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The influence of *Staphylococcus* infections on the evolution of hospitalized patients: The experience of the surgical department of IRGH Cluj-Napoca

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Abstract

Despite recent scientific advances in diagnosis and treatment of human infections, bacterial infections continue to affect human health. The rate of morbidity and mortality caused by staphylococcal infections remains high and continues to be a threat to public health worldwide. Staphylococcal infections affect the population at risk regardless the level of country development. The highest risk categories include people with immunodeficiency, those with prolonged antibiotic treatment and repeated hospitalizations, patients with implanted medical devices or undergoing medical invasive procedures. The objective of this study was to analyse the influence of staphylococcal infection diagnosed during hospitalization on the evolution of patients admitted during two consecutive years, in surgical and intensive care wards in IRGH (Regional Institute of Gastroenterology and Hepatology) Cluj-Napoca, Romania, having as main diagnosis of hospitalization surgical digestive diseases along with other comorbidities. The occurrence of staphylococcal infection was associated with increased morbidity and mortality rates in patients included in the study.

Keywords: antibiotic treatment; bacterial infection; *Staphylococcus aureus*; Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Introduction

Genus *Staphylococcus*is known to include 52 species and 28 subspecies, out of which *Staphylococcus aureus* is the most widespread bacterium (Lee *et al*., 2018). These bacteria range in sizes from 0.5 μm to 1 μm, are Gram positive, spherical in shape and divide into 1-2 planes to form clusters, are not mobile, do not form spores, are facultatively anaerobic, have aerobic respiration or fermentation and for feeding they need an organic source of nitrogen provided by several amino acids such as arginine, valine, vitamin B complex (Gajdács,

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2019; Algammal *et al*., 2020). The name *aureus* comes from the golden colour of the colonies growing in solid media (Harris *et al*., 2002; Myles and Datta, 2012).

Bacterial growth takes place under optimal conditions at 37 °C and a pH of 7.4 (Guo *et al*., 2020). Staphylococci tolerate high salt concentrations well and resist heat (Harris *et al*., 2002; Gajdács, 2019). Most staphylococcal species are coagulase-negative while most strains of *Staphylococcus aureus* are coagulase-positive (Foster, 1996; Matthews *et al*., 1997; Harris *et al*., 2002; Tong *et al*., 2015). The cell wall consists of a lipid membrane surrounded by a thin layer of peptidoglycan and lipoteichoic acid. The teichoic acid ensures the negative charge of the bacterial cell membrane, the peptidoglycan chains determine the rigidity of the bacterial wall, the spherical shape and provide protection against osmotic lysis (Oliveira *et al*., 2018).

Staphylococcus aureus is one of the most common bacteria that colonizes and infects both immunocompromised hospitalized patients and healthy population with normal immunity in the community (Harris *et al*., 2002), and is normally found on the skin, in the nasopharynx, armpit, groin, perineal area (Harris *et al*., 2002; Oliveira *et al*., 2018; Kourtis *et al*., 2019; Gajdács, 2019; Cong *et al*., 2020). The appearance of staphylococcal infection is influenced by the general and special conditions in which the body finds itself at a given time like malnutrition, poor hygiene, severe chronic diseases (cancer, diabetes mellitus, liver, and kidney failure), immune deficiency, prolonged and repeated hospital admissions, invasive medical procedures, prolonged antibiotic treatment, old age, skin infections (Lee *et al*., 2018; Oliveira *et al*., 2018; Siddiqui and Koirala, 2022).

Staphylococcus aureus causes a multitude of infections in both humans and animals, with different locations, such as abscesses, boils, carbuncles, folliculitis, cellulitis, osteomyelitis, arthritis, prosthesis infections, pneumonia, lung abscesses, gastroenteritis, food poisoning, meningitis, brain abscesses, urinary tract infections, nephritis, pyelonephritis, endocarditis, otitis media, septic shock (Graninger *et al*., 1995; Foster, 1996; Hassoun *et al*., 2017; Gao *et al*., 2018; Oliveira *et al*., 2018; Gajdács, 2019; Guo *et al*., 2020; Algammal *et al*., 2020; Taylor and Unakal, 2022). Before the antibiotic era, staph infection was considered deadly. With the advent of penicillin discovered by Alexander Fleming in 1940 this infection became treatable and even successful, but this period did not last long and in 1961 the first penicillin-resistant strain was reported (Guo *et al*., 2020). At present it is considered that more than 95% of *Staphylococcus aureus* is penicillin resistant through the production of penicillinase (Gajdács, 2019).

Methicillin resistant *Staphylococcus aureus* (MRSA) is classified into three groups with different characteristics, different antibiotic susceptibility and different treatment requirements (Siddiqui and Koirala, 2022). HA-MRSA (hospital acquired MRSA), CA-MRSA (community acquired MRSA) and LA-MRSA (livestock associated MRSA). CA-MRSA differs genetically from HA-MRSA because it affects apparently healthy, young people and causes less severe skin and soft tissue infections. LA-MRSA was first described in 2000, affects domestic animals and has arisen because of intensive antibiotic treatment of domestic animals, infected animals being a source of infection for humans (Gajdács, 2019). More than 60% of *Staphylococcus aureus* isolated from different cultures was resistant to methicillin (Gao *et al*., 2018).

MRSA infections increase morbidity and mortality in the elderly and patients with serious associated comorbidities such as renal and hepatic failure and increase the duration and cost of hospitalization (Lee *et al*., 2018; Gajdács, 2019; Guo *et al*., 2020; Sharaf *et al*., 2021; Siddiqui and Koirala, 2022;). The costs caused by MRSA infection exceed 3-4 billion dollars annually (Sharaf *et al*., 2021). The first treatment guidelines for MRSA infection appeared in the US in 2011 and aimed at the recommended management and treatment of this type of infection (Liu *et al*., 2011).

Materials and Methods

Location of the study and patients

The present study followed the evolution of 34 patients admitted to the surgical and intensive care wards of IRGH Cluj-Napoca (in Romanian: Institutul Regional de Gastroenterologie și Hepatologie 'Prof. Dr. Octavian Fodor'; in English: Regional Institute of Gastroenterology and Hepatology 'Prof. Dr. Octavian Fodor') during the period January 1, 2018 – December 31, 2019, in whom bacteria of the genus *Staphylococcus* were detected, performing a retrospective study, a study approved by the IRGH Ethics Committee.

The criteria considered for the presence or absence of Staphylococcus bacteria

The inclusion criteria in the study were represented by the presence of *Staphylococcus* bacteria during hospitalization regardless of age, associated diseases, results of biological samples collected during hospitalization, treatment, and evolution. Exclusion criteria were represented by the absence of confirmation of infection by laboratory methods.

Bacteria were detected in the microbiology laboratory using the BACT/ALERT R3D Automated Microbial Detection System (bio Merieux, Inc Durham NC) using calorimetric technology to detect microorganisms. The identification of bacteria and fungi as well as the determination of antibiotic susceptibility was performed with the VITEK2 COMPACT SYSTEM (bio Merieux, Inc Durham NC) with ready to use VITEK ID /AST cards.

Interpretation of the results

Interpretation of the results was performed according to EUCAST 2016-2017 (European Committee on Antimicrobial 2016-2017) standards.

Biological samples taken in the study were: leukocytes, red blood cells, haemoglobin, haematocrit, urea, creatinine, C-reactive protein, procalcitonin, TGO, TGP, glycemia, sodium, potassium, calcium, and magnesium. These samples were processed on the COBAS PRO C 503/E 801 machine available in the IRGH laboratory.

The study included data selected from the observation sheets of the patients admitted during the mentioned period, in Excel databases and statistically processed. Indexes of dispersion and centrality were calculating, as well as frequency tables. Normality of numerical data was assessed using Kolmogorov-Smirnov test. According to results, selection of parametric or non-parametric was made (Mann Whitney U Test/Student T test). Chi square test was used for significance calculation in case of crosstabular data. A significance threshold of $p<=0.05$ was selected. SPSS 17.0 software was used for data analyses.

Results

General characteristics of patients included in the study are presented in Table 1.

Table 1. Results of statistical processing of collected data

No	Patient characteristics		Number of patients	Percentage (%)
1	Age (average +/-SD) years		65,323+/-12.293	
2	Gender	Males	23	67.64
		Females	11	32.35
3	Environment of origin	Urban	18	52.94
		Rural	16	47.05
4	Associated diseases	Digestive	33	97.05
		Cardiac	30	88.23
		Diabetes mellitus	20	58.82
		Pulmonary	14	41.17
		Renal	13	38.23
		Neurological	11	32.35
5	Number of hospitalization days	Males average +/- SD	29.913+/-22.055	
		Females average +/- SD	33.091+/-27.6711	
6	Number of hospital days by environment of origin	Males average +/- SD	33.889+/-25.5571	
		Females average +/- SD	27.625+/-21.5590	

The patients in the study ranged in age from 26 to 85 years and the number of days of hospitalization ranged from 2 to 91 days. Of the total number of patients included in the study, 33 patients had digestive diseases, 30 patients had one or more heart diseases, 20 patients had type I or II diabetes, 14 patients had one or more lung diseases, 13 patients had kidney diseases and 11 patients had neurological diseases. The summary is presented in Table 2.

Table 2. Comorbidities in patients

No	Comorbidities	Diseases		No patients	Percentage (%)
1	Digestive	Neoplastic diseases	Total (stomach, colon, pancreas liver)	20	60.60
		Benign diseases	Total	13	39.39
			Organ's occlusions and perforations	7	21.21
			Acute pancreatitis	3	9.09
			Mesenteric bowel infarction	2	6.06
			Perianal fistula	1	3.03
2	Cardiac	Hypertension and ischaemic heart disease		28	82.3
		Heart failure		8	23.52
		Atrial fibrillation		7	20.58
		Mitral and/or aortic insufficiency		3	8.82
		Myocardial infarction		1	2.94
		Bacterial endocarditis		1	2.94
3	Diabetes mellitus	Type I and II diabetes mellitus		20	58.82
4	Pulmonary	Respiratory failure		9	26.47
		BPOC		5	14.70
		Pneumonia		4	11.76
		Pulmonary thromboembolism		3	8.82
		Lung collections		1	2.94
5	Renal	Acute and chronic renal failure		12	35.29
		Urinary tract infection		1	2.94
6	Neurological	Stroke		3	8.82
		Cerebral infarction		2	5.88
		Parkinson's disease		2	5.88
		Polyneuropathies		2	5.88

		Pyramid syndrome	1	2.94
		Alzheimer's disease	1	2.94

Correlating the values of the biochemical samples collected at admission with the comorbidities recorded and presented in Table 2, we obtained statistically significant values in the following cases and presented in Table 3.

Table 3. Correlation between biochemical samples and comorbidities recorded

No	Comorbidities	Corelation	Treatment	Recorded values	P-value
1	Cardiovascular disease	Red blood cell count	Absent	4.11+/-0.88	P=0.023
			Present	3.20+/-0.70	
		Haemoglobin	Absent	12.27+/-3.38	P=0.017
			Present	9.43+/-1.94	
		Haematocrit	Absent	36.57+/-8.53	P=0.028
			Present	9.43+/-1.94	
2	Digestive diseases	C-reactive protein	Absent	36.22	P=0.001
			Present	10.20+/-7.14	
3	Renal diseases	Red blood cell count	Absent	3.56+/-0.76	P=0.013
			Present	2.90+/-0.59	
		Haemoglobin	Absent	10.60+/-2.30	P=0.005
			Present	8.41+/-1.50	
		Haematocrit	Absent	32.21+/-6.52	P=0.009
			Present	26.42+/-4.58	
		Urea	Absent	56.04+/-52.94	P=0.005
			Present	118.08+/-62.90	
		Creatinine	Absent	1.15+/-1.25	P=0.05
			Present	1.99+/-0.99	
		C-reactive protein	Absent	8.41+/-6.58	P=0.047
			Present	14.55+/-9.61	
		Procalcitonin	Absent	1.55+/-3.21	P=0.012
			Present	5.45+/-4.63	
4	Diabetes mellitus	Urea	Absent	39.85+/-27.60	P=0.001
			Present	107.15+/-67.72	
		Creatinine	Absent	0.73+/-0.29	P=0.002
			Present	1.99+/-1.35	
		C-reactive protein	Absent	6.18+/-3.84	P=0.023
			Present	13.51+/-9.14	
		Blood glucose	Absent	88.32+/-16.29	P=0.003
			Present	145.72+/-65.08	

Bacterial coinfections were also detected in the patients studied, their type and prevalence were presented in Table 4.

Table 4. Bacteria found in patients

No	Bacteria highlighted	Number of positive samples
1	Coagulazo-negative staphylococcus	21
2	*Staphylococcus aureus*	17
3	*Acinetobacter baumannii*	10
	Enterococcus faecalis	10
4	*Pseudomonas aeruginosa*	9
	Klebsiella pneumoniae	9
5	*Escherichia coli*	5
6	*Enterococcus faecium*	4
7	*Proteus mirabilis*	2
8	*Streptococcus anginosus*	1
	Clostridium difficile	1
	Proteus vulgaris	1
	Salmonella spp	1
	Burkholderia cepacia	1

Moreover, coexistence of fungal infections was detected in some patients, Table 5 summarizes the data.

Table 5. Fungi found in patients

No	Found fungi	Number of positive samples
1	*Candida glabrata*	7
2	*Candida albicans*	5
3	*Candida tropicalis*	4
4	*Candida* nonalbicans	3
5	*Candida spherica*	2
6	*Candida krusei*	1
7	*Candida lipolytica*	1
9	*Candida parapsilosis*	1

Correlating the values of the biochemical samples collected at admission with the bacteria and fungi detected, we obtained few statistically significant values presented in **Table 6**. Significant correlations were detected between certain types of coinfection and blood parameter values.

Table 6. Correlation between biochemical samples collected at admission with the bacteria and fungi detected

No	Found fungi	Correlation	Treatment	Values of biological samples recorded	P value
1	*Pseudomonas aeruginosa*	Red blood cell count	Absent	3.48+/-0.81	P=0.028
			Present	2.83+/-0.34	
2	*Salmonella* spp.	Leukocyte	Absent	11.41+/-6.95	P=0.000
			Present	54.79	
3	*Clostridium difficile*	C-reactive protein	Absent	10.20+/-7.14	P=0.001
			Present	36.22	
4	*Burkholderia cepacia*	Urea	Absent	74.43+/-59.73	P=0.030
			Present	212	
		Creatinine	Absent	1.34+/-0.96	P=0.000
			Present	5.8	

5	*Escherichia coli*	TGO	Absent	55.25+/-60.79	P=0.045
			Present	271.71+/-550.54	
		TGP	Absent	49.63+/-58.93	P=0.025
			Present	180.14+/-276.59	
6	*Streptococcus anginosus*	Calcium	Absent	4.10+/-0.39	P=0.031
			Present	3.19	
7	*Proteus mirabilis*	Sodium	Absent	136.71+/-5.30	P=0.040
			Present	145.00+/-5.65	

The next table presents statistically significant data for detected fungi in patients (Table 7)

Table 7. Statistical data for found fungi in patients

No	Found fungi	Correlation	Treatment	Values of biological samples recorded	P value
1	*Candida tropicalis*	Leukocyte	Absent	11.44+/-7.21	P=0.047
			Present	22.02+/-22.13	
		Urea	Absent	68.41+/-56.54	P=0.011
			Present	152.50+/-69.71	
		Creatinine	Absent	1.30+/-0.95	P=0.018
			Present	2.80+/-2.18	
		Procalcitonin	Absent	2.45+/-3.81	P=0.021
			Present	74.42+/-0.80	
2	*Candida krusei*	Calcium	Absent	4.10+/-0.39	P=0.031
			Present	3.19	

Several types of samples were collected to detect bacteria and fungi, presented in Table 8.

Table 8. Samples collected to detect fungi

No	Collected samples	Number of positive samples	Coagulase-negative staphylococcus	*Staphylococcus aureus*	MRSA
1	Blood cultures	22	7	1	3
2	Central venous catheter insemination	19	7	0	3
3	Urinalysis	18	1	0	0
4	Tracheal secretions	12	2	1	6
5	Plague secretions	11	1	0	1
6	Peritoneal secretions	11	1	0	1
7	Drain tube secretions	1	1	1	0
8	Stool sample	1	0	0	0
9	Biliculture	1	1	0	0

Correlating the values of biochemical samples collected at admission with the type of bacteriological sample collected, we obtained statistically significant values in several cases, presented in **Table 9**. Certain localizations of infection induced alterations of specific blood parameters, as data suggests.

Table 9. Correlation between biological samples collected at admission and type of bacteriological samples

No	Type of sample taken	Correlation	Treatment	Values of biological samples recorded	P value
1	Tracheal secretions	Red blood cell count	Absent	3.56+/-0.75	P=0.008
			Present	2.85+/-0.57	
		Haemoglobin	Absent	10.51+/-2.27	P=0.008
			Present	8.40+/-1.62	
		Urea	Absent	55.00+/-54.25	P=0.001
			Present	125.18+/-55.12	
		Creatinine	Absent	1.03+/-0.72	P=0.002
			Present	2.29+/-1.52	
2	Urinalysis	Red blood cell count	Absent	3.65+/-0.87	P=0.011
			Present	3.00+/-0.50	
		Urea	Absent	55.50+/-43.80	P=0.040
			Present	100.30+/-72.21	
3	Stool sample	Leukocyte	Absent	1.41+/-6.95	P=0.000
			Present	54.78	
4	Pleural fluid	Urea	Absent	71.60+/-59.20	P=0.043
			Present	148+/-74.52	
5	Peritoneal secretions	Calcium	Absent	4.18+/-0.39	P=0.034
			Present	3.85+/-0.41	

Antibiotic treatment was carried out with several classes of antibiotics, administration considered the underlying disease, associated comorbidities, patient's condition, results of biological and bacteriological samples collected during hospitalization, age and drug allergies recorded. Table 10 summarizes the antibiotics used.

Table 10. Administered antibiotics

No	Class of antibiotics administered	Trade name	Number of patients given antibiotic class
1	Nitroimidazole	Metronidazole	25
2	3rd generation cephalosporins	Cefotaxime, Ceftamil, Cefort	22
3	Carbapenems	Meronem, Imipenem, Invanz	17
4	Glycopeptide	Vancomycin	17
5	Polypeptide	Colistin	15
6	Oxazolidinone	Linezolid	8
7	Combinations of penicillin with beta-lactamase inhibitors	Amoxiplus, Ampiplus, Piperacilina-tazobacta	7
8	Aminoglycoside	Amikozit, Gentamicina	6
9	Sulfonamides with trimethoprim	Sumetrolim	6
10	Fluoroquinolone	Ciprofloxacin, Levofloxacin, Norfloxacin	6
11	Penicillin	Amoxicillin, Ampicillin, Penicillin	3
12	2nd generation cephalosporins	Cefuroxime	1
13	Lincosamides	Clindamycin	1
14	Nitrofurans	Nitrofurantoin	1
15	Tetracycline	Tygacil	1

Antifungal treatment was carried out with two classes of drugs according to the fungigram, presented in **Table 11**.

Table 11. Antifungal treatments

No	Class of antifungals	Trade name	Number of patients given antifungal class
1	Antimycotics for systemic use	Caspofungin	2
2	Triazole derivative	Fluconazole, Voriconazol	21

Combinations of one or more classes of antibiotics were administered to the patients in the study, the most used being nitroimidazole, 3rd generation cephalosporins, carbapenems, glycopeptides and polypeptides.

Only one patient in the study group was administered combinations of 9 antibiotics respectively 8 antibiotics and 12 patients received only two antibiotic combinations.

Staphylococcus aureus was present in 17 patients, including in one patient with endocarditis, one with strangulated median eventration and one with perforated gastric ulcer. Out of all cases, 14 cases the staphylococcus were detected as methicillin resistant. MRSA was present in 9 patients with malignant conditions (gastric, colon, pancreatic and liver neoplasm), and in 5 patients with benign conditions (perianal fistula, acute pancreatitis, and organ perforation).

By correlating the values of the biological samples collected at admission and the antibiotic treatment administered we found statistically significant values presented in **Table 12**.

Table 12. Correlation between biological samples collected at admission and antibiotic treatment

No	Class of antibiotics administered	Correlation	Treatment	Values of biological samples recorded	P value
1	Penicillin	Haematocrit	Absent	9.98+/-2.23	P=0.026
			Present	7.50+/-1.65	
		Calcium	Absent	4.02+/-0.37	P=0.012
			Present	4.65+/-0.55	
2	Polypeptide	Red blood cell count	Absent	3.69+/-0.80	P=0.001
			Present	2.83+/-0.35	
		Haemoglobin	Absent	10.86+/-2.42	P=0.001
			Present	8.38+/-1.03	
		Haematocrit	Absent	32.98+/-6.90	P=0.001
			Present	26.20+/-3.05	
		Urea	Absent	52.22+/-41.12	P=0.007
			Present	110.26+/-72.04	
		Calcium	Absent	40.23+/-0.33	P=0.013
			Present	3.88+/-0.45	
3	Carbapenems	Red blood cell count	Absent	3.59+/-0.93	P=0.030
			Present	3.03+/-0.41	
		Haemoglobin	Absent	10.68+/-2.77	P=0.017
			Present	8.85+/-1.15	
		Haematocrit	Absent	32.82+/-2.77	P=0.037
			Present	27.71+/-3.07	
		Calcium	Absent	4.30+/-0.34	P=0.001
			present	3.84+/-0.37	
4	Sulfonamides with trimethoprim	Red blood cell count	Absent	3.43+/-0.77	P=0.05
			Present	61.92+/-49.00	
		Urea	Absent	172.0+/-56.44	P=0.000
			Present	1.21+/-0.92	
		Creatinine	Absent	2.68+/-1.73	P=0.005
			Present	2.32+/-3.75	
5	Aminoglycoside	Procalcitonin	Absent	2.32+/-3.75	P=0.036

			Present	6.36+/-4.91	
		Potassium	Absent	4.37+/-0.67	P=0.018
			present	12.88+/-19.16	
6	3rd generation cephalosporins	Sodium	Absent	134.08+/-5.71	P=0.014
			Present	138.90+/-4.84	
7	Oxazolidinone	Sodium	Absent	138.42+/-4.58	P=0.020
			Present	133.00+/-7.00	

By correlating the biological samples collected at the end of the hospitalization period with the antibiotic treatment administered we obtained the following statistically significant values, presented in **Table 13**.

Table 13. Correlation between biological samples collected before discharge

No	Class of antibiotics administered	Corelation	Treatment	Values of biological samples recorded	P value
1	Combinations of penicillin with beta-lactamase inhibitors	Leukocyte	Absent	12.76+/-4.77	P=0.014
			Present	7.89+/-2.25	
2	2nd generation cephalosporins	Potassium	Absent	4.17+/-0.57	P=0.031
			Present	5.50	
		Magnesium	Absent	1.54+/-0.21	P=0.047
			Present	1.10	
3	Polypeptide	Red blood cell count	Absent	4.58+/-0.80	P=0.010
			Present	3.88+/-0.60	
		Haematocrit	Absent	40.58+/-7.01	P=0.044
			Present	35.40+/-7.31	
		Procalcitonin	Absent	1.45+/-3.47	P=0.006
			Present	6.02+/-4.81	
		TGP	Absent	81.94+/97.11	P=0.023
			Present	21.33+/12.71	
4	Carbapenems	Red blood cell count	Absent	4.61+/-0.79	P=0.011
			Present	3.93+/-0.65	
		Haematocrit	Absent	41.20+/-6.60	P=0.022
			Present	35.40+/-7.40	
		Procalcitonin	Absent	1.55+/-3.58	P=0.017
			Present	5.62+/-4.89	
5	Sulfonamides with trimethoprim	Haematocrit	Absent	37.28+/-7.62	P=0.009
			Present	43.01+/-5.05	
		Potassium	Absent	4.10+/-0.56	P=0.024
			Present	4.71+/-0.60	
6	Glycopeptide	Red blood cell count	Absent	4.57+/-0.80	P=0.024
			Present	3.97+/-0.68	
		Calcium	Absent	4.61+/-0.37	P=0.010
			Present	4.26+/-0.35	
7	Nitroimidazol	C-reactive protein	Absent	4.70+/-4.42	P=0.039
			Present	12.40+/-9.02	

In the case of the antimycotic treatment administered, its correlation with the results of the biological samples collected on admission resulted in the following statistically significant values, presented in **Table 14**.

Table 14. Correlation between antimycotic treatment and biological samples collected on admission

No	Class of antimycotics administered	Correlation	Treatment	Values of biological samples recorded	P value
1	Triazole derivatives	C-reactive protein	Absent	16.74+/-10.30	P=0.007
			Present	8.23+/-5.82	
2	Antimycotics for systemic use	Calcium	Absent	4.03+/-0.37	P=0.008
			Present	4.83+/-0.57	

By correlating the antimycotic treatment administered with the results of the biological samples taken before discharge we obtained the following statistically significant values, presented in **Table 15**.

Table 15. Correlation between antimycotic treatment and biological samples taken before discharge

No	Class of antimycotics administered	Correlation	Treatment	Values of biological samples recorded	P value
1	Triazole derivatives	Red blood cell count	Absent	4.68+/-0.74	P=0.016
		Haemoglobin	Absent	14.02+/-2.12	P=0.037
			Present	12.05+/-2.78	
		Haematocrit	Absent	4.63+/-6.33	P=0.039
			Present	36.23+/-7.56	
		Procalcitonin	Absent	1.09+/-3.13	P=0.030
			Present	5.01+/-4.90	

From 34 patients taken in the study at discharge we obtained the following statistically significant data, presented in **Table 16**.

Table 16. Patient data at discharge

No	Condition declared at discharge	Number and percentage of patients	Females	Males	Malignant conditions	Benign conditions
1	Cured	5 14.7%	1 2.94%	4 11.76%	2 5.88%	3 8.82%
2	Improved	14 41.17%	6 17.64%	8 23.52%	10 29.41%	4 11.76%
3	Deceased	15 44.11%	4 11.76%	11 32.35%	8 23.52%	7 20.58%

By correlating the values of biological samples collected at admission with the patient's declared condition at discharge we obtained the following statistically significant data, presented in **Table 17**.

Table 17. Correlation between biological samples collected at admission and patient declared condition at discharge

No	Condition declared at discharge	Correlation	Treatment	Values of biological samples recorded	P value
1	Cured	Red blood cell count	Absent	3.20+/-0.71	P=0.042
			Present	3.95+/-0.83	
		Haemoglobin	Absent	9.38+/-1.85	P=0.017
			Present	11.98+/-3.02	
		Haematocrit	Absent	29.00+/-5.75	P=0.027
			Present	35.80+/-7.80	

2	Improved	Leucocyte	Absent	15.76+/-12.14	P=0.032
			Present	8.29+/-2.94	
		Urea	Absent	105.73+/-60.79	P=0.003
			Present	41.78+/-47.62	
		Creatinine	Absent	1.81+/-1.34	P=0.018
			Present	0.90+/0.70	
		Procalcitonin	Absent	4.45+/-4.59	P=0.012
			Present	0.28+/-0.31	
3	Deceased	Leucocyte	Absent	8.59/-2.85	P=0.006
			Present	17.87+/-13.37	
		Urea	Absent	40.52+/-42.04	P=0.000
			Present	130.28+/-49.78	
		Creatinine	Absent	0.91+/-0.65	P=0.001
			Present	2.18+/-1.40	
		Procalcitonin	Absent	0.22+/-0.26	P=0.000
			Present	5.91+/-4.42	

By correlating the biological samples collected before discharge with the patient's declared condition at discharge we obtained a single statistically significant value for leukocytes, presented in **Table 18**.

Table 18. Correlation between patient's condition at discharge and biological samples

No	Condition declared at discharge	Correlation	Treatment	Values of biological samples recorded	P value
1	Improved	Leukocyte	Absent	13.12+/-4.94	P=0.046
			Present	9.8+/-3.19	

Discussion

According to the literature, MRSA is responsible for a significant increase in the mortality rate of patients infected with this super bacterium (Gould, 2007). Before the advent of antibiotics, mortality due to staphylococcal infections was over 70% and decreased to about 30% after the introduction of penicillin (Gould, 2007).

Antimicrobial resistance has arisen because of the exaggerated and in some cases unjustified use of antibiotics and multi resistant bacteria pose a serious treatment problem (Guo *et al*., 2020) (art 26). Excessive and often unjustified administration of antibiotics has led to the emergence of antimicrobial resistance and multidrug-resistant bacteria, with MRSA being the most eloquent bacteria in this case, encountered both in hospitals and in the community, both in humans and animals, and considered the most worrying threat to the health of the world's population (Khan *et al*., 2018).

Severe staphylococcal infections increase mortality in CA-MRSA, women, patients with systemic infections and skin and soft tissue lesions, patients with implanted medical devices, immunosuppressed patients, or patients with serious illness (Hassoun *et al*., 2017). High mortality and morbidity in MRSA infection is also described in other studies published in peer-reviewed journals (Lee *et al*., 2018; Gajdács, 2019; Guo *et al*., 2020; Sharaf *et al*., 2021; Siddiqui and Koirala, 2022).

Like *Staphylococcus aureus*, MRSA can cause a multitude of infections with different locations: skin and soft tissue infections, osteo articular system infections (arthritis, osteomyelitis), pneumonia, acute endocarditis, infections of implanted medical devices, meningitis, brain, and spinal cord abscesses (Liu *et al*., 2011; Siddiqui and Koirala, 2022). Recently published international treatment guidelines show that MRSA infection can be

treated with several classes of antibiotics depending on the location of the infection. Thus, according to Brown *et al*. (2021), treatment of MRSA using UK published treatment guidelines is most performed with glycopeptide (vancomycin).

In uncomplicated skin infections, local antiseptics are recommended as the first treatment option, fusidic acid and mupirocin as the second option and systemic antibiotics according to the antibiogram in complicated infections. In case of abscesses, incision and drainage, antibiotic therapy according to the antibiogram, oral treatment with clindamycin or cotrimoxazole if MRSA is sensitive to these drugs are recommended. In case of severe skin infections, antibiotic therapy with glycopeptides (vancomycin or teicoplanin) is recommended and as secondary alternatives linezolid or daptomycin then tigecycline, clindamycin, cotrimoxazole and doxycycline as tertiary line (Brown *et al*., 2021). In case of complicated urinary tract infections glycopeptides remain the antibiotics of choice as well as in case of bone and joint infections, endocarditis, and pneumonia. In case of minor infections in the oral sphere cotrimoxazole or doxycycline and glycopeptide or linezolid are recommended in case of severe infections. In the case of intracranial infections, besides surgical treatment where possible, vancomycin or linezolid remain the drugs of first intention (Brown *et al*., 2021).

Vancomycin was discovered in 1957 by Dr. E.C Kornfield and is active against a large number of gram-positive bacteria such as *Staphylococcus, Enterococcus, Streptococcus, Pneumococcus, Listeria Corynebacterium* and *Clostridium* and has been used successfully for over 60 years and can be given to patients allergic to semisynthetic penicillin and cephalosporins (Rubinstein and Keynan, 2014; Cong *et al*., 2020). Treatment with Vancomycin should be tailored to the needs of the patient, the initial dose should be calculated based on body weight taking into account renal function, the usual recommended dose being 15-20 mg/kg body weight per 8-12 hours not exceeding 2g/dose. In severe cases the dose may be increased to 25-30 mg/kg body weight and the duration of treatment may be 7-14 days in uncomplicated cases and up to 4-6 weeks in endocarditis, osteoarticular infections and skin and soft tissue infections (Rybak *et al*., 2021). A 2018 study published by Chuan Gao et al shows that MRSA can develop resistance to vancomycin in 2000 with the first case of vancomycin-resistant staphylococcus being reported and, in this case, quinolones are another class of drugs useful in the treatment of MRSA infection if they are used rationally (Gao *et al*., 2018).

According to Siddiqui *et al*. (2021) by the treatment of mild forms of MRSA infections can be done orally with trimethoprim sulfamethoxazole, tetracycline (doxycycline or minocycline), clindamycin, linezolid and tedizolid or delafloxacin. Parenterally vancomycin remains the drug of choice for complicated infections or those not responding to oral treatment, along with daptomycin in the case of those allergic to vancomycin. Other options include ceftaroline and telavancin. Teicoplanin is another antibiotic from the class of glycopeptides with similar action to vancomycin and is better tolerated but not yet approved by the FDA in the US. Linezolid has demonstrated inferior action to vancomycin in clinical trials according to this article. MRSA endocarditis with a mortality of more than 30% responds to treatment with vancomycin intravenously but with a treatment duration of 6 weeks, while clindamycin and linezolid should not be used due to poorer treatment results compared to vancomycin or daptomycin (Siddiqui and Koirala, 2022).

A study published by Algammal *et al*. (2020) showed that linezolid can also be a solution for the treatment of MRSA infections but not for more than 14 days due to side effects (2).Other studies have shown positive effects in the treatment of MRSA using combinations of antibiotics such as rifampicin with trimethoprim sulfamethoxazole orally versus linezolid administered orally or parenterally, proving that the lower cost of treatment with the two drugs administered orally can be an alternative compared to other classes of antibiotics administered parenterally (Harbarth *et al*., 2015). Other studies show that vancomycin remains the antibiotic of first choice for severe MRSA infections along with Daptomycin and Linezolid and for moderate and mild infections Clindamycin, Doxycycline and Trimethoprim sulfamethoxazole are the antibiotics of choice (Lee *et al*., 2018).

Conclusions

Staphylococcus aureus is one of the most common bacteria both in the community and in the hospital, but it poses the most serious treatment problems. The emergence of MRSA further hinders the treatment of patients infected with this superbug, greatly increasing the costs of hospitalization and treatment in both poor and developed countries. Glycopeptides remain the antibiotics of first choice for these infections, but other classes of antibiotics have also proven effective in the treatment of these infections. Also, in this study the mortality of patients with severe disease in whom staphylococcal infections were detected was high, the duration of hospitalization prolonged and treatment costs high.

The prevention of bacterial infections is achieved by observing hygiene measures, correct hand washing, correct application of disinfection and sterilization procedures, compliance with treatment guidelines, compliance with doses, duration of treatment and route of administration of antibiotics (Khan *et al*., 2018).

Correct and timely diagnosis of staphylococcal infection by instituting appropriate and correct treatment according to international treatment guidelines remains a sure way to decrease unsatisfactory outcomes and prevent an increase in the number of infections and deaths (Hassoun *et al*., 2017; Kourtis *et al*., 2019; Brown *et al*., 2021).

Authors' Contributions

CC has collected data, contributed to systematization of results, and manuscript writing. SLP and TM contributed to all haematological and biochemical, as well as bacteriological tests in all included patients. MT and AP were involved in statistical analyses of data. ML structured the study design, manuscript review and correction, data interpretation.

All authors read and approved the final manuscript.

Ethical approval (for researches involving animals or humans)

The procedures performed involving human participants were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments. Consequently, the study obtained the approval from The Ethical Commission of IRGH (5025/12.04.2021, and 116/15.04.2021, respectively).

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Conflict of Interests

The authors declare that there are no conflicts of interest related to this article.

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