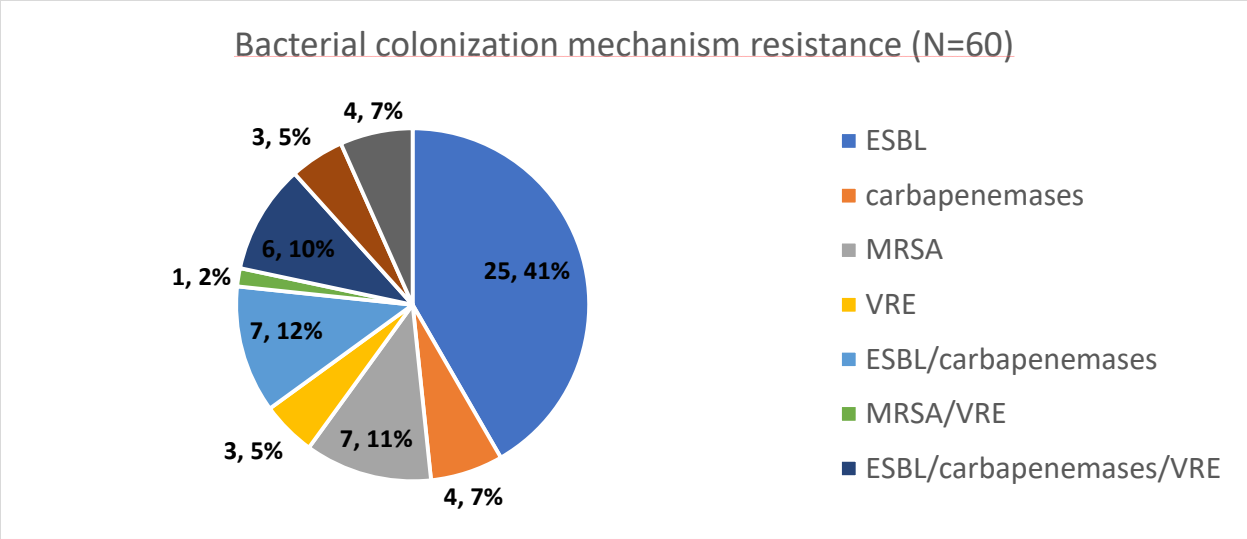


Figure 3.2. Bacterial colonization resistance mechanisms detected during bacteriological screening, in the intensive care unit, September 2017- March 2020.

In this graph, there were 24 resistance mechanisms of bacterial infections. There were 12 (50%) resistance mechanisms with ESBL, 4 (16.7%) with carbapenemases, 5 (20.8%) with MRSA, and 3 (12.5%) with VRE. The number of patients who had bacterial infections with resistance mechanisms was lower than that of the patients with bacterial colonization. (Figure 3.3).

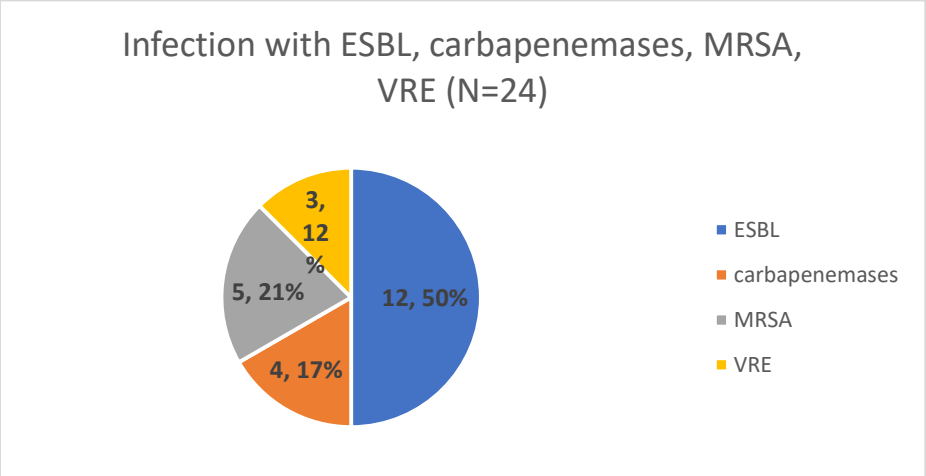


Figure 3.3. Bacterial infections detected during bacteriological screening, in the intensive care unit, September 2017-March 2020

Given the fact that only nine patients in the study had bacterial colonization and bacterial infection with resistance mechanisms and only five of the patients had the same strain and the same resistance mechanism, a relationship between bacterial colonization and the subsequent production of bacterial infection could not be established. There were two VRE strains with

bacterial colonization and infection, two ESBL strains, and one carbapenemase strain with bacterial colonization and bacterial infection. The resistance mechanisms of the bacterial strains are shown in Figure 3.4.

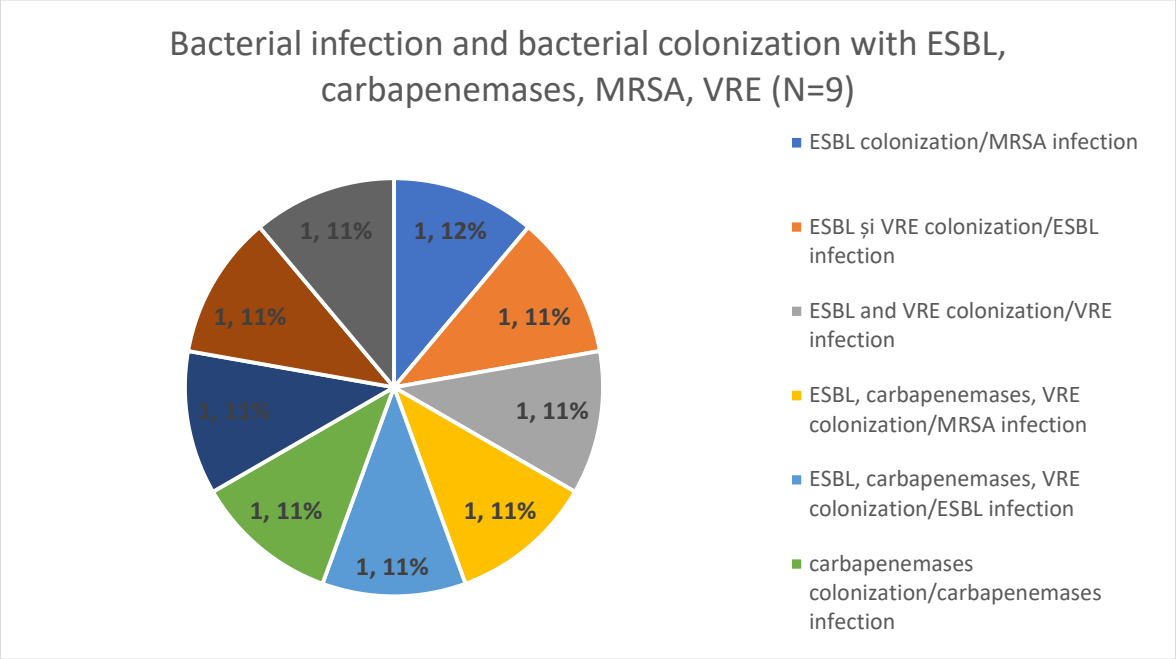


Figure 3.4. Resistance mechanisms of bacterial infections and bacterial colonization detected in the intensive care unit, September 2017-March 2020

### 3.1.3.3. Site of Bacterial Strains

The highest number of isolated bacterial strains was detected in the rectal swabs, a total of 32 (30.5%) strains. Nineteen (18.1%) bacterial strains were detected in urine culture, 8 (7.6%) in purulent secretions, 6 (5.7%) in sputum, 6 (5.7%) in rectal swabs associated with urine culture, 4 (3.8%) in rectal swabs associated with sputum, 4 (3.8%) in nasal swabs, and 4 (3.8%) in rectal swabs associated with nasal swabs. Three (2.9%) strains were detected in rectal swabs associated with purulent discharge. Two (1.9%) bacterial strains were detected in blood cultures, conjunctival secretions, rectal swabs associated with blood culture, nasal swabs associated with urine culture, purulent secretions associated with urine culture, and sputum associated with urine culture. A single strain was detected in otic discharge, rectal swab/nasal swab/urine culture, rectal swab/conjunctival discharge, blood culture/vaginal discharge, blood culture/purulent discharge, and urine culture/coproculture (Table 3.1).

The description of the site of bacterial colonization and bacterial infections can be seen in Table 3.1.

| Site of bacterial strains N (%) | Bacterial colonization and infections N=105 (%) | Total bacterial infections N=65 (%) | Bacterial infections with resistance mechanisms N=24 (%) | Bacterial infections without resistance mechanisms N=41 (%) | Bacterial colonization N=60 (%) |
|---|---|---|---|---|---|
| Blood | 2 (1.9%) | 2 (3.1%) | 1 (4.2%) | 1 (2.4%) | 0 (0%) |
| Conjunctival discharge | 2 (1.9%) | 2 (3.1%) | 2 (8.3%) | 2 (4.9%) | 0 (0%) |
| Otic discharge | 1 (1%) | 1 (1.5%) | 0 (0%) | 1 (2.4%) | 0 (0%) |
| Purulent discharge | 8 (7.6%) | 8 (12.3%) | 0 (0%) | 8 (19.5%) | 0 (0%) |
| Sputum | 6 (5.7%) | 6 (9.2%) | 1 (4.2%) | 8 (19.5%) | 0 (0%) |
| Urine | 19 (18.1%) | 19 (29.2%) | 15 (62.5%) | 14 (34.14%) | 0 (0%) |
| Rectal swab/nasal swab/urine | 1 (1%) | 1 (1.5%) | 0 (0%) | 0 (0%) | 1 (1.7%) |
| Rectal swab/urine | 6 (5.7%) | 6 (9.2%) | 0 (0%) | 0 (0%) | 6 (10%) |
| Rectal swab/blood | 2 (1.9%) | 2 (3.1%) | 2 (8.3%) | 0 (0%) | 2 (3.3%) |
| Nasal swab/urine | 2 (1.9%) | 2 (3.1%) | 0 (0%) | 0 (0%) | 2 (3.3%) |
| Rectal swab/sputum | 5 (4.8%) | 5 (7.7%) | 0 (0%) | 0 (0%) | 5 (8.3%) |
| Rectal swab/conjunctival discharge | 1 (1%) | 1 (1.5%) | 0 (0%) | 0 (0%) | 1 (1.7%) |
| Rectal swab/purulent discharge | 3 (2.9%) | 3 (4.6%) | 1 (4.2%) | 0 (0%) | 3 (5%) |
| Blood/vaginal discharge | 1 (1%) | 1 (1.5%) | 1 (4.2%) | 0 (0%) | 0 (0%) |
| Blood/purulent discharge | 1 (1%) | 1 (1.5%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Purulent discharge/urine | 2 (1.9%) | 2 (3.1%) | 0 (0%) | 1 (2.4%) | 0 (0%) |
| Sputum/urine | 2 (1.9%) | 2 (3.1%) | 0 (0%) | 1 (2.4%) | 0 (0%) |
| Urine culture /faecale | 1 (1%) | 1 (1.5%) | 0 (0%) | 1 (2.4%) | 0 (0%) |
| Rectal tampon | 31 (29.5%) | 0 (0%) | 0 (0%) | 0 (0%) | 31 (51.7%) |
| Nasal swab | 4 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) | 4 (6.7%) |
| Pharyngeal swab | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Rectal and nasal tampon | 4 (3.8%) | 0 (0%) | 0 (0%) | 0 (0%) | 4 (6.7%) |
| Nasal and pharyngeal swab | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1.7%) |

Table 3.1. Site of detection of bacterial infections and bacterial colonization, intensive care unit, September 2017-March 2020

### 3.1.3.4. Germs Spread Management Model in the Hospital

Thus, in relation to the data obtained from the study, a recommendation can be made to carry out carbapenemase testing with regard to the collection of microbiological products from hospitalized patients. This recommendation has been chosen because separate kits are required to perform these investigations and most hospitals do not perform these tests.

**Inclusion criteria:** performance of carbapenemases and resistance mechanisms (OXA, MBL, and KPC) in patients with detected infections with gram-negative bacilli (Escherichia Coli, Klebsiella spp., Proteus spp., Enterobacter spp., Pseudomonas aeruginosa, and Acinetobacter baumannii):

1. In patients with ESBL+ strains;
2. In patients with hospitalization in ICU wards in the last 12 months;
3. In patients transferred from other hospitals/institutionalized/on dialysis;
4. In patients with prolonged hospitalization >10 days;
5. In patients treated with backup antibiotics from the carbapenem class in the last 3 months;
6. In patients with sepsis/MSOF criteria;
7. In immunosuppressed patients (e.g., HIV, oncological, and treatment with immunosuppressive drugs);
8. In patients with XDR, PDR to the results of the antibiogram;
9. In patients with carbapenems sensitive to the antibiogram results, but with positive ESBL, XDR/PDR on the antibiogram);
10. For patients in the ICU who were hospitalized of at least 24 hours;
11. Upon admission to the intensive care unit if there are risk factors for infection with MDR germs at the decision of the intensive care physician;
12. On the recommendation of the infectious diseases doctor/intensive care/epidemiologist/ Preventing Health Care–Associated Infections (SPIAAM) commission;
13. In the outbreak of infection with MDR germs in the compartment/ward/hospital;
14. In patients with a history of CRE colonization/infection;
15. In patients with invasive medical devices (urinary catheter, drain tube, central venous catheter (CVC), IOT);
16. In patients with unfavorable evolution under antibiotic treatment administered on the doctor's recommendation;

17. In patients in whom the risk factors mentioned above cannot be found and the attending physician decides to carry out resistance mechanisms;
18. Admission to hospitals with increased prevalence of carbapenemases;
19. Resistance to the class of carbapenems on the result of the antibiogram.

Regarding the hospital's antimicrobial stewardship plan, various methods of monitoring patients and their associated risk factors can be used to prevent healthcare-associated infections. An implementation model that does not require additional costs is the formation of an online information system with the generation of a link that informs the medical staff regarding the salons, colonizations and bacterial infections of patients. Such a model is shown in Figures 3.5 and 3.6.

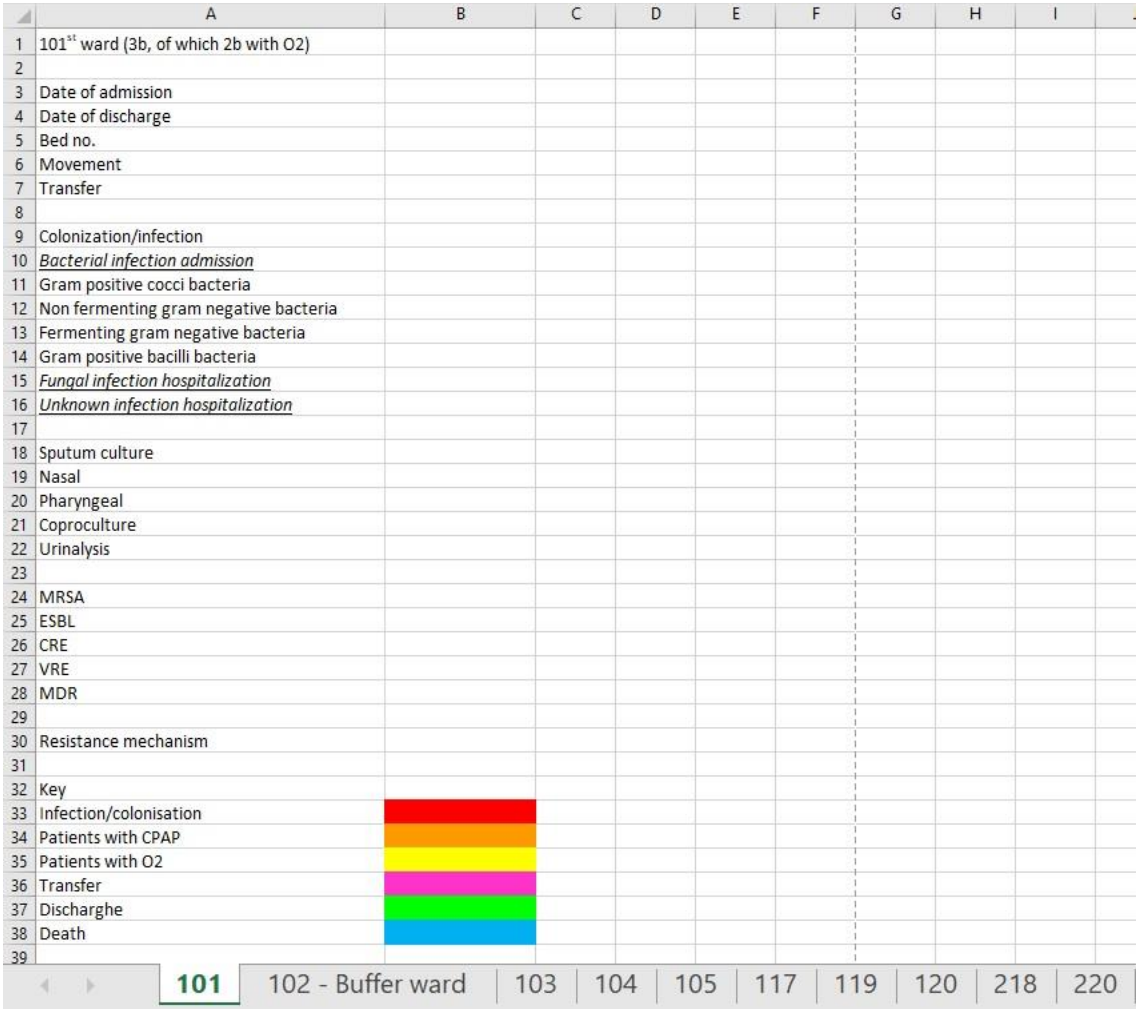


Figure 3.5. Online monitoring model of patients hospitalized in the Constanța Clinical Hospital for Infectious Diseases

Figure 3.6 specifies the bed, date of acquisition of colonization or infection, age, sex, patient transfer, bacterial strain and resistance from a ward.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 101st ward | | | | | | | |
| 1st bed | | | | | | | |
| Transfer (Hospital/ward) | Date and time | Patients initials | Sex | Age | Colonisation/ infection | Strain | MDRO |
| No | 28.06 | R.C.G. | F | 22 | C | Klebsiella spp. | PDR |
| | | | | | | | |
| | | | | | | | |
| 2nd bed | | | | | | | |
| Transfer (Hospital/ward) | Date and time | Patients initials | Sex | Age | Colonisation/ infection | Strain | MDRO |
| | | | | | | | |
| | | | | | | | |
| 3rd bed | | | | | | | |
| Transfer (Hospital/ward) | Date and time | Patients initials | Sex | Age | Colonisation/ infection | Strain | MDRO |
| | | | | | | | |

Figure 3.6. Model 2 of online monitoring of patients hospitalized in the Constanța Clinical Hospital for Infectious Diseases

In Figure 3.7 the link to access the monitoring of hospitalized patients from Figure 3.5 can be observed.

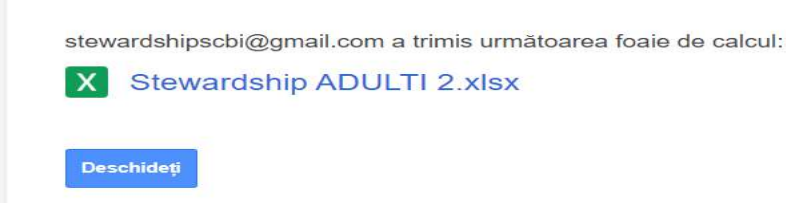


Figure 3.7. Link to online monitoring of patients admitted to the Constanța Clinical Hospital for Infectious Diseases

Other important measures to be implemented together with monitoring the circulation of germs, and recommendations for carrying out resistance mechanisms are as follows:

1. Implementing a buffer system for patients with confirmed or suspected MDR strains, or those transferred from other hospitals at a high risk of MDR. Another role of the buffer room is to exchange it with another room for regular disinfection in each room of the hospital. The Clostridioides difficile inpatient lounge will be maintained because of the increased risk of spore transmission to subsequent inpatients.

– The implementation and compliance to these recommendations will be the responsibility of the head nurse/ SPIAAM assistant (depending on the organization of each hospital).

2. Marking (known to all medical personnel) the rooms with MDRO stems and posting the necessary precautions on each door of the room for the necessary protection of the medical staff.

3. Compliance with hand hygiene and precautions (standard, contact, airborne transmission, and droplet transmission). The resident doctors in the hospital will evaluate and verify compliance to these, guiding the medical staff in the correct practice through courses, posters, and periodic recommendations, or as needed.

As a form of monitoring and implementing these IT system control mechanisms, tasks can be divided according to the organization of each hospital. For example, for the management of the computer program, we believe that the epidemiologist/ SPIAAM must follow the bacterial strains and write them down in the computer program, and the epidemiological situation will be transmitted daily at 9 a.m. and 2 p.m. through a link to fellow clinicians. The registrar will note in the computer program which room and bed each patient is in and their transfer with the specified date. Thus, every day at 9 a.m. and 2 p.m., a link would be sent with the epidemiological situation of hospitalized patients, which will be viewed by doctors in the hospital, thus helping the doctor on duty in the correct management of hospitalized cases.

The epidemiologist/SIAAM doctor, registrar, and hospital management will have access to data entry and modification. All doctors in the hospital will have access to view this information. The data entered will comply with patient confidentiality according to hospital rules.

### 3.1.4. Study I. Discussion

The prevalence of bacterial strains according to the data obtained, from September 2017 to March 2020, is 33% out of 320 patients, of which 7.5% had resistance mechanisms. The prevalence of bacterial strains that were considered to cause infections was 20.3%, of the 320 patients included in the study, and the prevalence of bacterial colonization detected in the intensive care unit was 18.7%. The most common bacterial strains detected were with Enterobacterales, regardless of whether it was bacterial infection or bacterial colonization. Of the total bacterial strains, only 9 (2.8%) patients had bacterial infection and bacterial colonization, of which only 5 (1.6%) had the same bacterial strain and the same resistance mechanism. Therefore, the percentage of infections associated with medical acts due to bacterial infections acquired from bacterial colonization was insignificant.

Regarding resistance mechanisms to ESBL, carbapenemases, MRSA, and VRE, the percentages were variable. ESBL-producing strains were the most numerous, with a percentage

of 14%. Carbapenemases were identified in a percentage of 5%, strains with MRSA in a percentage of 4%, and strains with VRE in a percentage of 4%.

### 3.1.5. Conclusions of Study I

1. The spread of germs with gram-negative bacteria, including Enterobacterales, especially Escherichia coli and Klebsiella spp., prevailed.
2. The bacterial strains detected were below 50%.
3. Bacterial colonizations were in a number of 60 (20%).
4. Bacterial infections with resistance mechanisms were in a number of 24 (7.5%).
5. Detected bacterial colonizations that acquired bacterial infections were in a small percentage, below 2%.
6. The predominant year in which patients with bacterial strains were hospitalized was 2019.
7. Screening and reporting of bacterial strains are important, being part of the antimicrobial stewardship plan.

## 3.2. Study II. Risk Factors for Bacterial Colonization and Bacterial Infections

### 3.2.1. Objectives

#### 3.2.1.1. Main Objectives

The 2nd study proposes as its main objectives:

– Assessing the risk factors of the spread of bacterial strains producing ESBL, carbapenemases, MRSA and VRE in the intensive care unit of the Constanța Clinical Hospital for Infectious Diseases, from the establishment of the intensive care unit until the beginning of the Coronavirus-19 (COVID-19) pandemic;

– Detection of risk factors for acquiring bacterial infections in patients with bacterial colonization;

– Establishing clinical and therapeutic implications in patients with bacterial colonization or bacterial infection with or without resistance mechanisms.

#### 3.2.1.2. Secondary Objectives

– Implementing a surveillance and monitoring plan model for at-risk patients and those with bacterial strains with detected resistance mechanisms.

### 3.2.1.3. Materials and Methods

Between September 2017 and March 2020, 60 bacterial colonizations with resistance mechanisms were found in the intensive care unit of the Constanța Clinical Hospital for Infectious Diseases, which were detected during bacteriological screening. A total of 320 patients who were hospitalized for at least 24 hours in the intensive care unit and who underwent at least one bacteriological screening in the intensive care unit were included in the study. The patient group was divided into patients who had bacterial colonization or bacterial infection with or without resistance mechanisms and patients who had neither bacterial colonization performed on bacteriological screening, nor bacterial infection with resistance mechanisms.

## 3.2.2. Bacterial Colonization and Risk Factors of Bacterial Colonization in the Intensive Care Unit of the Constanța Clinical Hospital for Infectious Diseases: September 2017-March 2020

### 3.2.2.1. Result

#### 3.2.2.1.1. Bacterial Colonization Risk Factors

After univariate analysis, only eight variables that significantly increased the risk of acquiring bacterial colonization were identified. In the multivariate analysis, hospital admission with staphylococcus aureus (OR, 26.87, 95% CI, 1.03-45.66, P≤ 0.05) was an independent risk factor for acquiring bacterial colonization, (Table 3.1).

| **Risk factors detected in univariate analysis-bacterial colonization** | **Multivariate analysis of bacterial colonization** | |
|---|---|---|
| | **OR (CI 95%)** | **P** |
| Carmeli score 1 point | 1.45 (0.31-6.62) | 0.63 |
| Carmeli score 3 points | 2.21 (1.02-5.04) | 0.058 |
| Charlson Comorbidity Index (CCI) ≥1 | 1.55 (0.563-4.28) | 0.39 |
| Previous 6-month exposure to hospitalization or antibiotics | - | - |
| Previous 6-month exposure to hospitalization | - | - |
| St. Andrei Constanta Emergency County Clinical Hospital | 1.60(0.65-3.92) | 0.30 |
| Admission with *Staphylococcus aureus* | **6.87 (1.03-45.66)** | **0.046** |
| Metronidazole and oral vancomycin | 1.75 (0.75-4.08) | 0.19 |
| Hepatic comorbidities | - | - |

Table 3.1. Multivariate analysis of variables of patients admitted to the intensive care unit, September 2017-March 2020.; OR= Odds ratio; CI= Confidence interval, the test was performed using binary logistic regression, and the P value in bold is statistically significant ($p \leq 0.05$).

### 3.2.2.1.2. Risk Factors for Bacterial Colonization with ESBL

Multivariate analysis showed that previous 6-month exposure to hospitalization and diabetes were independent risk factors for acquiring ESBL bacterial colonization. The statistical results performed can be found in Table 3.2.

| **Risk factors detected in the univariate analysis-ESBL colonization** | **Multivariate analysis of ESBL colonization** | |
|---|---|---|
| | **OR (CI 95%)** | **P** |
| Carmeli score > 1 point | 1.05 (0.30-3.72) | 0.93 |
| Carmeli score 3 points | 1.10 (0.52-2.23) | 0.80 |
| Charlson Comorbidity Index (CCI) ≥1 | 1.28 (0.43-3.81) | 0.65 |
| Charlson Comorbidity Index (CCI) ≥4 | 1.63 (0.78-3.39) | 0.19 |
| Previous 6-month exposure to hospitalization or antibiotics | 0.19 (0.01-2.80) | 0.23 |
| Previous 6-month exposure to hospitalization | **12.69 (1.09-147.02)** | **0.042** |
| Previous 6-month exposure to antibiotics | 1.225 (0.46-3.21) | 0.68 |
| >7 days of hospitalization in the intensive care unit | 1.00 (0.39-2.60) | 0.98 |
| >10 days of hospitalization in the intensive care unit | 1.36 (0.52-3.59) | 0.52 |
| St. Andrei Constanta Emergency County Clinical Hospital | 1.12 (0.48-2.59) | 0.78 |
| Comorbidities | 0.88 (0.24-3.16) | 0.85 |
| Diabetes | **6.0 (1.19-30.71)** | **0.029** |
| Neurological comorbidities and neoplasm | 16.19 (0.96-162.39) | 0.053 |
| Metronidazole and oral vancomycin | 1.31 (0.58-2.96) | 0.51 |

Table 3.2. Multivariate analysis - patients colonized with ESBL, intensive care unit, September 2017-March 2020. OR= Odds ratio; CI= Confidence interval, the test was performed by binary logistic regression, the P value in bold is statistically significant ($p \leq 0.05$).

### 3.2.2.1.3. Risk Factors for Bacterial Colonization with Carbapenemases.

Regarding the independent risk factors, multivariate analysis did not detect any independent risk factors, with a p-value > 0.05. The statistical data are presented in Table 3.3.

| **Risk factors detected in the univariate analysis - colonization with carbapenemases** | **Multivariate analysis of colonization with carbapenemases** | |
|---|---|---|
| | **OR (CI 95%)** | **P** |
| Carmeli score 3 points | 1.32 (0.45-3.89) | 0.61 |
| Previous 6-month exposure to hospitalization or antibiotics | - | - |
| Previous 6-month exposure to hospitalization | - | - |

| Risk factors detected in the univariate analysis - colonization with carbapenemases | Multivariate analysis of colonization with carbapenemases | |
|---|---|---|
| | **OR (CI 95%)** | **P** |
| Previous 6-month exposure to antibiotics | 2.15 (0.43-10.83) | 0.35 |
| Cardiological comorbidities and neoplasm | 5.16 (0.76-34.66) | 0.91 |
| Treatment with metronidazole and oral vancomycin | 2.58 (0.88-7.55) | 0.84 |
| Treatment with intravenous vancomycin | 1.48 (2.28-0.75) | 0.15 |

Table 3.3. Multivariate analysis, patients colonized with carbapenemases, in the intensive care unit, September 2017-March 2020. OR= Odds ratio; CI= Confidence interval, the test was performed by binary logistic regression

### 3.2.2.1.4. Risk Factors for Bacterial Colonization with MRSA

In Table 3.4, we note that the risk factors found in the univariate analysis are the same as those in the multivariate analysis. Hepatic comorbidities are independent risk factors for acquiring bacterial colonization with MRSA and increase the risk of acquiring MRSA by 14.23 times, and neurological and nephrological comorbidities are also independent risk factors that increase the risk of acquiring bacterial colonization by 21.35 times with MRSA.

| Risk factors detected in univariate analysis-MRSA | Multivariate analysis of patients bacterially colonized with MRSA | |
|---|---|---|
| | **OR (CI 95%)** | **P** |
| Hepatic comorbidities | **14.23 (2.19-92.17)** | **0.005** |
| Neurological and nephrological comorbidities | **21.35 (1.26-359.43)** | **0.034** |

Table 3.4. Multivariate analysis-patients bacterially colonized with MRSA, in the intensive care unit, September 2017-March 2020. OR= Odds ratio; CI= Confidence interval, the test was performed by binary logistic regression, the P value in bold is statistically significant ($p \leq 0.05$).

### 3.2.2.1.5. Risk Factors for Bacterial Colonization with VRE

In the multivariate analysis, no independent risk factor was detected for the acquisition of VRE bacterial colonization (Table 3.5).

| Risk factors detected in the univariate analysis-VRE | Multivariate analysis | |
|---|---|---|
| | **OR (CI 95%)** | **P** |
| Previous 6-month exposure to hospitalization or antibiotics | 1.06 (0.06-60.38) | 0.97 |
| Previous 6-month exposure to hospitalization | 2.72 (0.16-46.44) | 0.48 |
| Previous 6-month exposure to antibiotics | 2.49 (0.25-24.54) | 0.43 |

| Risk factors detected in the univariate analysis-VRE | Multivariate analysis | |
|---|---|---|
| | **OR (CI 95%)** | **P** |
| Constanta Clinical Hospital for Infectious Diseases | 4.74 (0.56-39.98) | 0.15 |
| Tulcea County Emergency Hospital | 4.97 (0.15-134.15) | 0.38 |
| Neurological comorbidities and neoplasm | 6.88 (0.50-94.52) | 0.14 |
| Treatment with aminoglycosides | 5.43 (0.77-36.16) | 0.89 |
| Treatment with metronidazole and oral vancomycin | 3.06 (0.76-12.27) | 0.11 |

Table 3.5. Multivariate analysis of patients colonized with VRE, in the intensive care unit, September 2017-March 2020. OR= Odds ratio; CI= Confidence interval, the test was performed by binary logistic regression, the P value in bold is statistically significant ($p \leq 0.05$).

### 3.2.3. Bacterial Infection and Risk Factors of Bacterial Infection With or Without Resistance Mechanisms in the Intensive Care Unit: September 2017- March 2020

#### 3.2.3.1. Result

In the multivariate analysis, previous institutionalization of patients was found to be an independent risk factor for the acquisition of bacterial infections.

| Risk factors detected in univariate analysis-bacterial infection | Multivariate analysis of bacterial infection | |
|---|---|---|
| | **OR (CI 95%)** | **P** |
| Age ≥ 65 years | 0.71 (0.26-1.94) | 0.51 |
| Carmeli score > 1 point | 1.51 (0.28-7.94) | 0.62 |
| Charlson Comorbidity Index (CCI) ≥4 | 2.10 (0.82-5.47) | 0.12 |
| Hospitalization with bacterial infection | 1.34 (0.41-4.33) | 0.62 |
| Previous 6-month exposure to hospitalization or antibiotics | 3.25 (0.40-26.37) | 0.26 |
| Previous 6-month exposure to hospitalization | 0.35 (0.08-1.55) | 0.16 |
| Previous 6-month exposure to antibiotics | 0.92 (0.22-3.75) | 0.91 |
| > 7 days of hospitalization | 0.89 (0.331-2.55) | 0.83 |
| > 10 days of hospitalization | 0.99 (0.33-2.94) | 0.99 |
| Institutionalized patient | **9.04 (1.17-69.67)** | **0.035** |
| *Clostridioides difficile* | 3.28 (0.87-12.39) | 0.07 |
| Comorbidities | 1.32 (0.30-5.80) | 0.70 |
| Two comorbidities | 1.14 (0.40-3.22) | 0.79 |
| Neurological and cardiological comorbidities | 3.65 (0.995-13.97) | 0.058 |
| Aminoglycosides | 4.87 (0.96-24.75) | 0.056 |
| Metronidazole and oral vancomycin | 0.69 (0.24-2.016) | 0.50 |

Table 3.6. Multivariate analysis of the variables of patients with bacterial infection, in the intensive care unit, September 2017-March 2020. OR= Odds ratio; CI= Confidence interval, the test was performed by binary logistic regression, the P value in bold is statistically significant ($p \leq 0.05$).

### 3.2.4. Bacterial Infection with Resistance Mechanisms and Risk Factors in the Intensive Care Unit: September 2017- March 2020

#### 3.2.4.1. Results

In Table 3.7 we may notice that, in the multivariate analysis performed, Charlson Comorbidity Index (CCI) ≥4 was detected as an independent risk factor for acquiring bacterial infection with resistance mechanisms**.**

| Risk factors detected in univariate analysis - bacterial infection with resistance mechanisms | **Multivariate analysis: bacterial infection with resistance mechanisms** | |
|---|---|---|
| | **OR (CI 95%)** | **P** |
| Age ≥ 65 years | 3.32 (0.65-16.90) | 0.14 |
| Tulcea County Emergency Hospital | 8.09 (0.18-35.34) | 0.27 |
| Carmeli Score > 1 point | 0.8 (0.06-9.65) | 0.87 |
| Nephrological comorbidities | 18.01 (0.05-5708.63) | 0.32 |
| Charlson Comorbidity Index (CCI) ≥4 | **3.60 (1.00-12.97)** | **0.050** |
| Previous 6-month exposure to hospitalization or antibiotics | 0.57 (0.02-16.39) | 0.74 |
| Previous 6-month exposure to antibiotics | 0.99 (0.13-7.11) | 0.99 |
| Neurological comorbidities and neoplasm | 4.21 (0.32-54.65) | 0.27 |
| Intravenous vancomycin | 3.01 (0.83-10.88) | 0.09 |
| Metronidazole and oral vancomycin | 1.10 (0.29-4.19) | 0.88 |
| >10 days of hospitalization in the intensive care unit | 1.50 (0.49-4.62) | 0.47 |
| Admission bacterial infection | 1.23 (0.22-6.90) | 0.81 |
| Previous 6-month exposure to hospitalization | 0.99 (0.13-7.11) | 0.99 |
| Aminoglycosides | 2.98 (0.34-26.13) | 0.32 |

Table 3.7. Multivariate analysis - patients with bacterial infection with resistance mechanisms, intensive care unit, September 2017-March 2020. OR= Odds ratio; CI= Confidence interval, the test was performed by binary logistic regression, the P value in bold is statistically significant ($p \leq 0.05$).

### 3.2.5. Study II. Discussion

From the data obtained in the 2nd study, we observed that independent risk factors differed according to each investigated category.

The risk factors detected in the univariate analysis that were not found in the multivariate analysis could not be associated with other possible risk factors, such as non-observance of

standard precautions, hand hygiene, or measures to prevent the transmission of bacterial strains from one patient to another. Colonized patients who were not decolonized and admitted to the same ward as a bacterially uncolonized patient may be a possible transmitter for acquiring bacterial colonization with the same strain and resistance mechanism in the bacterially uncolonized patient.

Thus, from the need to form an antimicrobial stewardship plan, we believe the following are necessary:

- Assessing the spread of germs in the hospital;
- Reporting of infections associated with the medical act;
- Implementing a computer software program with data on risk factors for the acquisition of bacterial colonization/infection in patients admitted to the hospital;
- Creating risk scores for unfavorable evolution and the possibility of hospitalization in the intensive care unit;
- Monitoring of patients in terms of their hygiene, bacterial or fungal colonization at admission or during admission, and non-modifiable risk factors;
- Elimination of modifiable risk factors for acquiring bacterial colonization/bacterial infection;
- Correlation of microbiological data with clinical data for the correct initiation of antibiotic, antifungal or antiviral treatment;
- Equipping the hospital with molecular microbiology methods;
- And decreasing the consumption of prescription antimicrobials and the administration of antibiotics by restricting it to hospitalization and 72 hours after the administration of the antibiotic.

### 3.2.6. Conclusions of Study II

In conclusion, we note that international studies do not confirm all the risk factors detected in our study; therefore, we can deduce that each hospital has certain individual risk factors. I believe it is important to identify the independent risk factors in each hospital because, in this way, correct decisions can be made in the screening of hospitalized patients and the risk of acquiring infections can be minimized in patients who are suspected of infection. It is necessary to know these risk factors especially if there are no data to confirm the diagnosis. Individual risk factors may also play a role in patient management decisions.

## 3.3. STUDY III. Risk Factors for the Death of Patients Admitted to the Intensive Care Unit of the Constanța Clinical Hospital for Infectious Diseases and the Mortality Rate.

### 3.3.1. Objectives

- Identification of the risk factors for death in patients hospitalized in the intensive care unit;
-Assessment of the mortality rate in the intensive care unit based on epidemiological criteria.

### 3.3.2. The Studied Cohort

All patients admitted to the intensive care unit who underwent bacteriological screening on admission to the intensive care unit and who stayed in the hospital for at least one day were included. A total of 320 patients were hospitalized between September 2019 and March 2020 in the intensive care unit of the Constanța Clinical Hospital for Infectious Diseases, of which 20 died, 31 were transferred, and 269 were discharged. The cases included exitus and control patients who were discharged or transferred to other hospitals.

### 3.3.3. Result

#### 3.3.3.1. Risk Factors for Death in Intensive Care Unit Patients

In the multivariate analysis, we observed that the independent risk factors associated with death were HIV infection and Clostridioides difficile infection. Patients with HIV infection had an 11.82 times greater risk of death, and patients with Clostridioides difficile had a 7.38 times greater risk of death.

| **Risk factors detected in univariate analysis – risk death** | **Multivariate analysis of bacterial infection with resistance mechanism** | |
|---|---|---|
| | **OR (CI 95%)** | **P** |
| Previous 6-month exposure to hospitalization or antibiotics | 3.05 (0.30-30.43) | 0.34 |
| >10 days of hospitalization in the intensive care unit | 2.57 (0.75-8.82) | 0.13 |
| Bacterial infection or bacterial colonization | 0.56 (0.16-1.99) | 0.37 |
| Admission with HIV infection | **11.82 (1.69-82.62)** | **0.013** |
| *Clostridioides difficile* | **7.38 (1.39-39.22)** | **0.019** |

Table 3.8. Multivariate analysis of the risk of death in the intensive care unit, September 2017-March 2020

##### 3.3.3.1.1. Mortality Rate in Patients Hospitalized in the ICU

Regarding mortality in the therapy department of the Constanța Clinical Hospital for Infectious Diseases, we note that in the period before the COVID-19 pandemic, September 2017

– March 2020, 20 (6.23%) patients died. As a distribution by years, in 2017 2 (8.69%) patients died, in 2018 8 (6.83%) patients died, in 2019 9 (5.19%) patients died, and in 2020 only one patient died (3.85 %).

### 3.3.3.1.2. Mortality Rate Related to Days of Hospitalization and Risk Factors for Death Determined in the Intensive Care Unit

In the Cox regression analysis performed, we observe that the days of hospitalization in patients admitted to the intensive care unit for HIV infection were statistically significantly associated with a higher risk of death, (p=0.004, HR, 5.34, 95% CI, 1.69-16.92). Patients at which the duration of hospitalization correlated with a higher estimated risk of death were those with Clostridioides difficile infection with p=0.005, HR 4.51, 95% CI, 1.56-13.05, those with exposure to antibiotics in the previous 6-month period having p=0.010, HR 7.09 95% CI, 1.59-3.67, while those with an exposure to antibiotics or hospitalization in the previous 6 months having p=0.043, HR 8.24, 95% CI, 1.07-63.31, (Table 3.9).

| **Death rate** | **P Value** | **HR [a]** | **CI 95% [b]** | |
|---|---|---|---|---|
| | | | **Lower** | **Upper** |
| Neurological cause - ICU hospitalization | 0.21 | 0.39 | 0.09 | 1.69 |
| Digestive cause - ICU hospitalization | 0.089 | 2.15 | 0.89 | 5.19 |
| SIRS Cause - ICU hospitalization | 0.74 | 1.28 | 0.29 | 5.62 |
| Hepatitis cause - ICU hospitalization | 0.74 | 0.74 | 0.09 | 5.59 |
| HIV infection | **0.004** | **5.34** | **1.69** | **16.92** |
| *Clostridioides difficile* | **0.005** | **4.51** | **1.56** | **13.05** |
| Influenza virus | 0.26 | 0.31 | 0.04 | 2.37 |
| *Mycobacterium tuberculosis* | 0.15 | 4.57 | 0.59 | 35.38 |
| Carmeli score > 1 point | 0.23 | 2.46 | 0.56 | 10.72 |
| Carmeli score > 3 points | 0.23 | 1.71 | 0.71 | 4.15 |
| Charlson Comorbidity Index (CCI) ≥1 | 0.30 | 1.91 | 0.56 | 6.55 |
| Charlson Comorbidity Index (CCI) ≥4 | 0.23 | 1.70 | 0.70 | 4.12 |
| 6 months previous exposure to hospitalization | 0.08 | 3.12 | 0.86 | 11.26 |
| 6 months previous exposure to antibiotics | **0.010** | **7.09** | **1.59** | **31.67** |
| 6 months previous exposure to hospitalization or antibiotics | **0.043** | **8.24** | **1.07** | **63.31** |
| Mechanical ventilation | 0.54 | 1.86 | 0.25 | 14.17 |
| Bacterial admission | 0.22 | 1.94 | 0.67 | 5.63 |
| Comorbidities | 0.36 | 2.01 | 0.46 | 8.81 |
| A single comorbidity | 0.77 | 1.14 | 0.47 | 2.75 |
| Two comorbidities | 0.58 | 1.29 | 0.52 | 3.17 |
| Pulmonological comorbidities | 0.76 | 0.73 | 0.98 | 5.50 |

| Death rate | P Value | HR [a] | CI 95% [b] | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Cardiological comorbidities | 0.25 | 1.74 | 0.67 | 4.54 |
| Hepatic comorbidities | 0.21 | 3.65 | 0.48 | 27.62 |
| Diabetes | 0.88 | 1.18 | 0.15 | 9.11 |
| Backup antibiotic administration | 0.12 | 0.47 | 0.19 | 1.20 |
| Administration of aminoglycosides in the hospital | 0.84 | 0.81 | 0.10 | 6.12 |
| Administration of trimethoprim/sulfamethoxazole in the hospital | 0.10 | 3.39 | 0.78 | 14.72 |
| Administration of tigecycline in the hospital | 0.60 | 1.48 | 0.34 | 6.50 |
| Administration of oral metronidazole and vancomycin in the hospital | 0.44 | 1.49 | 0.54 | 4.12 |
| Administration of glycopeptides in the hospital | 0.42 | 0.59 | 0.17 | 2.13 |
| Administration of fluoroquinolones in the hospital | 0.07 | 0.15 | 0.02 | 1.14 |
| Administration of linezolid in the hospital | 0.58 | 0.66 | 0.15 | 2.88 |
| Carbapenem administration in the hospital | 0.09 | 0.42 | 0.16 | 1.12 |
| Administration of antivirals in the hospital | 0.81 | 1.12 | 0.43 | 2.92 |
| Antifungal administration in the hospital | 0.39 | 0.58 | 0.17 | 2.00 |
| Corticosteroid administration in the hospital | 0.95 | 0.97 | 0.38 | 2.46 |

Table 3.9: tests were performed by Cox regression; bolded P values are statistically significant, ($p \leq 0.05$); a HR-hazard ratio; b CI-confidence interval.

### 3.3.4. Study III. Discussion

Mortality from both preventable and treatable causes is very high in Romania. The death rate from preventable causes was the third highest in the European Union (EU) in 2018, showing the need to improve health promotion and disease prevention. The leading causes of preventable mortality are ischemic heart disease, lung cancer and alcohol-related diseases. In Romania, mortality from treatable causes is the highest in the EU and more than double the average of EU countries. Thus, the major deficiencies of the health system through the ability to provide adequate and timely treatment to the population give high mortality rates from treatable causes. The main treatable causes are ischemic heart disease, stroke, pneumonia and colorectal cancer [6]. In 2018, in Romania, new screening programs were introduced, but per capita spending on prevention continued to decrease and, thus, Romania is the second country with the lowest spending in the EU [6]. As regards infectious diseases such as tuberculosis and measles, they continue to be an important public health problem in Romania [7].

Risk factors for death in intensive care unit patients are a much-discussed topic. In a Polish study of 347 intensive care units, Wojciech Weigl and collaborators observed that variables associated with survival in the intensive care unit were: tertiary level of hospital care;

high annual volume of patients admitted to the intensive care unit; younger age of the patient; female gender and a lower number of comorbidities [8]. In another study conducted in Canada, Michael E. Detsky and colleagues report that among patients who spend at least 3 days in an intensive care unit and who required even short periods of life support therapy, almost half will die and less than a third will return to baseline after 6 months, and, of those who survived, most patients returned home after 6 months [9]. During the COVID-19 pandemic, numerous studies were conducted to detect the risk factors associated with hospitalization in the intensive care unit. A large-scale study conducted in Brazil on a sample of 1,048,575 patients infected with SARS-CoV-2 supports the fact that obesity was the main risk factor for admission to the intensive care unit and death [10]. Regarding the study of risk factors for the death of patients in the intensive care unit, prior to the COVID-19 pandemic, no studies with data related to the situation in Romania were found in the research conducted.

### 3.3.5. Study III. Conclusions

- HIV infection is a known factor of immunodepression, and the study demonstrates that these patients have an increased risk of death;
- Infection with Clostridioides difficile also brings an increased risk of death in statistically analyzed patients.
- Days of hospitalization in certain categories (patients with infection, HIV, infection with Clostridioides difficile, with exposure to antibiotics in the previous 6 months or patients with and exposure to hospitalization or antibiotics in the previous 6 months) - increased risk of death in the intensive care unit.

## Chapter 4. The Conclusions of the Doctoral Thesis

The originality of the study lies in the fact that it is the only intensive care unit in Romania where the individual risk factors for the acquisition of bacterial colonization, bacterial infections and mortality were investigated and it is the only proposal for a free online IT platform designed for monitoring germs and the data necessary to know patient zero in acquiring infections associated with the medical act.

The present study addressed all the proposed objectives and demonstrated 3 very important points:

1. In the intensive care unit, assessing the spread of germs helps to form an antimicrobial stewardship plan, because by identifying the germs we can move to the second step, which is the identification of risk factors for acquiring colonization, infections and for mortality;
2. The independent risk factors for acquiring bacterial colonization are different from those for acquiring bacterial infections or mortality in the intensive care unit of the Constanța Clinical Hospital for Infectious Diseases. Thus, we demonstrated that it is essential to manage each patient according to the risk factors detected in the ward of the hospital where they were hospitalized;
3. We created the necessary statistical basis for the implementation of a local antimicrobial stewardship guide to which it is mandatory to add good practice guidelines regarding hand hygiene, compliance with hygiene and disinfection measures.

Thus, in the final form of the study, with the evaluated and identified statistical data, we can create local guidelines for the intensive care unit of the Constanta Clinical Hospital for Infectious Diseases:

– By constantly monitoring the bacterial strains detected through the recommended online platform;

– By observing and checking hygiene measures through the recommended online platform;

– By making recommendations or procedures regarding the management of urinary infections, pneumonia, intra-abdominal infections and sepsis, to adapt to international guidelines and the circulation of germs in the hospital.

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