IMPORTANCE OF IMPLEMENTING THE ANTIMICROBIAL STEWARDSHIP PROGRAM (ASP) IN THE ICU AND EMPHASIZING THE ROLE OF FULLY INTRODUCED MICROBIOLOGICAL SCREENING IN TERMS OF REDUCING THE LENGTH OF STAY AT THE ICU AND THE HOSPITAL, FOR BETTER CLINICAL OUTCOME

Jelena Micik
Acibadem Sistina, str. Skupi 5a, 1000 Skopje, R.N. Macedonia, jelena.micikj@acibademsistina.mk
Ljubica Shuturkova
Faculty of Pharmacy, University "Ss. Cyril and Methodius", Skopje, North Macedonia, ljsuturkova@ff.ukim.edu.mk
Zoran Sterjev
Faculty of Pharmacy, University "Ss. Cyril and Methodius", Skopje North Macedonia, zost@ff.ukim.edu.mk
Aleksandra Grozdanova
Faculty of Pharmacy, University "Ss. Cyril and Methodius", Skopje North Macedonia, agrozdanova@ff.ukim.edu.mk

Abstract: The principles of the national and international campaigns are attracting the public eye by emphasizing the rational use of currently available antibiotics. This has emerged due to the concerns regarding the high prevalence of pathogens that manifest resistance to antibiotics alongside the declining research activities to develop new antibiotics. Hence, the need to provide a multidisciplinary approach to counter antibiotic resistance, provide consistent efficacy and optimize the therapy of choice regarding the resistance and the implementation of the antimicrobial stewardship program in the ICU.
Following the assigned principles of this program, regarding treatment in the intensive care units, could potentially lead to increase in the rate of cured infections, followed by reduction of hospital costs and length of hospitalization. The objectives of the upcoming research have been formed upon the estimation of the antimicrobial stewardship program effectiveness in the ICU, through lowering the length of stay in the ICU and lowering the overall stay in the hospital ward expressed in days.
This research is a retrospective, correlated, group study that spans over a period of four years (2020 – 2023), and is conducted in the Cardiac Surgery Intensive Care Unit of "Acibadem Sistina" Clinical Hospital. A total of 1277 adult patients upon cardiac surgery and admission in the ICU, have been included in the study. Additional subdivision of patients into two groups was made with the following selection criteria: Group 1 (2020 – 2021) includes patients without initial microbiological screening and no antimicrobial stewardship program on the ICU ward, and Group 2 (2022-2023) includes patients with initial microbiological screening and implemented antimicrobial stewardship program.
Out of all patients in the study, 636 patients (49.80%) were assigned in group 1 and 641 patients (50.20%) in group 2, respectively. Regarding the obtained results for $Z=23.13$ and $p<0.01$ ($p=0.00$), it can be concluded that the length of stay in the ICU for the patients in group 1 is significantly higher than the length of stay of the patients in group 2.
The emphasis of the fully implemented microbiological screening, as part of the antimicrobial stewardship program in the ICU, can be seen through the crucial aspects as: detection of pathogens in due time, implementing of definite antimicrobial therapy as soon as possible, decreasing the length stay at ICU and overall length of stay in the hospital.
Keywords: antimicrobial resistance, antimicrobial stewardship program in the ICU, microbiological screening, Clinical Hospital "Acibadem Sistina"

1. INTRODUCTION

The term rational use of antibiotics implies proper selection of an antibiotic, administered in suitable regiment that consists of correct dose, frequency and accurate time interval. On the other side, the irrational use of antibiotics is closely related with high levels of antibacterial resistance, failure to implement a therapeutic regiment with suitable antibiotics and a significant concern about the high rate of mortality in the intensive care units (ICU) [1].
The principles of the national and international campaigns are attracting the public eye by emphasizing the rational use of currently available antibiotics. This has emerged due to the concerns regarding the high prevalence of pathogens that manifest resistance to antibiotics alongside the declining research activities to develop new antibiotics. As a result, a rise in the ineffectiveness of antibiotics has been documented as this aggravates the

treatment of common infections. Potentially, this leads to progression of the complications due to infections with extension of the hospital stay and increased incidence of mortality [3]. Hence, the need to provide a multidisciplinary approach to counter antibiotic resistance, provide consistent efficacy and optimize the therapy of choice regarding the resistance and the implementation of the antimicrobial stewardship program in the ICU [4]. This program, when implemented in the intensive care units, promotes the adequate use of antimicrobial products (including antibiotics) through securing better clinical results for the patients, lowering the microbial resistance and lowering the spread of infections caused by microorganisms resistant to more than one medication.

The antimicrobial stewardship program allows the prescribing doctors to ensure better clinical results for their patients and minimize the side effects due to optimization of the prescription of antibiotics. Following the assigned principles of this program, in aspect of the intensive care unit`s treatment, this could potentially lead to increase in the rate of cured infections, followed by reduction of hospital costs and length of hospitalization [4,5,6].

A conclusion based on large multicentered prevalence researches, confirms that a bacterial or fungal infection has been identified for more than 50% of the patients in the intensive care units. Common bacterial or fungal infections in the ICU, demand the need of fully implemented microbiological screening in everyday practice [7]. The critical importance of the antimicrobial stewardship, above all, has been closely related to the initial screening process, in such manner to obtain diagnostic information about the origin and the classification of the infections as soon as possible [8].

It is important to point out the current progress in the stewardship with the critically ill patients in the ICU, using biomarkers as a steering tool for antimicrobial treatment. In parallel to the microbiological screening, these biomarkers are currently the focus of the programs for antimicrobial stewardship. Regarding the intrinsic qualities that ought to be regarded as indicators of a perfect biomarker, the answer appears to be even more complexed. As a first rule, biomarkers have the ability to implicate an early elimination of an infective nature. The second characteristics stands upon their power to be used as a tool to measure the severity of an illness. At last, the third and most important attribute is the ability to predicate the direction of the clinical course for a patient in the ICU, when evaluating the information gathered from repeated measurements throughout a time interval [9,10]

2. MATERIALS AND METHODS

Research aim and objectives

Estimation of the antimicrobial stewardship program effectiveness through the following objectives:

- Lowering the length of stay in ICU
- Lowering of the overall hospitalization time

Research design

This research is a retrospective, correlated, group study that spans over a period of four years (2020 – 2023), and is conducted in the Cardiac Surgery Intensive Care Unit of "Acibadem Sistina" Clinical Hospital

Population sample

A total of 1277 adult patients upon cardiac surgery and admission in the ICU, have been included in the study. Additional subdivision of patients into two groups was made with the following selection criteria: Group 1 (2020 – 2021) consists of 636 (49.80%) of patients without initial microbiological screening and no antimicrobial stewardship program on the ICU ward, and 641 (50.20%) of patients in Group 2 (2022-2023) with initial microbiological screening and implemented antimicrobial stewardship program.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were predefined, in order to accomplish the research objectives.

Inclusion criteria:

- All patients that undergo cardiac surgery and have been admitted to the ICU will enter the study.
- Period 2020-2023

Exclusion criteria:

- Patients with post-cardiac intervention will be excluded from the study if fatal outcome happened within less than 5 days from entering the study.

Statistical analysis

- Statistical analysis of data has been conducted using the following programs: Statistica 7.1 for Windows and SPSS Statistics 23.0

Ethics approval

All methods used in the study were in accordance with the international guidelines, with the standards the Helsinki Declaration of 1975, revised in 1983 and approved by Ethics commission from Clinical Hospital Acibadem Sistina.

3. RESULTS

A total of 1277 patients have entered the study, out of which 636 (49.80%) patients compose **group 1 (2020 – 2021)** characterized without initial microbiological screening and no antimicrobial stewardship program, and 641 (50.20%) patients placed in **group 2 (2022 – 2023)** designated with initial microbiological screening and implemented antimicrobial stewardship program.

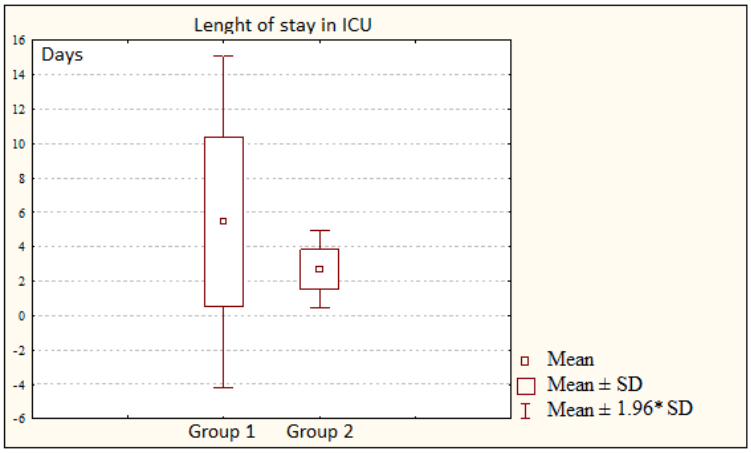
The descriptive statistics for length of stay in the ICU (expressed in days) for both groups is shown in **table 1** and **chart 1** as well.

Table 2 Descriptive statistics for length of stay in the ICU (expressed in days) for both groups.

Lenght of stay in ICU (days)	Valid N	Mean	Confidence -95,00%	Confidence +95,99%	Median	Minimum	Maximum	Std.Dev.
Group 1	636	5,44	5,06	5,83	4	1	53	4,93
Group 2	641	2,69	2,60	2,78	2	1	10	1,14

Source: Author

Chart 1 Descriptive statistics for length of stay in the ICU (expressed in days) for both groups



Source: Author

Table 1.1 Difference in lenght of stay in the ICU

Variable	Rank Sum Group 1	Rank Sum Group 2	U	Z	p-level	Valid N Group 1	Valid N Group 2
Lenght of stay in ICU	554518,5	261484,5	55723,50	23,13	**0,00**	636	641

Source: Author

Since Z = 23,13 and p<0,01(p=**0,00**) it can be concluded that length of stay in the ICU for the patients in group 1 is significantly higher than the length of stay of the patients in group 2 (table 1.1).

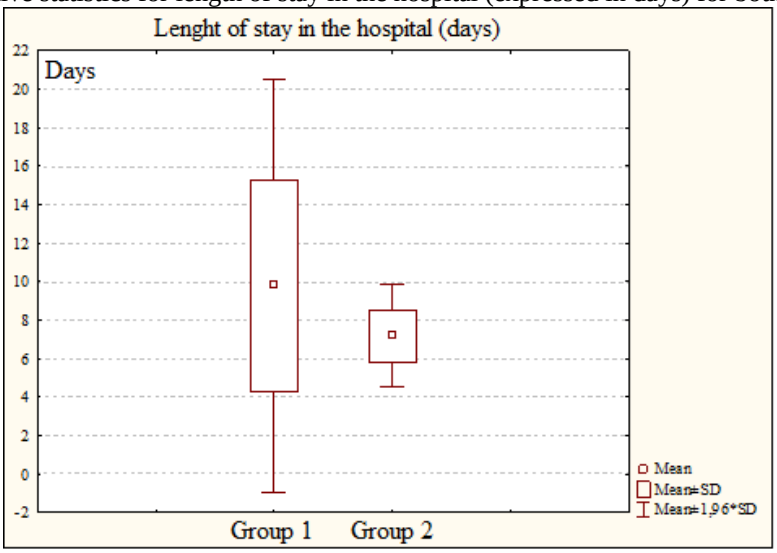
The descriptive statistics for length of stay in the hospital (expressed in days) for both groups of patients is shown in **table 2** and **chart 2** as well.

Table 2. Descriptive statistics for length of stay in the hospital (expressed in days) for both groups of patients

Lenght of stay in the hospital (days)	Valid N	Mean	Confidence -95,00%	Confidence +95,99%	Median	Minimum	Maximum	Std.Dev.
Group 1	636	9,81	9,38	10,23	8	5	54	5,48
Group 2	641	7,18	7,08	7,29	7	5	16	1,36

Source: Author

Chart 2. Descriptive statistics for length of stay in the hospital (expressed in days) for both groups of patients



Source: Author

Table 2.1 Difference in length of stay in the hospital for both groups of patients

Variable	Rank Sum Group 1	Rank Sum Group 2	U	Z	p-level	Valid N Group 1	Valid N Group 2
Lenght of stay in the hospital (days)	503164,5	312838,5	107077,5	14,99	**0,00**	636	641

Source: Author

Since Z = 14,99 and p<0,01(p=**0,00**) it can be concluded that length of stay in the hospital for the patients in group 1 is significantly higher than the length of stay for patients in group 2 (table 2.1).

4. DISCUSION

In the context of discussing the attached results, first and foremost there is a description of the length of stay in ICU for both groups, expressed in days. In other words, in group 1 the length of stay in the ICU expressed in days varies in the following interval: 5,44±4,93 days, ±95,00% CI: 5,06-5,83, the median is 4 days , the minimum length of stay is 1 day and the maximum is 53 days. Accordingly, in group 2 the length of stay in the ICU expressed in days varies in the following interval: 2,69±1,14 days, ±95,00% CI: 2,60-2,78; the median is 2 days, the minimum length of stay is 1 day and the maximum is 10 days.

Regarding the above-mentioned results, it can be concluded that the patients in group 1 have significantly higher length of stay in the ICU compared to the patients in group 2. Since Z = 23,13 and p<0,01(p=**0,00**), patients in group 1 have significantly higher length of stay in the ICU compared to the patients in group 2 (table 1.1). To be more specific, considering the obtained results, it can be concluded that the length of stay in ICU expressed in days for group 2 has decreased almost two-fold, as a result of the implemented program for antimicrobial stewardship in the ICU and fully conducted microbiological screening.

In the second half of the result interpretation, there is a description of the length of stay in the hospital expressed in days for both groups, accordingly. In group 1, the length of stay in hospital expressed in days varies in the following interval: 9,81±5,48 days, ±95,00% CI: 9,38-10,23, the median is 8 days , the minimum length of stay is 5 day and the maximum is 54 days. In comparison, the length of stay in hospital, expressed in days for patients in group 2 varies in the following interval: 7,18±1,36 days, ±95,00% CI: ,08-7,29, the median is 7 days , the minimum length of stay is 5 day and the maximum is 16 days.

Since Z = 14,99 and p<0,01(p=**0,00**), patients in group 1 have significantly higher length of stay in the hospital expressed in days, compared to the patients in group 2 (table 2.1) As demonstrated before, same conclusion can be deduced for the second variable as well. As a result of the effectively implemented program for antimicrobial stewardship in the ICU and fully conducted microbial screening, the length of stay in the hospital expressed in days has decreased significantly for patients in group 2.

5. CONCLUSION

Considering all facts presented, it can be concluded that the process of implementing the antimicrobial stewardship in the ICU is a crucial step. As part of this process and equally significant, is the fully implemented microbiological screening, as part of the antimicrobial stewardship program in the ICU. This can be observed through crucial aspects as: detection of pathogens in due time, implementing of definite antimicrobial therapy as soon as possible, decreasing of length stay at ICU and overall hospitalization of patients. In summary, all of these aspects will result in improving the overall clinical outcome of patients, reducing hospital costs, reduction of the high rates of antimicrobial resistance and emphasizing the practice for rational use of the antimicrobial therapy regiment.

REFERENCES

Kern WV. (2021), Organization of antibiotic stewardship in Europe: the way to go. Wien Med Wochenschr. 2021 Feb;171(Suppl 1):4-8. doi: 10.1007/s10354-020-00796-5. Epub, Feb 9. PMID: 33560499; PMCID: PMC7872948.

Le Saux N; (2014), Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Antimicrobial stewardship in daily practice: Managing an important resource. Can J Infect Dis Med Microbiol. Sep;25(5):241-5. PMID: 25371683; PMCID: PMC4211344.

Mokrani, D., Chommeloux, J., Pineton de Chambrun, M. et al. (2023), Antibiotic stewardship in the ICU: time to shift into overdrive. Ann. Intensive Care 13, 39 https://doi.org/10.1186/s13613-023-01134-9

Murila, B. L. et al. (2022), Rational use of antibiotics and covariates of clinical outcomes in patients admitted to intensive care units of a tertiary hospital in Kenya, Hospital practice, 50(2), pp. 151–158. doi: 10.1080/21548331.2022.2054632.

Rawson TM, Antcliffe DB, Wilson RC, Abdolrasouli A, Moore LSP. (2023), Management of Bacterial and Fungal Infections in the ICU: Diagnosis, Treatment, and Prevention Recommendations. Infect Drug Resist.;16:2709-2726 https://doi.org/10.2147/IDR.S390946.

Ture Z., Güner R., Alp E., (2023), Antimicrobial stewardship in the intensive care unit, Journal of Intensive Medicine, Volume 3, Issue 3, Pages 244-253, ISSN 2667-100X, https://doi.org/10.1016/j.jointm.2022.10.001.

Turgman O, Schinkel M, Wiersinga WJ. (2023), Host Response Biomarkers for Sepsis in the Emergency Room. Crit Care. Mar 21;27(1):97. doi: 10.1186/s13054-023-04367-z. PMID: 36941681; PMCID: PMC10027585.

Ventola CL. (2015) The antibiotic resistance crisis: part 1: causes and threats. P T. Apr;40(4):277-83. PMID: 25859123; PMCID: PMC4378521.

Vincent JL, Teixeira L. Sepsis biomarkers. (2014), Value and limitations. Am J Respir Crit Care Med. Nov 15;190(10):1081-2. doi: 10.1164/rccm.201410-1895ED. PMID: 25398103.

Walger P. (2016), Rationaler Einsatz von Antibiotika [Rational use of antibiotics]. Internist (Berl). Jun;57(6):551-68. German. doi: 10.1007/s00108-016-0071-5. PMID: 27246321.