THE "CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY OF BUCHAREST

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THE "CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY OF BUCHAREST

DOCTORAL SCHOOL

MEDICAL FIELD

PROGNOSTIC FACTORS FOR POSTOPERATIVE MENINGITIS IN NEUROSURGERY

PhD THESIS SUMMARY

PhD Supervisor:

PROFESSOR ADRIAN STREINU – CERCEL, PhD

PhD Candidate:

VICTOR – DANIEL DOROBĂŢ

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The"Carol Davila" University of Medicine and Pharmacy of Bucharest
Street Dionisie Lupu no. 37 Bucharest, Sector 2, 020021 Romania, Fiscal code: 4192910
Account: RO57TREZ70220F330500XXXX, Bank: TREASURY sect. 2
+40.21 318.0719; +40.21 318.0721; +40.21 318.0722
www.umfcd.ro

CONTENT

THE FUNDAMENTAL ISSUE

Undoubtedly, the era of innovation in technology and the Pharma industry, has fostered new perspectives and benefits in anti-infective therapy, whether we are talking about the viruses, bacteria or fungi. The use of these therapies, sometimes even hazardously, without the support provided by microbiological laboratory results, has caused the emergence of the phenomenon of resistance to anti-infective medication. Therefore, I appreciate that in this era of significant increase in antibiotic resistance, the possible infectious complications in surgical environments and the therapeutic attitude towards them - from the perspective of ensuring prevention - early diagnosis, treatment and monitoring represent *important, current, worthy of research topics* .

Both through the anatomical approach, but also through the importance of the central nervous system in the management of the whole body, the specificity of neurosurgical interventions is directly influenced by the possibility of infectious complications; among which - considering the location, the important possible number of sequelae and the high degree of disability - *postoperative bacterial meningitis* is the most serious, raising the issue of life-threatening risk.

Bacterial resistance and multi-resistance to antibiotics, found especially in surgical environments - considered a priority at the level of the World Health Organization - represents a concern and a problem of utmost importance for the medical world and will certainly not be found a solution to, if not tackled in a context multidisciplinary approach: infectious diseases, microbiology, epidemiology, surgery and intensive care units, through unitary improvement policies targeting the entire spectrum of activity associated with the medical act.

The procedures associated with neurosurgical interventions - which require a rigorous asepsis, due to the immunological particularities of this anatomical system considered privileged - require increased attention, not only from the perspective of infections associated with medical care, but also due to the fact that antibiotic concentration values that exceed the blood-brain barrier are not always predictable.

ASSUMPTION

The present paper will present concrete desirable results, obtained after the confirmation of three research hypotheses, which will be diligently pursued:

1) If, within a series of parameters (some from reference materials, but with an unverified applicability to local realities, others intuitive or observational) found both in the study group and in the control group, through statistical analysis, I will come to the identification of those that represent significant unfavorable prognostic factors, which influence the occurence of this pathology;

2) If, from studying the antibiotic classes and agents administered as part of the prophylactic / first-line antibiotic therapy in the study group, in relation to the previously identified risk factors, through statistical analysis, I will find those frequent, optimal treatment regimens for the subsequent positive outcome of these risky cases;

3) If, from the applicability of a prognostic score type system (qSOFA), as well as another developmental parameter, the condition at discharge, in relation to the previously identified risk factors and the spectrum of isolated etiological agents, through statistical analysis, I will find the final antibiotic therapy regimens, which ensures a favorable prognosis in patients diagnosed with postoperative meningitis in neurosurgery.

To support these hypotheses, I will start from the present reality at the patient's bedside and will research on a study group (neurosurgical patients who developed postoperative meningitis (32)), in referrence to a control group (neurosurgical patients who did not develop postoperative meningitis (620)), the selected parameters, through the prism of the role of each of them in determining this pathology.

OBJECTION

The main *scientific objective* pursued will be the evaluation of the weight of the prognostic factors that adversely influence the occurrence of postoperative neurosurgical meningitis, each "prospective" risk factor being consistently analyzed statistically, in order to arrive at the end, at the formulation of a "mathematically proven" conclusion.

The consistency of the statistical evaluation - in addition to the mathematical proof that supports the final conclusions within this framework - will be able to help medical institutions to outline a work protocol that ensures, on the one hand, the prevention of the occurence of postoperative meningitis, and on the other hand, the administration of

successful final antibiotic therapies, both in cases with a positive bacteriological examination result, and in those in which these results remain negative, the last representing a frequently encountered category.

Thus, the third chapter will start from the characteristics of a group of patients with postoperative meningitis after neurosurgical interventions, which will be described in detail by relating it to various parameters, and will get - through statistical analysis - to outline some prognosis factors which can influence the evolution in an unfavorable way; some of them will be modifiable by the therapeutic attitude, others not modifiable, but equally important through the particularities of managing the case that poses them.

In the fourth chapter, I will analyze the statistical correlations established between the classes of agents in the initial antibiotic therapy (prophylactic and first-line) and the previously stated prognostic factors, as well as with the clinical diagnoses that determined the interventions or certain elements of postoperative management and I wil statistically highlight the most frequent choices, which can be recommended to improve the evolution of patients.

The last but one chapter of the personal part will present statistical correlations established between the qSOFA score values and the condition at discharge, in relation to the final antibiotic therapy and the incriminated pathogens, which will lead to noteworthy therapeutic conclusions. I will try to demonstrate here, that the use of an easy, fast and repeatable prognostic score system made up of objective clinical elements, easy to obtain, is also desirable and applicable to the evolution of the neurosurgical patient, especially in those in whom we suspect the possibility of postoperative meningitis.

GENERAL RESEARCH METHODOLOGY

The proposed research project is of a retrospective type and was carried out on a number of 620 patients with neurosurgical interventions, from the "*Prof. Dr. Nicolae Oblu*" Emergency Clinical Hospital of Iaşi, during 2016-2019. They were selected based on both the diagnosis and other coordinates (age, gender, associated pathology, GCS, qSOFA, etc.), in order to obtain statistically relevant results.

The study group was made up of 32 patients with postoperative meningitis, selected from a group of 63 patients transferred for specific treatment to The "*Sf. Parascheva*" Infectious Diseases of Iaşi, with the diagnosis Obs: Postoperative Meningitis

(MPOP(+)).

The control group included 588 operated patients who did not develop postoperative meningitis (MPOP(-)). The percentage of MPOP(+) patients, from the total number of patients who underwent neurosurgical interventions in the study, was 5.1%.

In the fourth chapter, both the deaths (n = 4) from the initial study sample and the cases that did not have the administered agent recorded (n = 21) from the control group were excluded; however, we considered that in order to have a unified view of all enrolled patients in the MPOP(-) group, reporting the results should be carried out at the level of the entire sample, due to two reasons: the small percentage represented by the 21 patients (3.5%) and the presence of the anti-infective chemotherapy medication in question, among the classes already enrolled.

To define meningitis associated with neurosurgical medical care, the presence of at least one of the following clinical elements (signs or symptoms) must be recorded, without other detectable causes (Chen C. et al., 2014, pp. 2-3); of course, in the context of the existence of a surgical intervention in the immediate history:

- Fever (>38^0C);
- Headache;
- Vomiting;
- Meningeal contracture syndrome.

With the positivity of at least one of the following paraclinical examinations (Chen C. et al., 2014, pp. 2-3):

- Blood tests: blood count with leukocytosis; CSF tests: increase in proteinorachia and/or decrease in glycorachia;
- Gram positive staining from CSF and/or positive bacteriological examination;
- Microorganisms isolated from blood culture;
- Positive latex-agglutination reaction from CSF;
- Single diagnostic antibody titer (IgM) or four-fold rise in paired (IgG) levels for pathogens.

To record data regarding the use of antibiotic classes in initial/final antibiotic therapy, the abbreviations found at (https://microbiologie-clinique.com/antibiotic-family-abbreviation.html) were used:

The classes of antibiotics used in initial / final antibiotic therapy were as follows:

- aminoglycosides: Gentamicin - GEN, Amikacin - AMK;
- beta-lactams: Ampicillin – AMP; Amoxicillin + Clavulanic Acid - AMC;
- carbapenems: Meropenem - MEM;
- cephalosporins: Cefotaxime - CTX; Cefoxitin - CFX; Ceftriaxone - CRO; Ceftazidime - CZA;
- fluoroquinolones: Ciprofloxacin - CIP;
- glycopeptides: Vancomycin - VAN;
- lincosamides: Clindamycin - CLI;
- polymyxins: Colistin – COL;
- rifamycins: Rifampicin - RIF;
- sulfonamides+trimethoprim: Biseptol – SXT.

The formula for calculating the GCS score, the prognostic qSOFA score, as well as the classification of the general condition at discharge used in this study, are presented below.

The GCS (Glasgow Coma Scale) brings together the following parameters, as they are highlighted in table 1.I; available at (https://www.mdcalc.com/calc/64/glasgow-coma-scale-score-gcs):

- Motor Response (NT – 6 points);
- Verbal Answer (NT – 5 points);
- Ocular Response (NT – 4 points).

The GCS score (minimum value 3 points, maximum 15 points) has been tested in numerous studies and has been used successfully for decades in the quantification of the initial posttraumatic neurological status and later, by extension, the evolution. It underwent numerous sub classifications in degrees of coma, as well as specific circumstantial transformations (intubated, unresponsive patient). It constitutes one of the defining elements for calculating qSOFA.

Table 1.I GCS Score – Evaluation and Scoring
(https://www.mdcalc.com/calc/64/glasgow-coma-scale-score-gcs)

No. Points	Motor Response	No. Points	Answer Response	No. Points	Ocular Response
6	Follows commands	5	Oriented	4	Spontaneous
5	Locate the pain	4	Confused	3	On command
4	Withdraw to pain	3	Nonsense words	2	To pain
3	Flexion to pain	2	Unintelligible sounds	1	No response
2	Extension to pain	1	No response	NT	Not testable
1	No response	NT	Not testable		
NT	Not testable				

The qSOFA score (0,1,2,3 - quick Sequential (Sepsis Related) Organ Failure Assessment Score) is based on clinical parameters easy to establish and obtain and opens, at the time of examination, a window to the early identification of sepsis and organ dysfunction. It classifies patients with present infection, but not admitted to IT, by alotting one point to each of the three mentioned parameters, thus resulting the high risk / possible unfavorable evolution - those with 2/3 points, low risk - those with 0/1 points, so as highlighted next (Florescu S.A., 2021, page 264; http://qsofa.org/what.php). I will try to demonstrate an overlapping with the condition at discharge, but mentioning that the values of 2- 3 points inclusively are not based on eloquent criteria for outlining the generalized infectious framework, as some authors claim (Florescu S.A., 2021, page 265).

The score includes the following parameters (Florescu S.A., 2021, page 265):

- "Alteration of mental status (GCS<15 points) - (1 point)";
- "Respiratory rate > 22 - (1 point)";
- "Systolic blood pressure < 100 mmHg - (1 point)".

qSOFA Score - Synthesis, scoring and classification (http://qsofa.org/what.php)

qSOFA 0-1 Reduced Risk	qSOFA 2-3 Increased Risk
If sepsis is still suspected, monitoring, evaluation and initiation of treatment are continued; where appropriate, serial qSOFA assessments are also performed	qSOFA scores 2–3 are associated with a -3 to 14 fold- increase in in-hospital mortality. Evidence of organ dysfunction is evaluated by laboratory tests, including serum lactate, and the complete SOFA score is calculated. For patients with a qSOFA score of 2-3, sepsis should be considered, even if it did not exist previously.

Discharge status, which we will classify into the following subcategories: cured, improved, stable, deceased or categories: cured/improved, stable/death, provides an inaccurate measure of the initial severity of the case and the effectiveness of the final antibiotic therapy. The classification used in this study is shown next:

Classification of the condition at discharge
used to describe the MPOP(+) patient group

Status at discharge
-Healed-
-Improved-
-Stable-
-Deceased-

Regarding the statistical measurements carried out in this chapter and in the following ones, through them, the significant prognostic factors were analyzed.

Descriptive component: Factor analysis (implicitly of the parameters introduced), was indited in Microsoft Excel 365 and S.P.S.S. The obtained results are displayed in the form of various types of graphs (Column chart 2D, Bar chart 2D, Pie Chart 2D, 3D).

Analytical component: It uses the concepts of null and alternative hypothesis. The null hypothesis is the assumption that there is no association between exposure and diseas, actually, meaning that the statistical parameters (mean, OR, RR) being compared would come from a random sampling of the population, with any resulting difference due solely to chance. The alternative hypothesis supports the opposite of the null hypothesis (Holmes L. Jr., 2018, p.38).

The significance level (threshold) of a statistical test: The p-value represents the probability of obtaining the observable result, as well as the results located at the extremes, randomly, given that the null hypothesis would be true; a value lower than the threshold, suggesting that the null hypothesis will not prevail over the alternative one (Holmes L. Jr., 2018, pp. 38-39); therefore, I used two thresholds of statistical significance, respectively *<0.05 (statistically significant), but also ** <0.001 (highly statistically significant).
For the analysis of the association between qualitative variables, we used the Chi-square test and calculated, in the situations where statistically relevant differences were identified, the Odds Ratio (OR) and the relative risk (RR).

Finally, for the statistical and medical accuracy of the information presented, I have completed with the following clarification: the study group was made up of 32 MPOP(+) patients. Since three of them were children, and the medical information regarding the usefulness of the GCS score and by extension qSOFA is not unanimously accepted, the attitude to adopt would have meant excluding them. However, since they benefited from an interdisciplinary neurological consultation which established -in the case of some- a GCS value close to the normal one, we will also allot a qSOFA score of 1 point in their case and thus, they will be included in the present studies and the related statistical analyzes.

SUMMARY OF THE CHAPTERS

In the third chapter of the research, I detailed the distribution of the study group, in relation to a series of parameters (some intuitive, others from reference materials, but with an unverified applicability to local realities, others observational), insisting on those that were statistically proven to represent risk factors in the development of postoperative meningitis.

Reviewing them, can subdivide them into modifiable or unmodifiable. The first category is represented by: the presence of remote concurrent infections , prolonged hospitalization, especially in intensive care units, long laborious surgical interventions (more than three hours), some invasive therapeutic procedures (intubation and mechanical ventilation) and certain specific complications in postoperative management (CSF fistulas).

The unmodifiable unfavorable prognostic factors, represented by old age, the value of the GCS score at the time of the onset of the septic phenomenon < 12 points, the personal pathological history involving irreversible alterations of some organs with concomitant functional impairment, in the case of the liver or lungs, the clinical diagnosis for which the intervention is performed , especially the oncological one, together with the previous ones both in the case of the singular presence, and even more collective, issue a warning call alarm, regarding the management and evolution of such a patient.

Table 1.II shows the significant prognostic factors that could be important in the evolution of neurosurgical patients towards an infectious status. As can be seen from the

statistical analysis of the two groups, the unfavorable prognostic factors for the evolution towards postoperative meningitis were the following:

- Hospital stay parameters: average lenght of hospital stay, average lenght of postoperative hospital stay;
- Personal history: pulmonary impairment, hepatic impairment;
- GCS score < 12 points;
- Lenght of surgical procedures: procedures above 3 hours;
- The clinical diagnosis of the intervention: oncological, cerebral abscess, epidural abscess;
- Presence of other simultaneous remote infections;
- The presence of some associated invasive procedures: intubation and mechanical ventilation;
- Some postoperative management elements: Leaks (fistulas) of CSF, ICU admission.

Table 1.II Descriptive and analytical statistics regarding the prognostic factors in postoperative meningitis

	GROUPS OF PATIENTS			p-Value[x]	OR / RR [a]	(95% CI OR / RR[a])
	MPOP(+)	MPOP(-)	TOTAL			
	N (%) / m ± SD	N (%) / m ± SD	N (%) / m ± SD			
HOSPITAL STAY PARAMETERS						
Avg. Lenght of Hospital stay	20.38 ± 6.955	15.58 ± 9,285	15.85 ± 9.246	**0.000****		
Avg. Lenght of postop. Hospital stay	15.22 ± 7.038	11.48 ± 8,581	11.69 ± 8.563	**0.000****		
PERSONAL HISTORY						
Pulmonary impairment	4 (12.5)	35 (6.0)	39 (6.3)	**0.001****	**4.309**	**1.641 ÷ 11.312**
Hepatic impairment	3 (9.4)	0 (0.0)	3 (0.5)	**0.000****	**24.520 [a]**	**16.703 ÷ 35.996 [a]**
GCS SCORE						
GCS score	11.40 ± 3.150	12.80 ± 2.820	12.73 ± 2.847	**0.000****		
GCS score < 12 points	16 (50.0)	109 (18.5)	125 (20.1)	**0.000****	**3.683**	**1.704 ÷ 7.961**
LENGTH OF SURGICAL PROCEDURES						
<180 minutes	0 (0.0)	35 (6.0)	35 (5.7)	**0.024***		

THE CLINICAL DIAGNOSIS OF THE INTERVENTION						
Oncological	8 (25.0)	315 (53.6)	323 (52.4)	**0.010****	**.347**	**.150 ÷ .800**
Cerebral abscess	8 (25.0)	0 (0.0)	8 (1.3)	**0.000****	**30.400 [a]**	**19.756 ÷ 46.779 [a]**
Epidural abscess	2 (6.2)	0 (0.0)	2 (0.3)	**0.000****	**23.615[a]**	**16.212 ÷ 34.400[a]**
PRESENCE OF OTHER SIMULTANEOUS REMOTE INFECTIONS						
Other simultaneous remote infections	10 (35.7)	119 (20.2)	129 (20.9)	**0.049***	**2.190**	**0.985 ÷ 4.867**
PRESENCE OF SOME ASSOCIATED INVASIVE PROCEDURES						
Intubation and Mechanical Ventilation	6 (21.4)	581 (98.8)	587 (95.3)	**0.000****	**.003**	**.001 ÷ .011**
SOME POSTOPERATIVE MANAGEMENT ELEMENTS						
CSF Leaks (fistulas)	7 (21.8)	14 (2.4)	21 (3.3)	**0.000****	**8.913**	**2.958 ÷ 26.854**
ICU admission	6 (21.4)	546 (97.6)	552 (89.6)	**0.000****	**.021**	**.008 ÷ .055**
	[x] Pearson Chi-squared / Mann Whitney test					

ABV: ** - highly statistically significant, * - statistically significant.

In contrast, the necessary elements for a favorable management can be outlined: ambulatory care, with the collection of microbiological samples and possible antibiotic treatment prior to the intervention, as well as the beginning/optimization of the treatment for chronic conditions in order to stabilize them and shorten the postoperative hospital stay; the implementation of some case management elements, with a degree of invasiveness adapted to the clinical circumstances; for those surgical interventions where the introduction of fast track surgery protocols is possible; the adaptation of preoperative antibiotic prophylaxis to the most frequently identified etiological agents at the institutional level; carrying out the intraoperative planning, with the reduction of ineffective periods, which often requires surgeon's awareness of their own professional level its adaptation to the pathology they want to address, thus avoiding reinterventions.

In the fourth chapter, I analyzed the statistical correlations between the classes of agents in prophylactic / first-line antibiotic therapy and the previously stated prognostic factors, as well as with the clinical diagnoses that led to the surgeries or certain elements of postoperative management, highlighting the most frequent choices, statistically. Third-generation cephalosporins, fluoroquinolones or aminoglycosides are widely spread, but

what stood out was the association of carbapenems (Meropenem) with glycopeptides (Vancomycin) as the therapy of choice, targetting both the gram-negative germs and the gram-positive ones. A special note should be made about the pharmacology of the agents used, which, in addition to being applicable to the bacterial spectrum, must also have properties of crossing the blood-brain barrier, with the output of a satisfactory concentration at the level of the CNS.

The administration frequency of antibiotic classes from prophylactic / first-line therapy, at the level of patient groups included in the study, as well as the statistical significance for those whose use did not lead to the development of MPOP(+), can be found in table 1.III and figure 1.1:

The most frequent administrations at the level of both batches of antibiotic classes in prophylactic / empiric schemes are : cephalosporins (Ceftriaxone - CRO, Cefotaxime - CTX, Ceftazidime - CZA) (47.3%), followed by beta-lactams (Amoxicillin + Clavulanic Acid) (17.4%), aminoglycosides (Gentamicin) (15.4%) and fluoroquinolones (Ciprofloxacin) (13.7%).

Actually, cephalosporins (Ceftriaxone, Cefotaxime, Ceftazidime) are the most frequently administered agents, both at the level of the MPOP(+) group (32.1%), and at the level of the MPOP(-) group (48.1%), but without any statistically relevant differences between the two categories of patients. Statistically relevant differences between the MPOP(+) and MPOP(-) groups were found in the case of glycopeptides, 14.3% in the MPOP(+) group versus 1.2% in the MPOP(-) group and lincosamides, 3.6% in the MPOP group (+) versus 0% in the MPOP(-) group.

Table 1.III The distribution of groups of patients included in the study in relation to the frequency of administration of the antibiotic classes in the initial antibiotic therapy

Antibiotic – Agents MPOP(+) and MPOP(-) group	**MPOP(+)**		**MPOP(-)**		**MPOP(+) şi MPOP(-)**		**Chi-Squared p-Value**
	n	**%**	**n**	**%**	**N**	**%**	
Aminoglycosides	1	3.6%	91	16.0%	92	15.4%	.103
Beta-lac. + Clavulanic acid	6	21.4%	98	17.2%	104	17.4%	.449
Sulfonam. + Trimethoprim	0	0.0%	7	1.2%	7	1.1%	.721
Carbapenems	2	7.1%	7	1.2%	9	1.5%	.059
Cephalosporins (3)	9	32.1%	273	48.1%	282	47.3%	.138
Fluoroquinolones	5	17.9%	77	13.5%	82	13.7%	.369
Glycopeptides	4	14.3%	7	1.2%	11	1.8%	**.001****
Lincosamides	1	3.6%	0	0.0%	1	0.1%	**.045***
Rifamycins	0	0.0%	7	1.2%	7	1.1%	.721

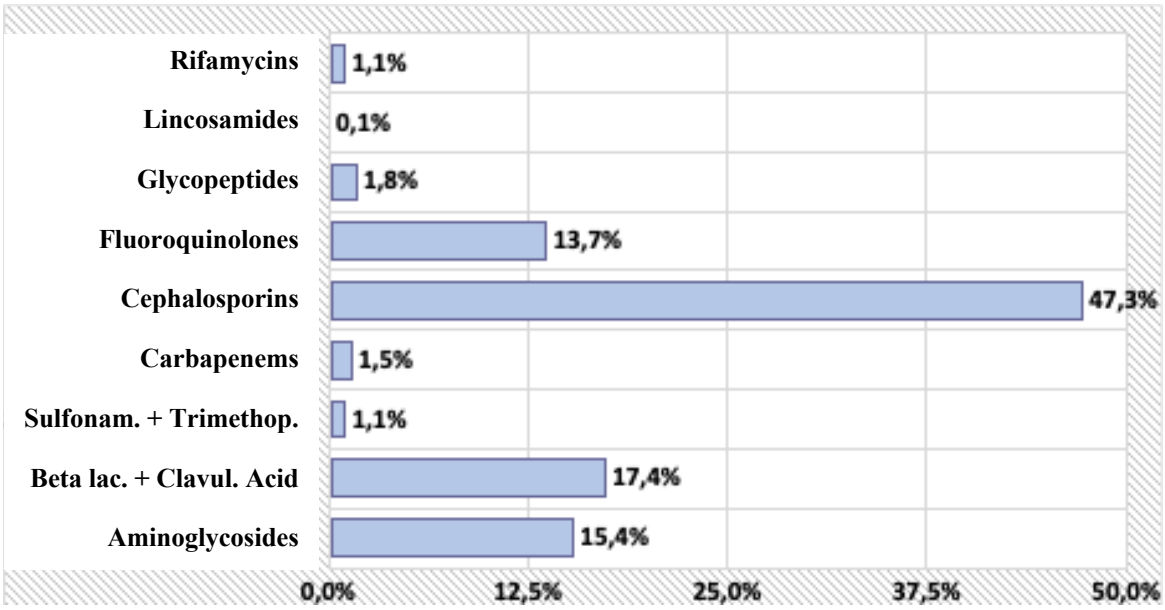

Fig. 1.1 The cumulative distribution of both groups of patients included in the study, in relation to the frequency of administration of antibiotic classes in prophylactic / empiric antibiotic therapy

The last but one chapter represents a corollary of the values of the qSOFA score and the condition at discharge, in relation to the final antibiotic therapy and the incriminated pathogens, which leads to important therapeutic conclusions, with applicability both to cases where a germ was isolated and to those without specified etiology. I have demonstrated here that the use of an easy, fast and repeatable prognostic score system, made up of easily obtainable objective clinical elements, is also applicable and desirable to the postoperative evolution of the neurosurgical patient, even more so, on those in whom we suspect the possibility of a postoperative meningitis. In addition, the correlation of its values, with some of the previously stated prognostic factors and with the final antibiotic regimens, represented their additional validation. The distribution of the group of MPOP(+) patients, in relation to the qSOFA prognostic score and the discharge status, can be found in tables 1.IV – 1.V and figures 1.2 – 1.3:

Table 1.IV Distribution of the group of MPOP(+) patients, in relation to the qSOFA prognostic score

	qSOFA SCORE	n	%
	0	8	25.0
	1	15	46.9
	2	6	18.8
	3	3	9.4
	Total (N)	**32**	**100.0**

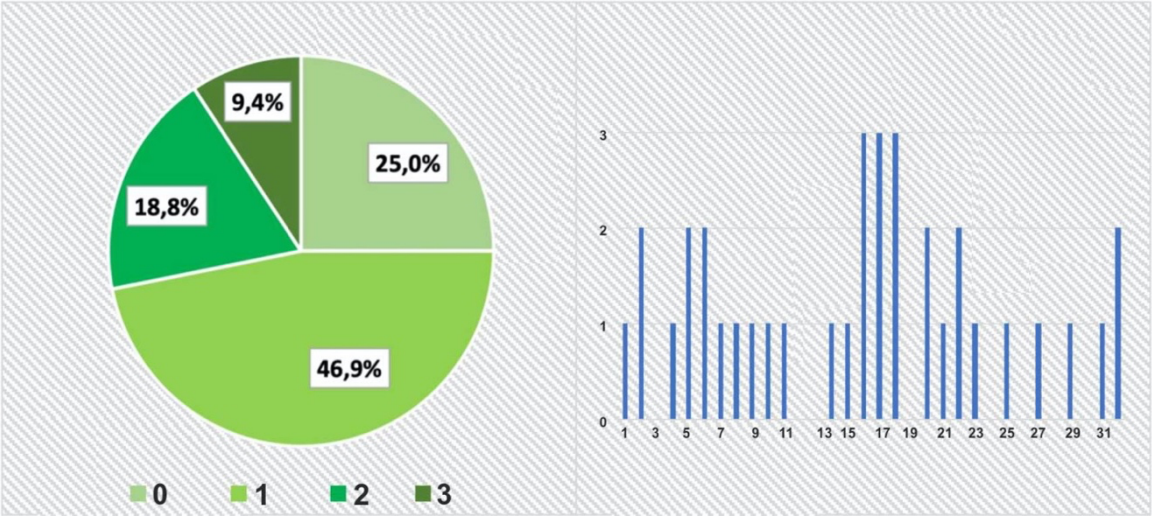

Fig. 1.2 Distribution of the group of MPOP(+) patients, in relation to the qSOFA prognostic score

Table 1.V Distribution of the group of MPOP(+) patients, in relation to the condition at discharge

	DISCHARGE STATUS	n	%
	Healed	1	3.1
	Improved	22	68.8
	Stable	5	15.6
	Deceased	4	12.5
	Total (N)	**32**	**100.0**

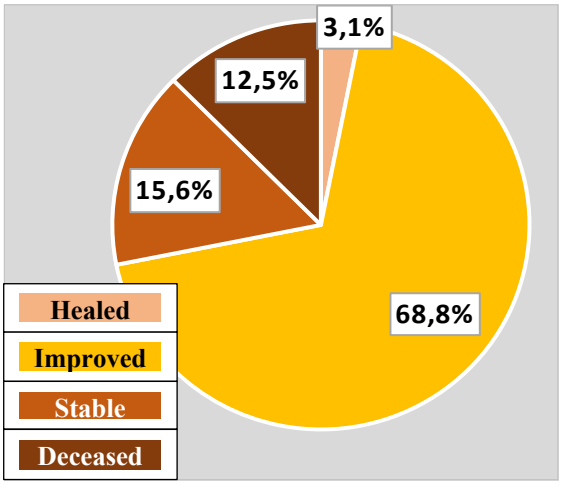

Fig. 1.3 The distribution of the group of MPOP(+) patients, in relation to the condition at discharge

From the analysis undertaken, it can be seen that the highest proportion of patients improved / cured at discharge are those with a qSOFA score of 1 point, representing 34.3% of the MPOP(+) group.

Among those who improved (22 cases), qSOFA scores of 1 point (45.5%) are predominant, followed by scores of 0 points (27.3%), 2 points (22.7%) and 3 points (4.5%). Only one case was declared cured at discharge, being evaluated with a qSOFA score of 1 point. The patients who were stable at discharge (5 cases) mainly came from patients with a qSOFA score of 1 point (80.0%), followed by a qSOFA score of 0 points (20.0%). Among the patients who were declared deceased at discharge (4 cases), 50.0% were evaluated with a qSOFA score of 3, 25.0% with a qSOFA score of 2, 25.0% with a qSOFA score of 0. A synthesis of the distribution of qSOFA scores, in relation to the status at discharge of MPOP(+) patients, is presented in table 1.VI and figure 1.4:

Table 1.VI Pearson Chi-square analysis of the group of MPOP(+) patients, regarding the correlation between qSOFA scores and discharge status

Pearson Chi-squared=2.649 p = .449, NS		STATUS AT DISCHARGE Healed / Improved		Stable / Deceased		Total	
Spearman coefficient = 0,105 (p=0,569)		**n**	**%**	**n**	**%**	**n**	**%**
qSOFA	**0**	6	26.1%	2	22.2%	8	25.0%
	1	11	47.8%	4	44.4%	15	46.9%
	2	5	21.7%	1	11.1%	6	18.8%
	3	1	4.3%	2	22.2%	3	9.4%
Total (N)		**23**	**100%**	**9**	**100%**	**32**	**100%**

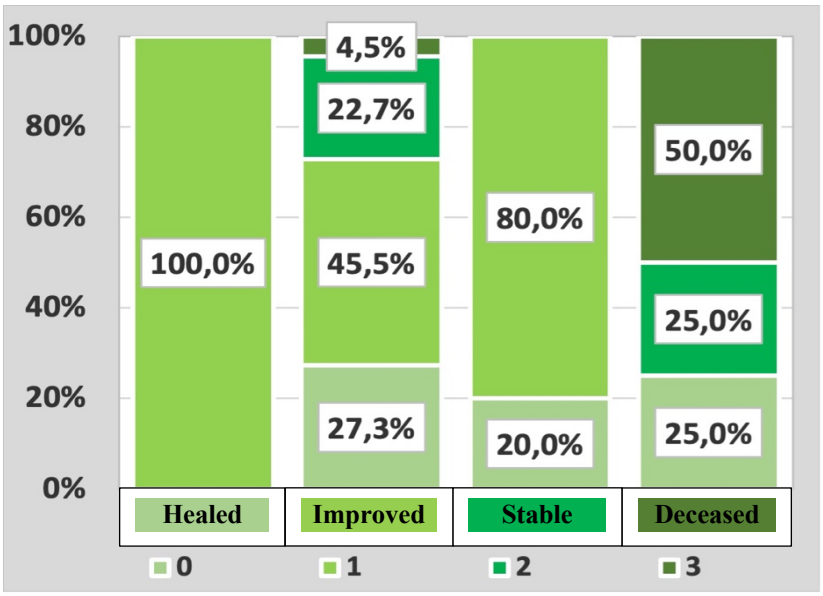

Fig. 1.4 Distribution of qSOFA scores in MPOP(+) patients in relation to discharge status

Statistical analysis regarding the correlation between the qSOFA score and the GCS score in the MPOP(+) group, is displayed in table 1.VII. Among the patients with GCS scores < 10 points, there is an equal fraction of 3 points qSOFA (50.0%) and 2 points qSOFA (50.0%); the 10 - 11 points GCS score group was divided unequally, between 1 point qSOFA (70.0%) and 2 point qSOFA (30.0%); among the patients with 12 – 15 points GCS score, there is again an equal fraction of 1 point qSOFA (50.0%) and 0 point qSOFA (50.0%).

Tabel 1.VII Pearson Chi-square analysis of the group of MPOP(+) patients, regarding the correlation between qSOFA scores and GCS Score

GCS Score	qSOFA								Pearson Chi-squared	Spearman Coefficient
	0		1		2		3			
	n	%	n	%	n	%	n	%		
< 10 (n = 6)					3	50.0	3	50.0	Chi^2 = 31,787	Rho = -,808
10-11 (n = 10)			7	70.0	3	30.0			p = ,000**	p =,000**
12-15 (n = 16)	8	50.0	8	50.0						
Total / qSOFA Score(n)	8	25.0	15	46.9	6	18.8	3	9.4		

In the MPOP(+) group, among the patients who received third-generation cephalosporins (n=9), all were discharged with an improved or stable status; 55.6% qSOFA score 1 point, 22.2% qSOFA 2 points, 22.2% qSOFA 3 points, proving their important role in therapy.

Regarding the use of antibiotics from the class of carbapenems (Meropenem) and glycopeptides (Vancomycin), it is noticeable that of the total number of patients who received Meropenem (n=19), 12 patients (63.1%) were improved / cured patients at discharge: 50.0 % qSOFA score 1, 25.0% score 0 and score 2, and 7 patients (26.9%) with stable status/death: 57.1% qSOFA score 1, 14.3% score 0 and score 2.

From the total of patients who received Vancomycin (n=23), 16 patients (50.0%) were discharged with an improved / cured status: 56.3% qSOFA score 1, 18.8% score 0 and score 2, and 7 patients (21.8%) with stable status / death: 42.9% qSOFA 1 point, 14.3% qSOFA 0 points, and 2 points.

The observed differences have clinical relevance, although they do not reach the threshold of statistical significance, a possible explanation being the relatively limited casuistry. A distribution of the group of MPOP(+) patients, in relation to the qSOFA prognostic score, the discharge status and the antibiotics administered in the final antibiotic therapy regimen, can be found in tables 1.VIII – 1.IX and figures 1.5 – 1.8:

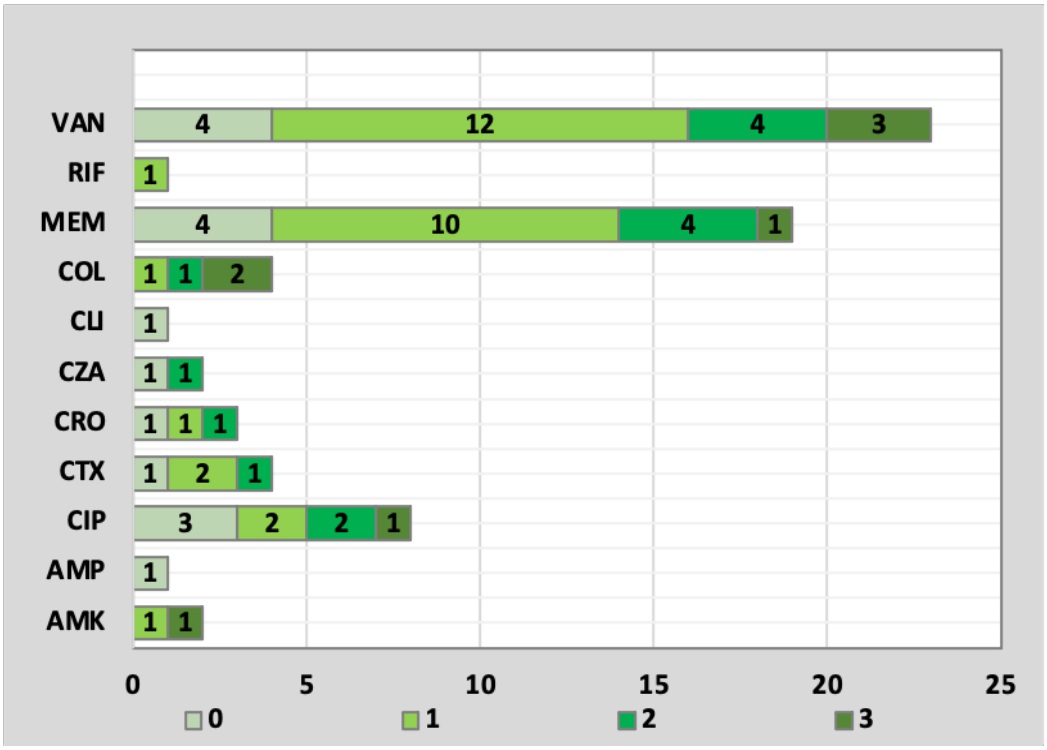

Fig. 1.5 The distribution of the group of MPOP(+) patients, in relation to the qSOFA prognostic score and the antibiotic agents administered in the final antibiotic therapy regimens

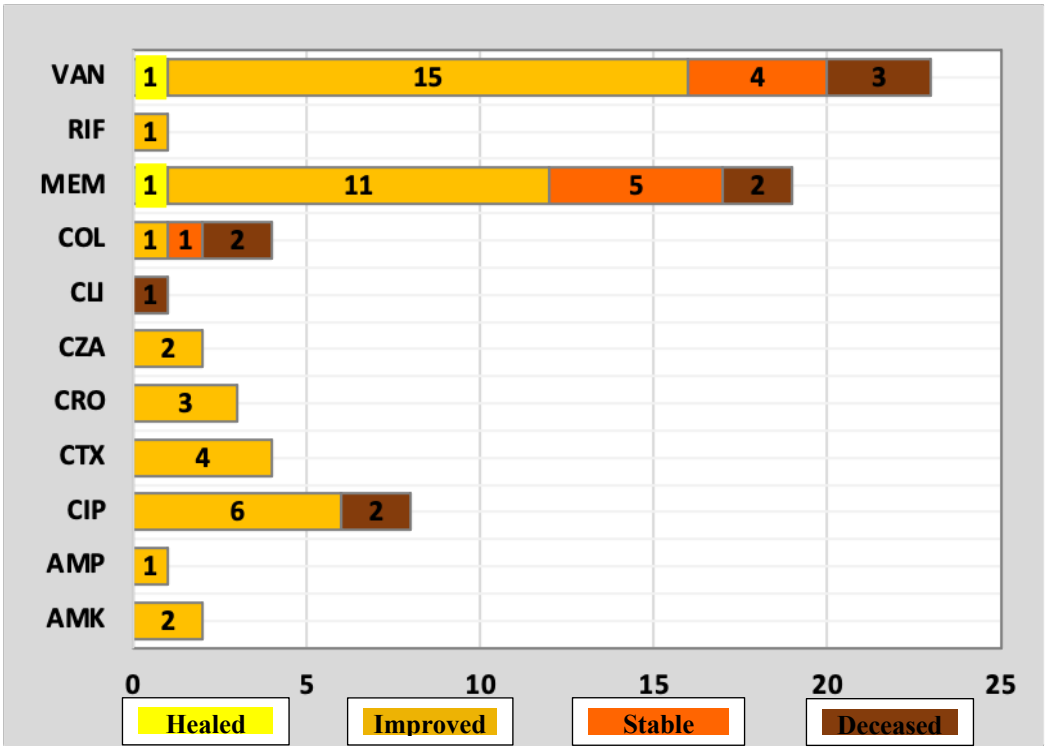

Fig. 1.6 The distribution of the group of MPOP(+) patients, in relation to the condition at discharge and the antibiotic agents administered in the final antibiotic therapy regimens.

Table 1.VIII Pearson Chi-square analysis of the group of MPOP(+) patients, regarding the correlation between qSOFA scores, discharge status and antibiotic agents administered in the final antibiotic therapy regimens

Status at discharge / Antibiotics - Agents	qSOFA 0		qSOFA 1		qSOFA 2		qSOFA 3		Pearson Chi-squared	Conting. coeffic.
	n	%	n	%	n	%	n	%		
AMK (n = 2)										
healed / improved (n = 2)	0	0.0	1	50.0	0	0.0	1	50.0	-	-
stable / deceased (n = 0)	0	0.0	0	0.0	0	0.0	0	0.0	-	-
AMP (n = 1)										
healed / improved (n = 1)	1	100	0	0.0	0	0.0	0	0.0	-	-
stable / deceased (n = 0)	0	0.0	0	0.0	0	0.0	0	0,0	-	-
CIP (n = 8)										
healed / improved (n = 6)	2	33.3	2	33.3	2	33.3	0	0.0	$Chi^2 = 4.444$	.598
stable / deceased (n = 2)	1	50.0	0	0.0	0	0.0	1	50.0	p = .217	p = .217
CLI (n = 1)										
healed / improved (n = 0)	0	0.0	0	0.0	0	0.0	0	0.0	-	-
stable / deceased (n = 1)	1	100	0	0.0	0	0.0	0	0.0	-	-
COL (n = 4)										
healed / improved (n = 1)	0	0.0	0	0.0	0	0.0	1	100	$Chi^2 = 1.333$	.500
stable / deceased (n = 3)	0	0.0	1	33.3	1	33.3	1	33.3	p = .513	p = .513
CRO (n = 3)										
healed / improved (n = 3)	1	33.3	1	33.3	1	33.3	0	0.0	-	-
stable / deceased (n = 0)	0	0.0	0	0.0	0	0.0	0	0.0	-	-
CTX (n = 4)										
healed / improved (n = 4)	1	25.0	2	50.0	1	25.0	0	0.0	-	-
stable / deceased (n = 0)	0	0.0	0	0.0	0	0.0	0	0.0	-	-
CZA (n = 2)										
healed / improved (n = 2)	1	50.0	0	0.0	1	50.0	0	0.0	-	-
stable / deceased (n = 0)	0	0.0	0	0.0	0	0.0	0	0.0	-	-
MEM (n = 19)										
healed/improved (n = 12)	3	25.0	6	50.0	3	25.0	0	0.0	$Chi^2 = 2.239$	.325
stable/deceased (n = 7)	1	14.3	4	57.1	1	14.3	1	14.3	p = .524	p = .524
RIF (n = 1)										
healed / improved (n = 1)	0	0.0	1	100	0	0.0	0	0.0	-	-
stable / deceased (n = 0)	0	0.0	0	0.0	0	0.0	0	0.0	-	-
VAN (n = 23)										
healed/improved (n = 16)	3	18.8	9	56.3	3	18.8	1	6.3	$Chi^2 = 2.139$	.292
stable / deceased (n = 7)	1	14.3	3	42.9	1	14.3	2	28.6	p = .544	p = .544

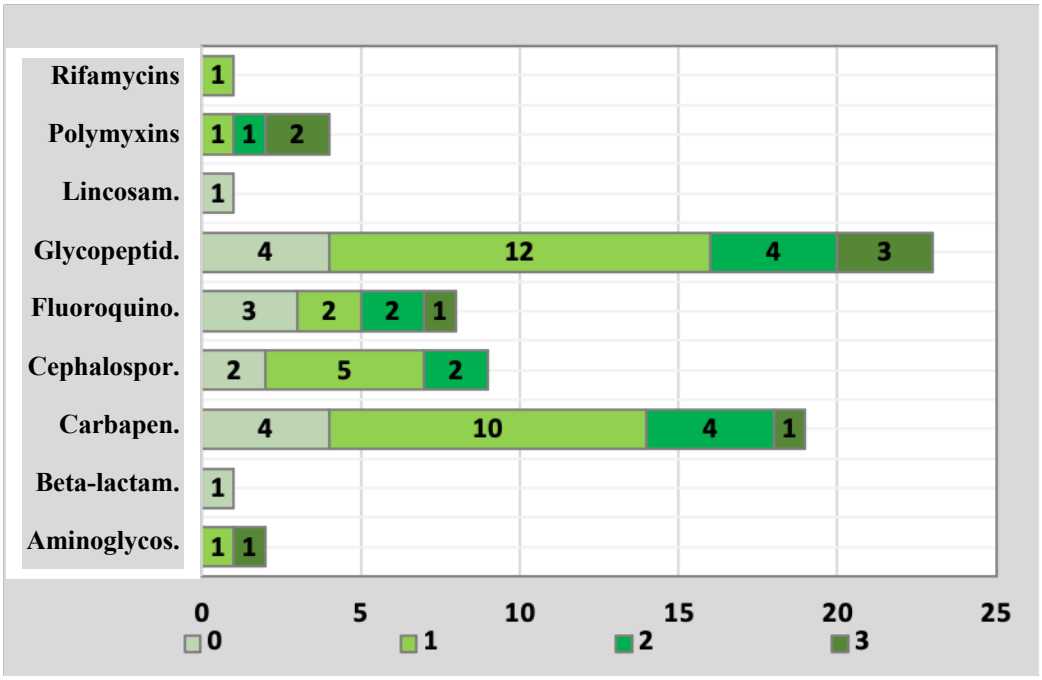

Fig. 1.7 The distribution of the group of MPOP(+) patients, in relation to the qSOFA prognostic score and the antibiotic classes administered in the final antibiotic therapy regimens

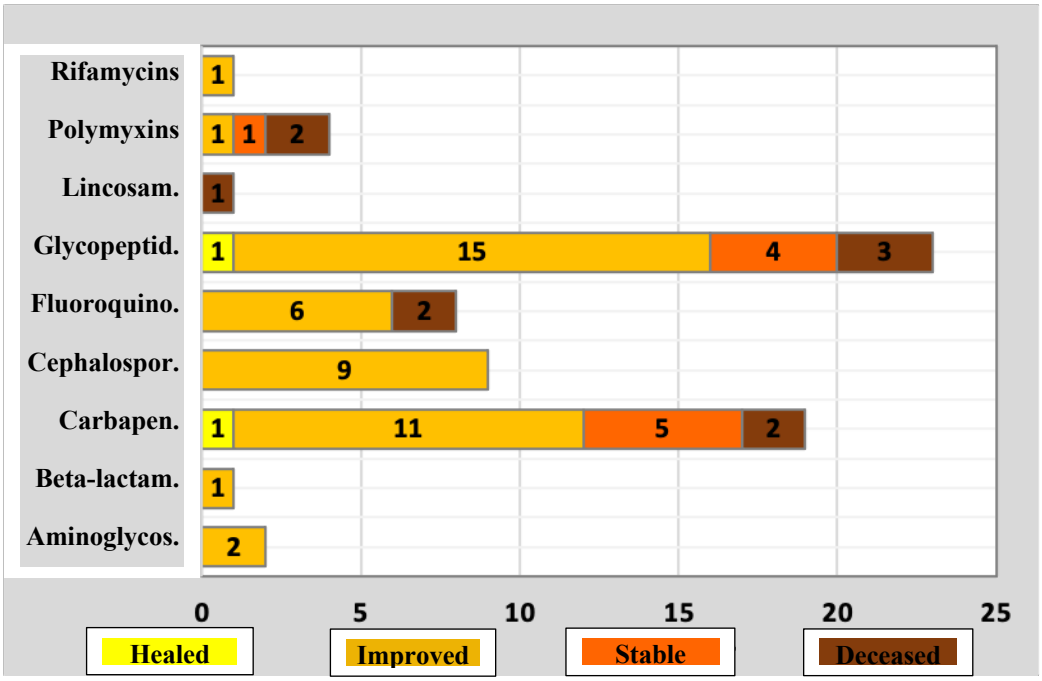

Fig. 1.8 The distribution of the group of MPOP(+) patients, in relation to the condition at discharge and the antibiotic classes administered in the final antibiotic therapy regimens.

Table 1.IX Pearson Chi-square analysis of the group of MPOP(+) patients, regarding the correlation between qSOFA scores, discharge status and antibiotic classes administered in the final antibiotic therapy regimens

Status at discharge / Antibiotics - Classes	**qSOFA**								Pearson Chi-squared	Conting. coeff.
	0		**1**		**2**		**3**			
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**		
Aminoglycosides (N = 2)										
Healed / Improved (n = 2)	0	0.0	1	50.0	0	0.0	1	50.0	-	-
Stable / Deceased (n = 0)	0	0.0	0	0.0	0	0.0	0	0.0	-	-
Beta-lactams (N = 1)										
Healed / Improved (n = 1)	1	100	0	0.0	0	0.0	0	0.0	-	-
Stable / Deceased (n = 0)	0	0.0	0	0.0	0	0.0	0	0.0	-	-
Carbapenems (N = 19)										
Healed / Improved (n = 12)	3	25.0	6	50.0	3	25.0	0	0.0	$Chi^2 = 2.239$	.325
Stable / Deceased (n = 7)	1	14.3	4	57.1	1	14.3	1	14.3	p = .524	p = .524
Cephalosporins (N = 9)										
Healed / Improved (n = 9)	2	22.2	5	55.6	2	22.2	0	0.0	-	-
Stable / Deceased (n = 0)	0	0.0	0	0.0	0	0.0	0	0.0	-	-
Fluoroquinolones (N = 8)										
Healed / Improved (n = 6)	2	33.3	2	33.3	2	33.3	0	0.0	$Chi^2 = 4.444$	.598
Stable / Deceased (n = 2)	1	50.0	0	0.0	0	0.0	1	50.0	p = .217	p = .217
Glycopeptides (N = 23)										
Healed / Improved (n = 16)	3	18.8	9	56.3	3	18.8	1	6.3	$Chi^2 = 2.139$	.292
Stable / Deceased (n = 7)	1	14.3	3	42.9	1	14.3	2	28.6	p = .544	p = .544
Lincosamides (N = 1)										
Healed / Improved (n = 0)	0	0.0	0	0.0	0	0.0	0	0.0	-	-
Stable / Deceased (n = 1)	1	100	0	0.0	0	0.0	0	0.0	-	-
Polymyxins (N = 4)										
Healed / Improved (n = 1)	0	0.0	0	0.0	0	0.0	1	100	$Chi^2 = 1.333$	.500
Stable / Deceased (n = 3)	0	0.0	1	33.3	1	33.3	1	33.3	p = .513	p = .513
Rifamycins (N = 1)										
Healed / Improved (n = 1)	0	0.0	1	100	0	0.0	0	0.0	-	-
Stable / Deceased (n = 0)	0	0.0	0	0.0	0	0.0	0	0.0	-	-

CONCLUSIONS AND PERSONAL CONTRIBUTIONS

CONCLUSIONS

1. This study represents a current and objective evaluation of the presence of postoperative meningitis, after neurosurgical interventions, in the geographical area studied; the incidence value of only 5.1%, attests to the rarity of this septic complication, but which has a high potential for increased morbidity and sequelae;
2. The classic symptomatology, often difficult to confirm or even absent, superimposed on a varied postoperative neurological status, in a patient whose causal pathology very often includes meningeal irritation per se, further delays the diagnosis;

3. The study group, although limited, presented, in the case of the etiological agents identified, both a superimposed spectrum and a preserved sensitivity to the antimicrobial agents administered most frequently in studies of this pathology in the reference materials;
4. Descriptive and analytical statistics highlighted the risk factors for the occurrence of post-neurosurgical meningitis; they can be divided into two categories, depending on the medical capacity to intervene on them: unmodifiable (old age, GCS score < 12 points, personal pathological antecedents involving irreversible alterations of some organs with concurrent functional impairment, in the case of the liver or the lungs, the clinical diagnosis for which the intervention is performed, especially the oncological one) or modifiable;
5. Unfavorable prognostic factors that can be modified by the medical attitude can be: the presence of remote concurrent infections at the time of the onset of the study pathology, extended hospitalization, especially in risk environments such as intensive care units, surgical interventions with a duration of for more than 3 hours, the use of only strictly necessary invasive therapeutic and nursing procedures, with the avoidance or shortening the time of using them whenever this is possible (in question, intubation and mechanical ventilation), the presence of certain complications in the postoperative management (CSF fistulas), are also the starting points for outlining some decisional changes;
6. In the situation where certain clinical signs occur and, of course, there is also the related surgical context, broad-spectrum antibiotic therapy must be initiated promptly, before the bacteriological tests results are obtained, which in a large percentage of cases is and will remain negative, with the possibility of subsequent variants of evolutionary changes or according to the antibiogram, if available;
7. The statistics performed shows the overlap of chemotherapeutic classes used both in the prophylactic regimens and in the first-line treatment; many times, the agents administered preoperatively are continued after the onset of the infectious phenomenon;
8. The data of this research also prove that the use of surgical antibiotic prophylaxis, which is a method intensively used clinically, both acclaimed and controversial, has a beneficial role in the prevention of postoperative meningitis;

9. The distribution of antibacterial agents within the study group highlighted the possible combinations of antibiotics that can be administered, both to the patient with an identified etiological agent, but also in situations where the bacteriological examination is negative;
10. The continuous evolution of bacterial microorganisms, as well as the specificity of each medical institution for certain pathogens, determines an individual analysis of each case; many times, however, since transfer admissions are involved, it is useful to collaborate with specialists from the hospital of origin or with the epidemiologist of the hospital where the treatment is carried out, for effective coverage of both Gram spectra and multiresistant strains;
11. The qSOFA prognostic score has been proven - by the ease of obtaining the necessary parameters and the speed of its calculation, easy to apply and of practical value, existing in variable percentages of superposition with the condition at discharge;
12. This partial superposition leads to data which certify the important role of the successful early isolation of etiological agents, the management of personal pathological antecedents, the avoidance of prolonged hospitalizations;
13. Moreover, its correlations with the prognostic factors identified in the first chapter of the personal study, as well as those with the antimicrobial agents (classes) in the final treatment regimens presented in the last but one chapter, validate their role in determining the evolution of patients and allow the outline of some combinations of antibiotics used successfully at different levels of severity;
14. This last but one chapter represents a corollary of strategic directions for a medical attitude which can ensure the early highlighting of the circumstances of an unfavorable evolution, as well as the optimal therapy in this instance.

PERSONAL CONTRIBUTIONS

The present work has been built around two desiderata ones, resulting from the three hypotheses described initially, which were intertwined to form an overall picture of the studied pathology. The first, has its origin in the presented theoretical and informational substrata, where I aimed to obtain a synthesis of the studies available in the medical literature, with an update of the information. On this basis, I conceived the first chapter, in which I researched a series of parameters (some mentioned by studies already carried out, others intuitive or observational), in order to reveal- through statistical

analysis- the ones that become significant unfavorable prognostic factors, in the occurrence of post-neurosurgical meningitis. The second desiderata, materialized in the other two chapters, consisted in providing some practical benefits, statistically validated, for the identification of both an initial and final antibiotic therapy tegimen, with the aim of obtaining a favorable prognosis, as well as the detection of the superposibility of a system of prognostic score, applied to the patients in question, with another hospitalization cardinal parameter.

The paucity of neurosurgical departments, equipment and specialists in the geographical area studied (Moldova), found even in large cities, translates the existence of a reduced interventional spectrum, which often only targets emergency traumatic pathology, not performing routine, laborious chronic surgery on the cephalic extremity.
This fact - often found in other regions - causes the overcrowding of university centers (in question, Iaşi), with the performance of a large number of interventions, in a reduced period of time, per se correlated with multiple shortcomings. Thus, the following should be noted: accelerated wear out of electronic equipment and surgical tools, overworked and exhausted staff, shortened/omitted epidemiologic times/steps when sterilizing the surgery room, surgical kits, medical wards, hallways, difficult post-operative monitoring and nursing with clinical elements that can be overlooked, reports/records of considerable thickness, but partially completed or inaccurately completed. Infection control sheets associated with medical care are no exception, often being drawn up long after the death or discharge of the patient.

The technical-economic shortcomings recorded in the study were represented by: the absence of a unitary IT infrastructure in the two hospitals where the research was carried out, the impossibility of the existing systems to filter the search results, especially in the light of secondary diagnoses or certain laboratory tests, the lack of a complete electronic archiving system of individual files, as well as the absence of clear interhospital conduct, regarding the initiation and the location of treatment of this patient, often transferred from and to the center where the surgical intervention was performed and the infectious diseases specialised center. The period of the study, unfortunately, also overlapped with the COVID-19 pandemic, which determined the drastic restriction of the surgical pathology addressed (especially chronic) and the difficult physical access to the observation sheets to fill in the missing fields in the electronic records. In addition, the pre-pandemic case file was archived and moved to specialized centers, from where the

extraction proved to be cumbersome, as there was no possibility of obtaining possession of individual files from different time intervals.

The originality of the work comes from two different areas. A first area brings together the practical clinical elements, in which we will find: the absence of a specific institutional protocol for this complication, with particular emphasis on prevention, diagnosis and treatment; the absence of an in-depth investigation of the risk factors that can be corrected in order to prevent, even in the specialized hospital; the high variability found in the initial antibiotic regimens administered; difficult diagnosis, which often delays the treatment and the possible need to use a prognostic scoring system to improve assessment. A second area, which brings together the microbiological, epidemiological and, further, economic-social implications in which we will find: respecting the autochthonous possibilities of isolating the predominant etiological agents and highlighting their sensitivity; the lack of aother material, even more so of frequent updates, due to the small number of patients that can be enrolled (the study group could only consist of 32 patients, in a three-year period, from university emergency hospitals, with complex and numerous cases); the low incidence also recorded in our study of 5.1%, but with important possible sequelae and and consequences both on the patient's quality of life and on their social reintegration.

I believe that the objectives proposed from the beginning have been achieved within the three chapters. Specifically: I defined those prognostic factors that impacted the development of the study pathology, emphasizing those that can be modified by the therapeutic attitude, I synthesized and outlined the most frequent regimens of the initial antibiotic therapy by referring to the particularities of the control group, we analyzed the circumstance in which a prognostic score supports a correlation with the development of septic complications and the condition at discharge from the perspective of the final antibiotic therapy and the etiological agents involved, all of this, through analytical or descriptive statistical confirmation, obtaining a superposition of the results with those of other authors.

Aware -from daily practice- both of the seriousness of the occurrence of a postoperative septic complication, all the more threatening, if the target organs are part of the central nervous system, and of the continuous evolution of the spectrum of bacterial multiresistance, which restricts the therapeutic arsenal, especially in the risk wards, I

considered the elements derived from the studies carried out in the present work to be of real use to the attending physicians.

As a result of the present work and in compliance with the presented results, a series of current benefits can be noted, each of which can be used as a starting point for further studies: economic, operative, antibiotherapeutic (prophylaxis, initial regimens, final regimens (revised or not)), surgical, intensive care - postoperative care, interclinic collaboration.

Of course, this topic is far from being fully elucidated for multiple reasons, among which I will mention: the permanent variability of the etiological spectrum, the occurence of the latest generation of antibacterial agents, the focus and constant development of new structural and technological means of antisepsis, all forcing us to regular informational updates.

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