TIMOČKI MEDICINSKI GLASNIK

TIMOK MEDICAL GAZETTE

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The Bulletin of the Zajecar branch of the Serbian Medical Association

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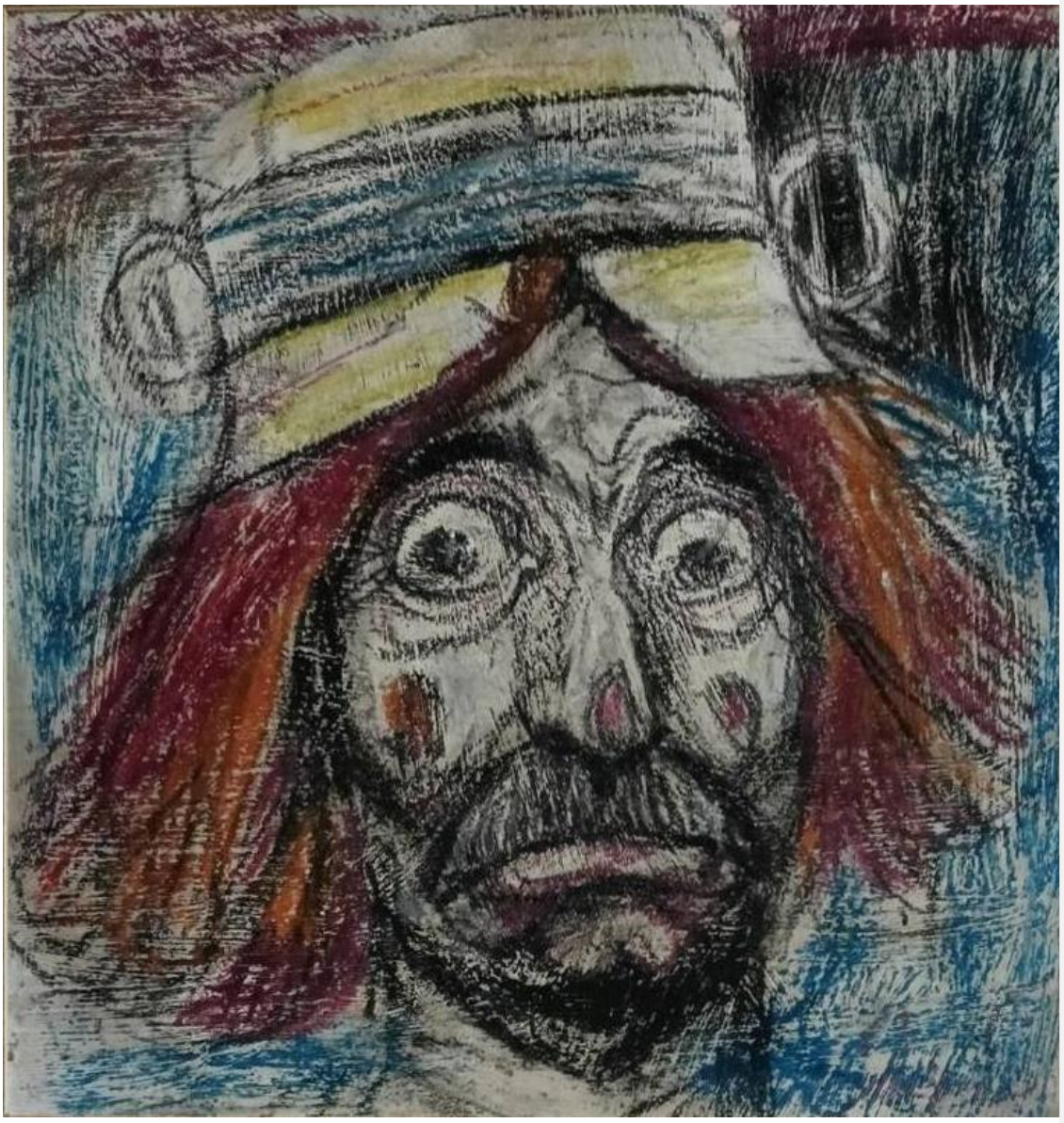

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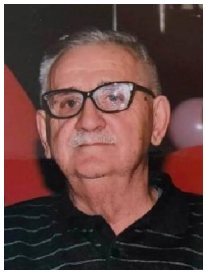
TIMOK MEDICAL GAZETTE

IN MEMORIAM



Dr. Radomir Milosavljević, Doctor of Dentistry, Orthodontics Specialist
(1949-2025)

Our colleague Radomir Milosavljević has left us forever, having left an indelible mark during a period of development and operation of the Health Center in Zaječar. He was known as an exceptionally honest, hardworking, and highly responsible person. As a young dentist, in 1975, he joined our Medical Center. The management at the time soon recognized his high moral qualities and included him in the system of work organization within the Health Center.

Thanks to his ability and organization, all villages in the municipality received a nurse daily and a doctor several days a week. Additionally, under Occupational Medicine, all major companies (KTK Timočanka, Timogradnja, Putevi, Hladnjača) and factories (Kristal, Porcelain, Cables), as well as the mines (Avramica and Lubnica), had a doctor and nurse available every day.

The dental service was one of the most developed in Serbia, at the level of the Niš and Kragujevac faculties, and in some aspects, even ahead of them. All elementary schools, the high school center, and the city's kindergarten had dental offices. All of this functioned thanks to Dr. Rade's dedication.

Dr. Rade completed his specialization in 1973 in the field of pediatric and preventive dentistry—orthodontics. He was among the first in Serbia to master the fixed orthodontics method for correcting jaw and tooth anomalies. Thanks to his expertise, babies born with severe anomalies—such as cleft palate (palatoschisis)—received an orthodontic obturator appliance within weeks after birth to allow breastfeeding. This severe jaw anomaly was only treated at the Dental Faculty Clinic and in our Medical Center. Moreover, he served as a consultant in several Serbian cities, educating colleagues on the new fixed orthodontics method.

After 20 years of working at the Medical Center, in 1993, he founded his private dental practice, "Ortodent," where he remained dedicated to his patients until his last day. He trained his staff, including his daughter Dr. Nataša, who continues to run the practice successfully, much to the satisfaction of numerous patients.

His son, Aleksandar, Ph.D., is engaged in scientific research and currently works at a prestigious international institute in Paris, where he lives with his family.

Dr. Rade was one of the few who returned a staff apartment to Zaječar and moved back to his village, Vražogrnac. On the hill near the village—Preovac—he built his oasis of peace among orchards and vineyards, where his grandchildren spent their early childhood carefree in a natural environment.

He was very well-liked in society. In his village, he enjoyed spending time with his fellow hunters, and in the city, with his colleagues. For the last twenty years, every morning before work, he would have the first morning coffee, then attend to his patients at the practice, and return to Preovac. He was never ashamed of working in his orchard and vineyard. He was an excellent vintner and made high-quality wines, which we often enjoyed during the "wine tastings" Dr. Rade organized for his colleagues.

His family can be proud to have had Rade as a husband, father, and grandfather. He was an outstanding father to successful children in their professions and a grandfather to now grown grandchildren, excellent students, and high schoolers.

Most importantly, together with his wife Lidija, through upbringing and hard work, he raised wonderful children and guided them on the right path, instilling love, honesty, and kindness in them.

Numerous patients will remember him for the care and expertise he provided for nearly half a century.

We, his colleagues, will remember him for his friendliness, kindness, and willingness to help everyone.

To say he was a good person is an understatement. He was much more than that!

Zaječar,
February 2025.

Dr Branislav Predić

ROTATIONAL THROMBOELASTOMETRY GUIDED BLOOD COMPONENT ADMINISTRATION

Radovan Dinić (1), Almira Šabani (1), Jasmina Grujić (2)

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Abstract: Introduction: Rotational thromboelastometry is a diagnostic tool extensively utilized for patients at high risk of bleeding, particularly those experiencing trauma or undergoing significant surgical procedures. This test is notable for providing rapid results, facilitating timely decisions regarding the application of individualized transfusion therapies, thereby optimizing the rational use of blood components. **Aim:**The objective of this study is to assess the utilization of blood components in the transfusion treatment of patients at the Emergency Center of the University Clinical Center of Serbia, based on the outcomes of rotational thromboelastometry. The analysis aims to evaluate the frequency of these interventions in the studied population and to highlight the advantages of this treatment modality.
Material and methods: This retrospective study analyzed trauma patients who underwent rotational thromboelastometry at the Hospital Blood Bank, Department of Pre-transfusion Testing, Emergency Center of the University Clinical Center of Serbia, from January 1st 2023, to December 31st 2023. Data regarding the results of the thromboelastometry tests and subsequent blood component therapies were extracted from the Service's protocols. **Results**: During the study period, 776 patients were evaluated by means ofrotational thromboelastometry, of which 358 (46.13%) required blood component therapy. Cryoprecipitate was administered to 48 (13.40%) patients, platelet concentrate to 69 (19.27%), and a combination of cryoprecipitate and platelets to 61 (17.03%) patients. Additional therapeutic approaches included the administration of platelets, desmopressin, and tranexamic acid, while fresh frozen plasma was utilized the least, in only 17 (4.74%) patients. **Conclusion:**The analysis of blood components used for therapeutic purposes in relation to the rotational thromboelastometry demonstrated a wide range of therapeutic modalities in the treatmentof patients. This testing method facilitates individualized therapy with blood components, subsequently diminishing the needfor transfusions, enhancingallows for better diagnostic precision, and reduces costs associated with long-term managementof patients.
Key words: rotational thromboelastometry, therapy, trauma, transfusion, bleeding

INTRODUCTION

Rotational thromboelastometry (ROTEM) is a test whichis an integral part of "Point-of-Care" testing. It is characterized by being performed within a short time frame after the patient's sample is taken, allowing timely decisions regarding the transfusion management of the patient. The results are obtained quickly, which enables a rapid modification of therapy if needed [1]. ROTEM testing is being increasingly integrated into the routine diagnostic algorithm and management of bleeding in patients at high risk of bleeding, such as trauma patients. At the Emergency Center of the University Clinical Center of Serbia, the majority of patients are those admitted urgently as a result of trauma. A rapid clinical assessment of the injured patient's condition allows the prediction of trauma-induced coagulopathy (TIC) and the need to activate the massive transfusion protocol [2]. For these purposes, multiple ROTEM tests can be used to distinguish between mechanical and hemostatic bleeding, identify disorders in various stages of the hemostatic process, thereby enabling targeted and rational use of blood and blood components. ROTEM is a functional test that graphically displays the formation and breakdown of a clot, allowing monitoring of the progression or resolution of coagulopathy following a trauma [3].

ROTEM screening tests

The basic screening tests are the EXTEM and INTEM tests. These screening tests provide

general information about the status of the hemostasis system. The EXTEM test is sensitive to the deficiency of coagulation factors in the extrinsic pathway, while the INTEM test is sensitive to the deficiency of coagulation factors in the intrinsic pathway, as well as to the anticoagulant effects of heparin and thrombin inhibitors. Both tests are sensitive to platelet participation in clot firmness, fibrinogen levels, fibrin polymerization, factor XIII deficiency, and hyperfibrinolysis [4,5].

Additional ROTEM tests

The analysis of the hemostasis system is expanded by performing additional tests: FIBTEM, APTEM and HEPTEM.

The FIBTEM test is an EXTEM test for the fibrin component of the clot. FIBTEM eliminates the contribution of platelets in clot formation and allows detection of fibrinogen deficiency or fibrin polymerization disorders.

The APTEM test is based on the EXTEM test and allows detection of fulminant hyperfibrinolysis. This test helps identify the need for administering antifibrinolytic therapy. It enables the assessment of whether antifibrinolytic therapy alone normalizes coagulation or if additional measures are required (e.g., administration of fibrinogen or platelets).

The HEPTEM test is an INTEM test that allows identification of hemostasis deficiencies even in the presence of heparin and represents an INTEM test without interference from heparin or heparin anticoagulants [5,6].

The parameters of ROTEM analysis

The primary result is a reaction curve in the form of a thromboelastogram, which describes the dynamics of blood clot formation, its size, firmness, and elasticity throughout all the phases of the coagulation process. In routine clinical practice, the following thromboelastogram parameters are analyzed [6].

1. Clotting Time (CT)

CT reflects the time from the activation of coagulation to the initial formation of the blood clot, i.e., until the clot reaches a firmness of 2 mm. A prolonged CT is theresult of coagulation factor deficiency, hyperfibrinolysis, hypofibrinogenemia, and the presence of heparin. A shortened CT is a result of hypercoagulability.

2. Clot Formation Time (CFT)

CFT reflects the time required to achieve firmness of a 20 mmclot. CFT reflectsthe initial polymerization of fibrin, specifically the interaction between fibrinogen and platelets.

3. α- Angle

The alpha angle represents the angle between the horizontal baseline and the tangent that touches the coagulation curve at the point where the firmness of the blood clot of2 mm is achieved. It reflects the quantitative and qualitative relation between fibrinogen and platelets.

4. Maximum Clot Firmness (MCF)

MCF represents the maximum amplitude achieved during testing and indicates the stability of the fibrin clot. In the EXTEM and INTEM tests, MCF reflects the levels of fibrinogen and platelets, while in the FIBTEM test it indicates the concentration and functionality of fibrinogen.

5. Maximum Lysis (ML)

ML represents the maximum fibrinolytic activity observed during the analysis and indicates the percentage of blood clot lysis.

AIM

The aim of this study is to assess the utilization of blood components in the transfusion treatment of trauma patients at the Emergency Center of the University Clinical Center of Serbia, based on the outcomes of rotational thromboelastometry. The analysis aims to evaluate the frequency of these interventions in the studied population and to highlight the advantages of this type of treatment for patients.

MATERIALS AND METHODS

This retrospective study analyzed trauma patients who underwent ROTEM testing in the Hospital Blood Bank, Department of Pre-Transfusion Testing, at the Emergency Center of the University Clinical Center of Serbia, from January 1st 2023, to December 31st 2023. Based on the obtained results, therapy was administered to each patient. Testing on the ROTEM analyzer was conducted using a tube containing 3.2% sodium citrate as an anticoagulant (Vacutainer Brand, Belliver Industrial Estate, Plymouth, UK, 4.5 ml, 9 NC 0.129 M). A volume of 300 μL of resuspended blood was taken from the tube for each of the two tests (EXTEM and FIBTEM) using a pipette with predefined aspiration and expiration time intervals, it was placed into the "cup & pin" chamber where specific activators for each test were added. Upon activation of each test, the

results were monitored on the ROTEM analyzer screen (Figure 1), and once the values were obtained, the result was printed, described, and distributed along with the proposed therapy to the departments that had requested the procedure.

Figure 1. Illustration of the ROTEM graphical record showing all phases of hemostasis. Sourced from: 10.1515/acm-2015-0006.

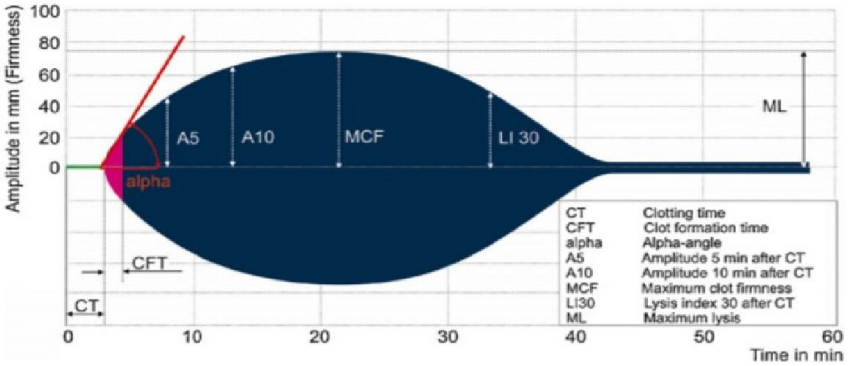


Table 1 presents the ROTEM reference values,on the basis of which the therapy was administered to patients.

Table 1. ROTEM parameters, normal values

	CT(s)	CFT(s)	Alpha(°)	A10(mm)	A20(mm)	MCF(mm)	ML(%)
EXTEM	38-79	34-159	63-83	43-65	50-71	50-72	0-15
INTEM	100-240	30-110	70-83	44-66	50-71	50-72	0-15
FIBTEM	38-62	/	/	7-23	8-24	9-25	/

RESULTS

During the observation period, ROTEM testing was performed on 776 patients. Based on the obtained results, 358 of them (46.13%) required therapy with blood components, while 418 (53.87%) did not need such therapy (Table 2).

Table 2. Need for component therapy based on ROTEM parameter values

	N	%
Patients who received therapy with blood components	358	46.13%
Patients who did not receive therapy with blood components	418	53.87%
Total	776	100%

The occurrence of clinical bleeding in patients by gender is shown in Table 3. There is a statistically significant difference in the presence of clinical bleeding related to gender(X^2 = 7.989, p=0.005). Among female patients, 53.88% exhibit clinical bleeding, while 43.83% of male patients show signs of bleeding.

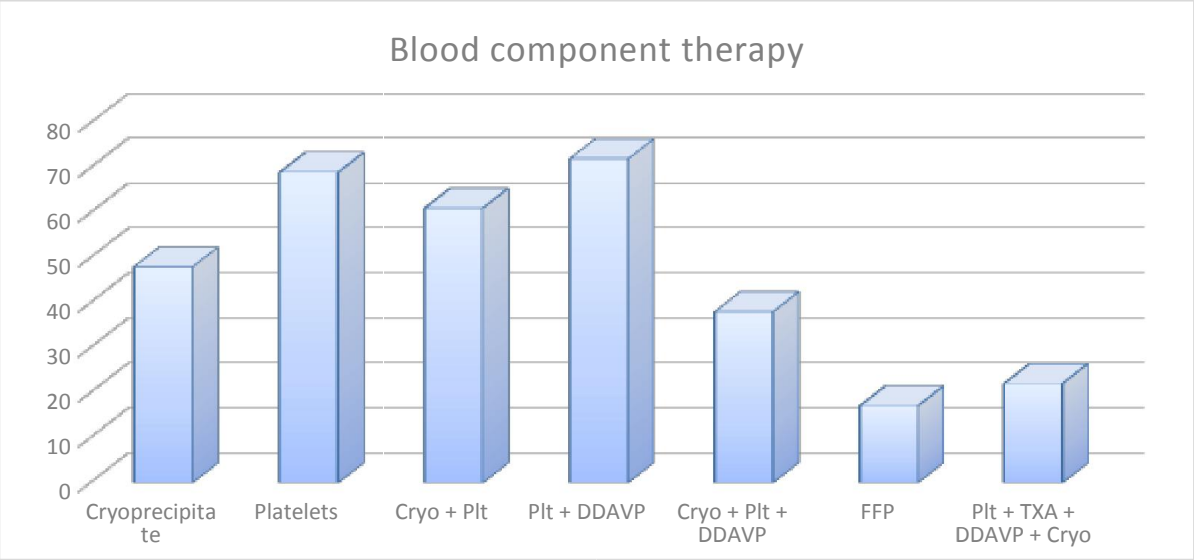
Table 3. Presence of signs of clinical bleedingby gender			
	Signs of clinical bleeding		
Gender	Yes %	No %	Total %
M	233 42.83 %	311 57.17%	544 100%
F	125 53.88%	107 46.12%	232 100%
Total	358 46.13%	418 53.87%	776 100%

The occurrence of clinical bleeding in patients by age is shown in Table 4. There is a statistically significant difference in the presence of signsofbleeding based on the results of the X^2 test ($X^2 = 104.902$, $p<0.001$). Bleeding was most prevalent in the age group of 75 to 84 (85.71%) and least prevalent in the age group of 35 to 44 (19.39%).

Table 4. Presence of signs of clinical bleeding by age			
	Signs of clinical bleeding		
Age (years)	Yes %	No %	Total %
23-34	25 31.65%	54 68.35%	79 100%
35-44	38 19.39%	158 80.61%	196 100%
45-54	101 52.33%	92 47.67%	193 100%
55-64	139 63.18%	81 36.82%	220 100%
65-74	43 58.11%	31 41.89%	74 100%
75-84	12 85.71%	2 14.29%	14 100%
Total	358 46.13%	418 53.87%	776 100%

The distribution of blood component usage among patients is shown in **Figure 2.** Observing the distribution of blood components, we can see that cryoprecipitate was administered to 48 patients (13.40%), platelets to 69 patients (19.27%), and cryoprecipitate and platelets simultaneously to 61 patients (17.03%). The administration of platelets and desmopressin (DDAVP) was necessary for 72 patients (20.11%). Fresh frozen plasma (FFP) was used in only 17 patients (4.74%). A combination of platelets, tranexamic acid (TXA), DDAVP, and cryoprecipitate was administered to 22 patients (6.14%), while cryoprecipitate, platelets, and DDAVP were given to 38 patients (10.6%).

Figure 2. Administered Blood Component Therapy



In 31 patients (8.65%), a tendency towards hypercoagulability was confirmed, and in 11 of these patients (35.48%), the administration of Kybernin P 500 was recommended as a substitution for antithrombin deficiency.

DISCUSSION

The aim of this study was to assess the impact of ROTEM-guided transfusions on the use of blood components in traumapatients. ROTEM-guided therapy with blood components is associated with improved patient outcomes, particularly as it also reduces the need for allogeneic blood transfusions. Our study had a significantly higher proportion of male patients (70.1%) compared to females. Gender differences among trauma patients have been well documented in various studies, with a higher prevalence of males. Specifically, men are more frequently represented as polytrauma patients, often due to risky behaviors that include alcohol consumption and driving under the influence of alcohol [1]. Additionally, most causes for multiple injuries are indeed the result of traffic accidents and work-related injuries, which often occur in younger male populations who are more mobile and engaged in physically demanding jobs [1,2]. Moreover, traumas also occur among the elderly because of falls and fractures [1,3].

Studies have shown that ROTEM can significantly reduce transfusion requirements in cardiac surgery patients, trauma cases, and liver transplantation [7,8]. Görlinger et al. found that the use of ROTEM in cardiac surgery patients decreases the need for red blood cells, FFP and platelets, thereby reducing the risks of complications associated with blood transfusions [9].

The results of our study show that ROTEM-guided transfusion primarily led to increased use of fibrinogen in the form of cryoprecipitate, either as the sole component administered in 13.40% of patients or in combination with other components. Research indicates that ROTEM identifies functional fibrinogen deficiency more reliably than standard hemostasis tests. Several studies have demonstrated that patients with acquired fibrinogen deficiency have increased morbidity and mortality during trauma or procedures that may cause bleeding [10,11]. Schochl et al. demonstrated that ROTEM-guided therapy enables rapid correction of hypofibrinogenemia in severely traumatized patients, reducing the need for large FFP transfusion volumes and associated risks [12]. In cases of trauma-induced coagulopathy (TIC), acquired hypofibrinogenemia is the earliest sign of coagulopathy [9,12]. Fibrinogen levels decrease due to blood loss and hemodilution from the use of crystalloids. A decline in fibrinogen can be observed within the first hour of bleedingas the liver is unable to compensate for such a rapid loss in a short period. [13]. Rapid identification of hypofibrinogenemia is crucial for the effective treatment of

coagulopathy.
ROTEM also allows the assessment of platelet deficiency and guides to targeted platelet therapy. The study by Collins et al. demonstrated that ROTEM can identify platelet deficiency in patients with massive bleeding, enabling adequate and timely platelet therapy, thereby reducing the risks of thrombocytopenia and associated complications [14]. Thrombocytopenia is one of the factors predicting the risk of death in trauma patients [9,15]. By using ROTEM, the need for platelet transfusion can be determined shortly after the patient's admission. Ruger et al. suggested that the use of ROTEM and the rapid detection in vivo changes in coagulation following trauma contribute to the timely administration of platelets, as there is a good correlation between ROTEM, standard coagulation parametersand platelet count [16].In the group of patients we analyzed, platelets were used in multiple therapeutic modalities, both as a sole therapy in 19.27% of patients and as a part of combined therapy with cryoprecipitate, DDAVP and TXA. The use of 1000 mg TXA in trauma patients is part of a protocol that has been shown to reduce the incidence of intraoperative and postoperative hemorrhagic syndrome and was administered to 6.14% of our patients as part of a therapy that included platelets, DDAVP and cryoprecipitate[17]. The use of DDAVP is indicated in cases of reduced platelet activity and was administered to 20.11% of patients in combination with platelets and to 6.14% of patients as part of a therapy including platelets, cryoprecipitate and TXA.
With the use of ROTEM, it was observed that FFP was the least used component. Prior to the implementation of ROTEM, the protocols in place for trauma patients were based on the application of a predetermined ratio of red blood cells, platelets, and FFP in a fixed 1:1:1 ratio. ROTEM allows for more precise identification of coagulation disorders, leading to a more rational use of FFP. Traditional laboratory tests, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT)often do not provide a full perspective of coagulation, which can result in the overuse of FFP [18]. The study by Weber et al. showed that the use of ROTEM leads to a significant reduction in the use of FFP in cardiac surgery, while individualized therapy with blood components leads to faster stopping of bleedingin patients [19].
By analyzing ROTEM parameters in the studied patients, the substitution of appropriate blood components or the application of hemostatic medicine was performed through targeted individual therapy for the patient. In this way, ROTEM-guided transfusion therapy reduced the use of unnecessary blood component transfusions and associated risks, with more efficiency in managing bleeding in the patients.

CONCLUSION

The analysis of blood components used for therapeutic purposes guided by the rotational thromboelastometry demonstrated a wide range of therapeutic modalities in patient treatment. This testing method facilitates individualized therapy with blood components, subsequently diminishing the necessity for transfusions, enabling betterdiagnostic precision, and reducing costs associated with long-term patient management. Further studies and integration into standard clinical practices are warranted to enhance its effectiveness in patient care optimization and coagulopathy management.

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DETERMINATION OF ANTIBODIES TO THYROID PEROXIDASE - FURTHER EXPERIENCES

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ABSTRACT: Introduction: Thyroid peroxidase autoantibodies are a very important diagnostic parameter. They are mainly found in patients with autoimmune thyroid diseases (Hashimoto's thyroiditis, spontaneous hypothyroidism, Bazedov's disease). **Objective:** Analysis of the results of the method we use in clinical practice. **Material and working methods:** Autoantibodies to thyrocytic peroxidase were determined using the Monobind method, USA. So far we have made over 2000 determinations. The method consists of a chemiluminescent immunoassay, using thyroid peroxidase labeled with biotin and plastic tubes coated with streptavidin. Calibration was done with international standard 66/387 for thyroid microsomes. **Results**: In the last 8 years, we have done over 2000 determinations with hundreds of people. In about fifty of them the examined parameter was done as a "follow-up" study. **Conclusion:** We presented the results of determination of antibodies to thyrocytic peroxidase. The method we used gives very reliable results. During the "follow-up" study, the results were sometimes not constant in the same subject.

Key words: Autoantibodies, Thyroid microsomes, Hypothyroidism, Thyroid peroxidase

INTRODUCTION

Thyroid peroxidase (TPO) is an enzyme that plays a role in the biosynthesis of thyroid hormones (it catalyzes the oxidation of iodide to tyrosyl residues in thyroglobulin). It is located on the apical surface of the thyroid [1]. During the destructive processes of the thyroid gland, it initiates the formation of antibodies (TPOAb) as an autoantigen [2]. These autoantibodies are used in practice as a marker of autoimmune thyroid diseases [3]. They can also be found in some other autoimmune (non-thyroid) conditions [4]. Before using the analysis of antibodies to thyroid peroxidase, testing of antibodies to thyroglobulin and later to thyroid microsomes was used to determine thyroid autoantibodies. In recent years, it has been clarified that the antigenic substance in microsomes is actually thyroid peroxidase. The author published his experiences for the first time in 1985 [5] and published them in a foreign magazine in 1998 [6]. It was last published in this journal in 2017 [7] At that time, we used several methods for determining TPOAb from the following manufacturers: Thermo, Roche, Cobas, Beckman Coulter, and Monobind, USA. In this paper, only the results of this last manufacturer are presented, on a large number of samples, on several examined patients, on healthy people (control group) and in one part in the form of a "follow-up" study.

PURPOSE OF THE WORK

We tried to choose the method that suits us best: one that can be used in a small number of samples, on an inexpensive measuring device, one that gives reproducible results, one that has "normal values" like other methods (some of the methods used have reference values up to 9 IU/ml, most of the others have between 35 and 60). In patients and in a healthy control group, we monitored reproducibility over a longer period of time.

PATIENTS AND METHODS

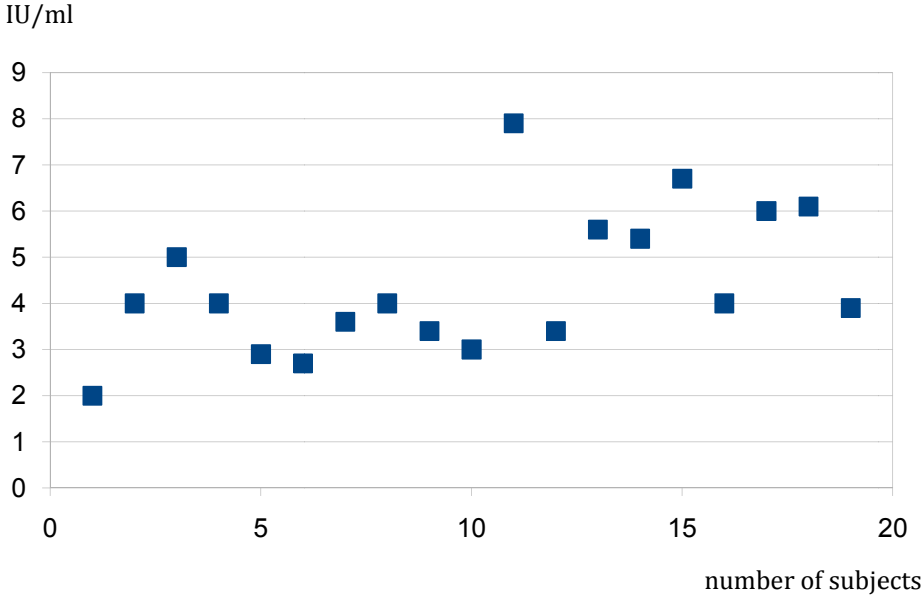
Chemiluminescent immunoassay was used to determine autoantibodies to thyroid peroxidase. Monobind microplates Limit value is 40. Monobind Inc.- Lake Forest, CA 92630 USA. The samples were measured on a Lumi Stat device. The device is designed to be used for a small number of samples.

We started the method 8 years ago, we have done over 2000 samples. In about fifty patients, we also carried out systematic monitoring (follow-up study), at 3-4 months, during 3-6 years.

RESULTS

In the last 8 years, since we have been doing TPOAb determination using the Monobind method, we have done 2040 samples. We treated a large control group of healthy individuals or patients with non-thyroid diseases. We have shown the values in graph 1.

Graph 1. TPOAb in a control group of healthy individuals or patients with non-thyroid diseases.



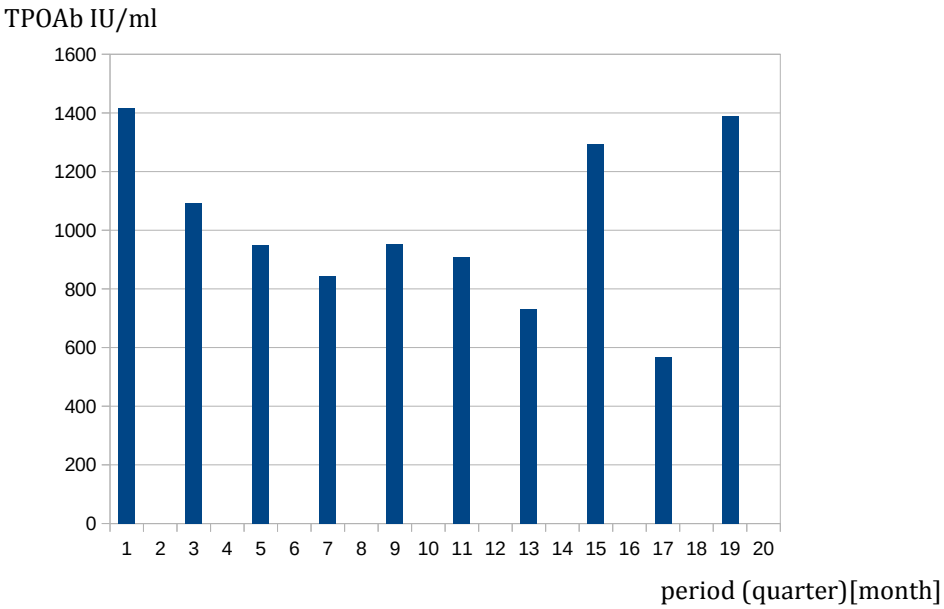
The group of patients with autoimmune thyroiditis (Hashimoto's), consisted of 323 patients with hypothyroidism, and 156 who were still in the euthyroid phase, although we prescribed l-thyrokinin replacement for most of them, especially if the values of antibodies to thyroid peroxidase were very high .

In the last couple of years, we processed the results we obtained from the same patients during follow-up. We wanted to verify the observations we made in a previous study (7), namely that the results are not sufficiently constant in patients on thyroxine substitution therapy. We have illustrated this observation in graphs 2 and 3.

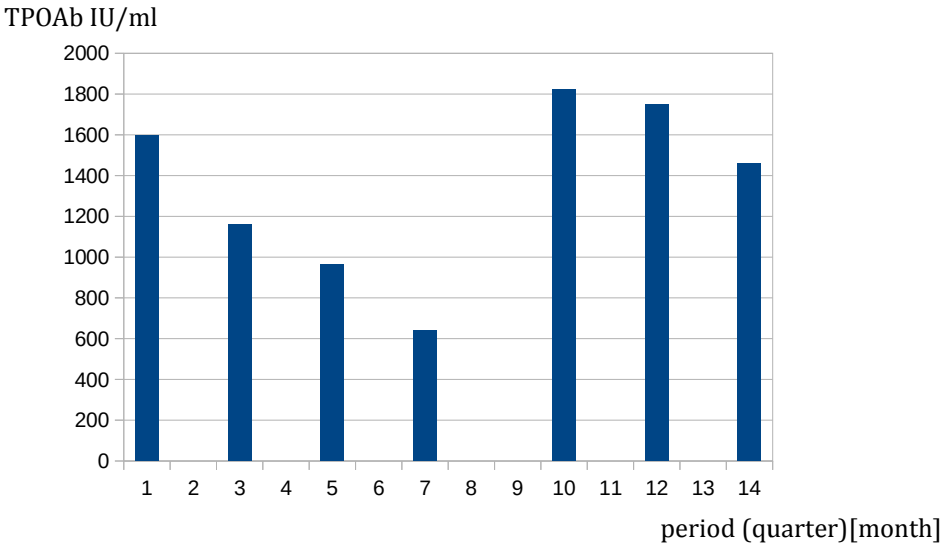
DISCUSSION

Thyroid peroxidase antibodies (TPOAb) are a parameter used in clinical work to evaluate chronic thyroid diseases. It is especially useful in the first described autoimmune disease - Hashimoto's thyroiditis. The height of this parameter probably depends on the degree of destruction of the thyroid tissue. Unlike the second parameter of thyroid autoimmunity - thyrotropin receptor antibodies (TRAb), which returns to normal with the passing of immunogenic hyperthyroidism, TPOAb is almost always constant. That's why in these papers we examined what could influence the level of these antibodies. We considered the technical details first. Different kits for testing this parameter do not always have the same "normal values", for example, the Beckman Coulter company has reference values up to 9 IJ/ml, unlike other methods that have upper limits of normal from 35-60 (7). It is likely that other epitopes were used for immunization in the production of autoantibodies. A practical tip is to always use the same method if you want to monitor the parameter in the same patient. This is especially important if one wants to use some drugs or supplements (selenium) to influence the course of the disease (8,9). In this work, during the "follow-up" studies, we noticed that about 30% of patients who were only on thyroxine replacement therapy, and do not take other drugs that could eventually affect this parameter (TPOAb), do not have a constant level (graph 2 and 3).

Graph 2. Monitoring of thyrocytic peroxidase antibody concentrations from 2016 to 2021 in patient P.B.



Graph 3. Monitoring of thyrocytic peroxidase antibody concentrations from 2016 –2019 in patient S.C.



CONCLUSION

We presented the results of determination of antibodies to thyrocytic peroxidase. The method we used provides reliable data. The parameter itself is not reliable in routine work - during the continuous monitoring of its value, oscillations occasionally occur for which we have not found an explanation. Is there an occasional increase in destructive processes? In further work, we will try to find an answer to that question.

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CORRELATION OF PSYCHOTIC DISORDERS WITH ALCOHOL AND OTHER PSYCHOACTIVE SUBSTANCES ABUSE

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Abstract: INTRODUCTION. Drug abuse can lead to substance-induced psychosis. Psychotic symptoms can, as well, appear as part of the abstinence syndrome, commonly in alcohol addiction. AIMS.Determining the prevalence of alcohol and other substance abuse by patients hospitalized for psychotic disorders; Determining whether there are differences in sociodemographic, psychiatric and somatoneurological parameters between those who used alcohol and drugs and those who did not. MATERIAL AND METHODS. The research was conducted as a retrospective study in which 181 patients hospitalized at the male ward for psychotic disorders of the Clinic for Psychiatry in Novi Sad were included. Medical documentation and clinical data grouped into 16 variables were analyzed. The results are presented using pictures, tables and graphs. The JMP 9 program was used for statistical data analysis, with t-test and χ^2 test. Significance level p=0.05. RESULTS. Alcohol was consumed by 41% of patients and drugs by as many as 32% of respondents. Of the drugs, the most prevalent was misuse of THC (13%), followed by polytoxicomania abuse (10%), stimulants (7%) and opioids (2%), while only one respondent was recorded as having misused hallucinogens. Abuse of THC, stimulants and polydrug abuse are associated with younger age. The most common somatoneurological comorbidity was hypertension. Compliance with therapy is statistically significantly worse in the group of alcoholics. CONLUSION. The use of alcohol and drugs is highly prevalent in the population of male patients. Comorbid abuse of these substances adversely affects the onset, course and treatment of psychosis.

Key words: psychosis; alcohol; psychoactive substances; opioids; hallucinogens

INTRODUCTION

Psychosis is a condition that disrupts mental functions, including thinking, perception, and mood, leading to a significant reduction in social and occupational functioning [1]. Symptoms are divided into positive (delusions, hallucinations, agitation) and negative (social withdrawal, emotional blunting) [2], interfering with a person's ability to think and communicate [3]. The etiology of psychosis encompasses genetic and environmental factors, with a significant role played by the dopaminergic and glutamatergic systems [1,2,4]. Psychotic disorders, including schizophrenia and schizoaffective disorder, frequently constitute the predominant clinical presentation; however, psychotic symptoms may also manifest in other conditions, such as those associated with substance abuse (SA)[5-6]. Substance abuse can induce psychotic symptoms during intoxication, particularly with hallucinogens and stimulants [8-9], while marijuana and alcohol increase the risk of psychosis with prolonged consumption [10-11]. Sometimes, substance-induced psychosis develops, and in cases of persistent symptoms, they are associated with a predisposition to psychosis [5-7]. Additionally, withdrawal syndromes, such as delirium tremens, often include psychotic manifestations [12]. Neurophysiological changes induced by SA, particularly in the dopaminergic and glutamatergic systems, explain the similarities in the pathophysiology and treatment of induced and endogenous psychoses [4,7,13,14]. Conversely, mental disorders often lead to substance abuse as a form of "self-medication" [1-3,7,14], while the use of alcohol and drugs negatively impacts the course and prognosis of psychosis [1-2,7].

The goals of this research are to determine the extent to which alcohol and/or other psychoactive substances (PAS) are present in

the population of adult psychotic patients hospitalized at the Psychiatry Clinic. Another objective is to establish whether there are differences in sociodemographic parameters between these patients and psychotic patients who have not abused alcohol and/or other PAS, as well as whether there are differences in psychiatric and somatoneurological characteristics between the two groups of patients (comorbidities, previous treatment, compliance, etc.).

MATERIAL AND METHODS

The study was conducted as a retrospective study, which included 181 patients hospitalized at the male ward for psychotic disorders at the Psychiatry Clinic in Novi Sad. Medical documentation and clinical data of patients treated from October 1st, 2020, to October 1st, 2021, were analyzed. Since we encountered patients who were hospitalized multiple times during this period, only the most recent hospitalization was considered for such cases.

The collected data were organized into variables that corresponded to the research domain:

1. Primary diagnosis for which the patient was hospitalized
2. Age
3. Educational level (elementary school, high school, university)
4. Marital status (married, single, divorced)
5. With whom the patient lives/ Living arrangements (alone, in a care facility, with parents, with close relatives, in a family setting, other – with a partner, with one child)
6. Presence of other psychiatric comorbidities
7. Previous psychiatric treatment
8. Presence of somatoneurological comorbidities
9. History of previous hospitalizations
10. Compliance with therapy (absent, poor, regular, questionable)
11. Alcohol consumption
12. THC consumption (marijuana, hashish)
13. Opioid consumption (heroin)
14. Psychostimulant consumption (cocaine, amphetamine, speed/methamphetamine)
15. Hallucinogen use (LSD, PCP, ecstasy)
16. Polysubstance abuse

For all patients data were obtained from medical histories. The use of materials for research purposes was approved by the Ethics Committee of the Clinical Center of Vojvodina. Given that we were unable to obtain all 16 variables for every patient, the research was based solely on the available data. Thus, out of the 181 hospitalized patients, complete data on alcohol and other psychoactive substances (PAS) use were obtained for 165 of them, and only these patients were included in the observation and analysis. The results initially presented the prevalence of alcohol, THC, opioid, stimulant, hallucinogen use and polysubstance abuse among the participants, expressed as percentages. Responses were recorded exclusively on two levels:as positive (yes) or negative (no) predictive values. Next, differences in sociodemographic parameters were examined between those who did and did not abuse alcohol and/or other PAS. The use of each substance individually, as well as the presence of polysubstance abuse, was compared in relation to the following parameters: age, with whom the patient lives, educational level and marital status. In this part of the results, the most frequent results recorded within individual parameters were summarized and presented as percentages (e.g., with whom they live – with parents 59%).

For the third research objective, the results examined differences in psychiatric and somatoneurological characteristics between the two groups of patients. The analysis focused on the presence of previous psychiatric treatment, prior hospitalizations, compliance with therapyand the presence of somatoneurological and psychiatric comorbidities. The results were presented in tablesand for all parameters except compliance with therapy, a positive predictive value was used as the starting point (e.g., the existence of previous hospitalizations was assumed). The results were presented using images, tables, and graphs. For statistical data analysis, JMP 9 software was used, employing t-test and X^2 test. The significance level was set at $p=0.05$.

RESULTS

Out of 181 participants, data regarding the consumption of alcohol and other psychoactive substances (PAS) were collected for 165 individuals. The most commonly consumed substance was alcohol, reported by 41% of patients. THC, in the form of marijuana and hashish, was used by 13% of participants. Opioids were abused by 2% and stimulants by 7% of the participants. Among all psychoactive substances, hallucinogens had the lowest

consumption rate, with only 1% of participants using them. Polysubstance abuse was identified in 17 patients, constituting 10% of the total sample of hospitalized individuals. A statistically significant difference ($p<0.05$) was observed between the number of patients who consumed alcohol and those who did not. Furthermore, a highly statistically significant difference ($p<0.01$) was found among patients who abused THC, opioids, stimulants and hallucinogens within their respective groups. A significance level of $p<0.01$ was also observed in polysubstance abuse.

Based on the obtained data, no statistically significant difference was found in sociodemographic parameters between those who did and did not consume alcohol. The majority of participants in both groups lived with their parents, had a high school education and were single(Table 1).

Table 1. Alcohol and Sociodemographic Parameters

	Alcohol consumers	Non-consumers of alcohol	p value
Age	36-40 years	35-40 years	p>0,05
With whom they live	with parents (45.2%)	with parents (63.4%)	
Educational level	high school (69.5%)	high school (60.8%)	
Marital status	single(80.3%)	single(83.5%)	

A statistically significant difference ($p < 0.05$) was observed with regard to THC use in the younger age group.95% of those who consumed THC were aged 19-30 years. Analysis of other parameters revealed that patients in both groups most commonly lived with their parents, were single, and had a high school education (Table 2).

Table 2. THC and Sociodemographic Parameters

	THC consumers	Non-consumers of THC	p value
Age	19-30 years	38-42 years	p<0,05*
With whom they live	with parents (66.7%)	with parents (53.7%)	p>0,05
Educational level	high school (53.3%)	high school (66.7%)	
Marital status	single(95.2%)	single(79.4%)	

While the distribution of opioid use is associated with both adolescence and middle adulthood (95% of patients who consumed them were in the 19-46 age range), the highest percentage of those without opioid comorbidity belongs to the middle adulthood group (36-41 years). This difference was marked as statistically significant ($p<0.05$) (Table 3).

Table 3. Opioids and Sociodemographic Parameters

	Opioids consumers	Non-consumers of opioids	p value
Age	19-46 years	36-41 years	p<0,05*
With whom they live	with close relatives (30%) with parents (30%) other (30%)	with parents (55.9%)	p>0,05
Educational level	high school (50%) unfinished elementary school(50%)	high school (64.4%)	
Marital status	single(100%)	single(81.2%)	

Participants in both groups are predominantly singleand live with their parents. A statistically significant difference ($p<0.05$) was observed in the use of stimulants, which is more common in younger age groups. Additionally, a strong statistical significance ($p<0.01$) was noted in the parameter 'educational level,' where the majority of consumers have not completed primary education (Table 4).

Table 4. Stimulants and Sociodemographic Parameters

	Stimulants consumers	Non-consumers of simulants	p value
Age	19-35 years	37-42 years	p<0,05*
With whom they live	with parents (63.6%)	with parents (54.9%)	p>0,05
Educational level	unfinished elementary school (66.7%)	high school (65.3%)	p<0,01*
Marital status	single (90.9%)	single (80.9%)	p>0,05

Among all the participants, the presence of hallucinogen abuse was confirmed in only one male, aged 22. His medical history indicated that he lived with close relatives, was single and had not completed primary education yet (Table 5).

Table 5. Hallucinogens and Sociodemographic Parameters

	Hallucinogens consumers	Non-consumers od hallucinogens	p value
Age (average value)	22 years	45,5 years	
With whom they live	with close relatives (100%)	with parents (55.8%)	p>0,05
Educational level	unfinished elementary school (100%)	high school (64.9%)	p<0,01*
Marital status	single (100%)	single (81.5%)	p>0,05

Polysubstance abuse as a comorbidity in patients with schizophrenia was predominantly recorded in the age group of 20-33 years. Participants with polysubstance abuse most commonly lived with their parents (62.5%), had incomplete primary education (50%) and were single (93.8%) (Table 6).

Table 6. Polysubstance Abuse and Sociodemographic Parameters

	The Presence of Polysubstance Abuse	The Absence of Polysubstance Abuse	p value
Age	20-33 years	38-42 years	p<0,05*
With whom they live	with parents (62.5%)	with parents (54.7%)	p>0,05
Educational level	unfinished elementary school (51%)	high school (66.7%)	p<0,01*
Marital status	single (93.8%)	single (80.1%)	p>0,05

A statistically significant higher percentage of patients with a history of psychiatric treatment was observed in the groups of non-consumers of THCand individuals with polysubstance abuse (Table 7).

Table 7. Percentage of Patients with a History of Psychiatric Treatment

	Consumed (%)	Didn't consume (%)	p value
Alcohol	85	80.6	p>0,05
THC	57.1	86.1	p<0,01*
Opioids	75	82.6	p>0,05
Stimulants	58.3	41.6	p<0,05*
Hallucinogens	0	82.9	p<0,05*
Polysubstance Abuse	58.8	41.2	p<0,01*

The presence of prior hospitalizations in patients was more commonly observed in the groups of those who did not consume stimulants and THC and those without polysubstance abuse (Table 8).

Table 8. Percentage of Participants with a History of Prior Hospitalizations

	Consumed (%)	Didn't consume (%)	p value
Alcohol	76.1	74.5	p>0,05
THC	47.6	79.2	p<0,01*
Opioids	75	75.2	p>0,05
Stimulants	50	77.1	p<0,05*
Hallucinogens	0	75.6	p>0,05
Polysubstance Abuse	47.05	78.4	p<0,01*

Regular compliance with medication intake was most frequently observed among hospitalized patients with THC comorbidity (38.46%) (Table 9).

Table 9. Compliance with Medication and Its Association with Alcohol and Other Substance Abuse

	regular		poor		absent		p value
	c(%)	nc(%)	c(%)	nc(%)	c(%)	nc(%)	
alcohol	12.5	35.9	39.3	29.5	45.4	33.3	p<0,05*
THC	38.46	24.8	38.46	32.2	23.07	41.3	p>0,05
opioids	33.3	26	0	33.6	66.7	38.9	
stimulants	14.3	26.8	14.3	33.9	71.4	37.8	
hallucinogens	/	26.1	/	32.8	/	39.5	
polysubstance abuse	10	27.4	30	33.1	60	37.9	

Legend: c-consumed, nc-didn't consume, /-without data

Among individuals who consumed alcohol, 52 patients (78.78%) had no somatoneurological comorbidities, with hypertension being the most prevalent comorbid condition (observed in 5 patients, or 7.6%). In the group of THC users, hypertension, type 2 diabetes mellitus and intestinal candidiasis were equally frequent. In the opioid user group, as well as in those with polysubstance abuse, the prevalence of HIV+ status and intestinal candidiasis was identical. An analysis of participants who abused stimulants revealed the presence of HIV+ status only. No data on the presence of somatoneurological comorbidities were found for patients using hallucinogens. The majority (49.2%) of patients exhibited no psychiatric comorbidities. In the stimulant group, psychiatric comorbidities included anxiety and personality disorders.

DISCUSSION

The global prevalence of psychotic disorders is relatively low, ranging from 0.2% to 3.5%. However, these disorders are more frequently observed in impoverished areas of large cities, where increased substance availability and consumption coincide with a lack of adequate management due to insufficient medical oversight. Consequently, investigating the bidirectional correlation between psychotic disorders and substance abuse is of significant importance. Unfortunately, it is not feasible to establish a direct causal relationship between a specific harmful substance and the mental state of already affected individuals, as these patients often combine various impure chemical compounds. Substance abuse is often driven by a variety of motivations, sometimes even simply to mitigate the adverse effects of antipsychotic medications. Harmful substances exert their effects by temporarily alleviating the deficit in the dysregulated dopaminergic system, which is associated with motivational processes and the reward system [14, 15].

Numerous studies conducted in 2019, 2008, and as far back as 1994, place alcohol, alongside cannabis and cocaine, at the apex of the comorbidity pyramid for patients with schizophrenia. This is consistent with our own research, which indicates that 41% of participants consumed alcohol, 13% used THC, and 7% used stimulants [14, 16, 17]. A comprehensive, multi-decade study conducted in Israel between 1963 and 2016 revealed that one-third of hospitalized patients with chronic psychotic disorders had a dual diagnosis, with the concurrent abuse of harmful psychoactive substances [18]. The initial analysis of our study's results similarly aligns with these findings. Specifically, 13% of participants reported using THC, 2% used opioids, 7% used

stimulants and 10% exhibited polysubstance abuse, leading to a total of 32% of individuals with a dual diagnosis, which approximates one-third of the entire sample. Furthermore, a Spanish retrospective study indicated that 22% of psychoactive substance users also had a psychotic disorder [19], while another publication demonstrated that 30% of PAS users transitioned to schizophrenia [20].

Since studies focusing on the sociodemographic characteristics of patients with dual diagnoses have not received the attention they deserve, it was challenging to find adequate results and hypotheses for comparing these parameters. Nevertheless, a study conducted at the Psychiatry Clinic in a small town in southern India yielded results that correlate with ours. Specifically, no statistically significant difference was found in sociodemographic parameters between individuals who consumed alcohol and those who did not. Additionally, the average age of consumers was 39 years, whereas in our study, 95% of participants were within the age range of 36-40 years [21].

The prevalence of psychotic disorders in the general population was most prominent among younger individuals, those who were single or divorced, and those with a high school education [22]. The abuse of cannabinoids in patients with psychotic disorders was most commonly observed in the age group of 17-22 years. This aligns with our study, in which a statistically significant distribution was also noted among younger individuals (ages 19-30) in the group of THC users [23]. The use of cannabinoids has been linked to lower levels of education in one study [24]. However, since the term 'lower educational level' is not clearly defined, it is not possible to compare results with certainty. The majority of participants in our study who used cannabinoids had a high school education (53.3%).Regarding the acquired level of education and the parameter 'educational level,' a statistically significant difference was observed between the groups of opioid users, hallucinogen users, stimulant users, polysubstance abusers and those who did not consume any of these substances. Specifically, 50% of opioid users, 66.7% of stimulant users, 100% of hallucinogen users and 51% of polysubstance users had not completed primary education.

The global prevalence of schizophrenia is approximately 1%, and the potential complications of substance abuse in patients with schizophrenia include: reduced medication adherence, increased frequency and number of hospitalizations and an elevated risk of violent behavior and suicide [15]. In our study, a significant lack of adherence was observed among schizophrenic patients who consumed alcohol (45.4%), opioids (66.7%), stimulants (71.4%), as well as those with polysubstance abuse (60%). The occurrence of prior hospitalizations in our study was more frequently observed in the group of participants who did not consume stimulants or THC as well as in those without polysubstance abuse. This finding deviates from the previously mentioned research. In the analysis of the presence of somatoneurological comorbidities, hypertension was identified as the most common among patients who abused alcohol and psychoactive substances. According to one study, the prevalence of hypertension was found to be 39% among patients with schizophrenia. The causal relationship follows a logical sequence. Specifically, schizophrenia is treated with antipsychotics, which often have the undesirable side effect of weight gain and obesity places a strain on the entire cardiovascular system, consequently leading to increased blood pressure [25].

While the abuse of alcohol and other psychoactive substances in patients with schizophrenia is generally harmful, it has also been associated with several potentially positive effects. One study observed that individuals with schizophrenia who had used cannabis and alcohol during the premorbid period were significantly more sociable and subjectively better able to cope with stress. The beneficial effects of benzodiazepines were also confirmed, as their well-known action temporarily suppressed psychotic symptoms. Additionally, psychostimulants were found to slightly lessen apathy, which is a negative symptom of the psychotic disorder. [15].

CONCLUSION

The study revealed that harmful use of psychoactive substances is present in 73% of patients hospitalized in psychiatry, with alcohol being the most prevalent (41%), which may be linked to cultural factors and its legal availability. Drug abuse (32%) significantly

exceeds data from the general population, and the results indicate the adverse effects of drugs, particularly THC, on the early onset and severe course of psychotic disorders. Patients who abuse THC more frequently experience severe psychotic exacerbations, despite better medication adherence, which contradicts pseudoscientific claims about the "beneficial" effects of "soft" drugs. Common characteristics among patients include lower levels of education, living with parents and being single, which correlate with socio-occupational dysfunctions. The most common somatic comorbidity was hypertension, while personality and anxiety disorders were more frequent among stimulant abusers. The limitations of the study, such as the small sample size and focus on male patients with psychotic disorders, highlight the need for broader studies that would include diverse patient groups to provide a more comprehensive understanding of the relationship between psychoactive substances and psychosis.

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INTERMITTENT FASTING: IS IT BENEFICIAL FOR HEALTH?

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Summary: During evolution, animals, including humans, developed in conditions of relative food scarcity. Adapting to such life circumstances, they developed adaptive metabolic changes that allowed them to function well even during periods when food was not available. Intermittent fasting (IF) encompasses eating patterns in which individuals refrain from consuming nutrients for extended periods or consume them in small quantities with alternating periods of normal food intake. IF has become an increasingly popular dietary practice, and its application can be found in various cultural, spiritual, religious, and health traditions throughout human civilization. New evidence has shown that the health benefits of IF extend beyond caloric restriction and weight loss. These benefits include metabolic changes in energy production and overall improvement in physiological markers of metabolic health. It is believed that IF reduces systemic inflammation and plays a role in the prevention and treatment of chronic diseases. In this paper, we aim to review available discussions on the physiological significance and impact of intermittent fasting on health.

Key words: intermittent fasting, therapeutic method, fasting in history, fasting and health, metabolic changes, ketone bodies, autophagy, gluconeogenesis, regeneration and stress, caloric restriction, lipolysis, sirtuins, cardiometabolic effects, atherosclerosis

INTRODUCTION

Intermittent fasting or fasting as a therapeutic method has been used at least since the 5th century BC. At that time, Hippocrates recommended abstinence from food or drink for patients exhibiting certain disease symptoms. Some doctors later recognized the instinct of fasting (in patients who, in certain diseased states, naturally experience a loss of appetite) and believed that providing food during such conditions was unnecessary and possibly even harmful, believing that fasting was an important natural part of the recovery process. The understanding of the physiological effects of fasting began to develop in the second half of the 19th century when some of the first organized fasting studies were conducted on animals and humans. In the 20th century, as knowledge of nutrition and the nutritional needs of the human body grew, fasting methods became more sophisticated, and a wide range of ways to apply this form of eating emerged.

The term fasting for Orthodox Christians refers to the abstention from certain types of food, primarily meat, dairy products, and eggs, and in some fasting periods, even fish, oil, and alcoholic beverages are avoided. In this paper, fasting will refer to the occasional interruption of the intake of any type of food (or the consumption of food and caloric drinks in minimal quantities) during periods typically ranging from 12-36 hours. Intermittent fasting (IF) can be practiced daily, alternating every other day, twice a week, or once a week. Fasting can be practiced for religious reasons as well as for health purposes. Members of certain religious communities traditionally fast on specific days of the week or calendar year. In many healthcare institutions, patients under medical supervision follow a fasting regimen or calorie restriction to control body weight, prevent, or treat diseases.

Fasting differs from caloric restriction (CR), where daily caloric intake is chronically reduced by 20-40%, but meal frequency is maintained. Unlike fasting and CR, starvation is chronic nutritional insufficiency often used as a substitute for the word fasting, but it is also used to define extreme forms of fasting (e.g., starvation), which can lead to degeneration and death. Research on animal models, as well as studies on humans, shows that fasting leads to ketogenesis, promotes strong changes in metabolic pathways and cellular processes such as stress resistance, lipolysis, and autophagy, and can have medical applications [1].

Intermittent fasting is technically not just a diet plan but a way of eating that focuses on timing rather than the type of food. Studies on animals and humans have shown that many health benefits of intermittent fasting are not solely a result of reduced free radical production or weight loss. Instead, intermittent fasting triggers evolutionarily preserved, adaptive cellular responses that improve glucose regulation, increase stress resistance, and suppress inflammation. During fasting, cells activate pathways that enhance defense against oxidative and metabolic stress and those that remove or repair damaged molecules [2]. The remarkable effects of typical CR (20-40%) on aging and diseases in mice and rats are often seen as mammalian responses during evolution to adapt to periods of limited food availability. However, the cellular and molecular mechanisms responsible for the protective effects of CR likely evolved billions of years earlier in prokaryotes attempting to survive in environments that were largely or completely devoid of energy sources [3]. For example, the bacterium E. coli, transferred from a nutrient-rich medium to a calorie-free medium, survives four times longer, an effect reversed by adding various nutrients, but not acetate, a carbon source associated with starvation conditions [4]. The shortening of the bacterium's lifespan in a rich medium, but not acetate, suggests that a ketone-body-like carbon source such as acetate could be part of an "alternative metabolic program" that evolved over billions of years in microorganisms, now allowing mammals to survive periods of food scarcity by obtaining most of their energy through fatty acid and ketone body catabolism, including acetoacetate and β-hydroxybutyrate [5]. In Saccharomyces cerevisiae (brewer's yeast), transferring cells from a standard growth medium to water also causes consistent double chronological lifespan extension, as well as a significant increase in resistance to multiple stressors [6]. Another organism model where fasting extends lifespan is the nematode Caenorhabditis elegans. Food deprivation conditions achieved by feeding the worms with little or no bacteria lead to significant lifespan extension [1]. In the fruit fly, most studies suggest that intermittent food deprivation does not affect lifespan. However, it has consistently been shown that reducing or diluting food extends the longevity of Drosophila, suggesting that flies may benefit from dietary restriction but may be sensitive even to short periods of starvation. Taken together, these results indicate that food deprivation can lead to lifespan-extending effects across a wide range of organisms but also emphasize that different organisms have different responses to fasting [1]..

Metabolic Changes During Fasting

In most mammals, the liver serves as the main reservoir for glucose, which is stored in the form of glycogen. In humans, depending on the level of physical activity, after 12 to 24 hours of fasting, the glucose levels in the serum drop by 20% or more. The glycogen reserves in the liver become depleted. The body shifts to a metabolic state in which the liver and kidneys produce glucose from non-carbohydrate sources, such as glycogenic amino acids from muscles (isoleucine, phenylalanine, tyrosine, tryptophan), glycerol from fats, and lactic acid, followed by lipolysis in adipose tissue, releasing free fatty acids and glycerol, which the body uses as energy. While most tissues can use fatty acids for energy, during extended fasting periods, the brain, in addition to glucose, relies on ketone bodies β-hydroxybutyrate and acetoacetate for energy consumption. Ketone bodies are produced in hepatocytes from acetyl-CoA formed through β-oxidation of fatty acids released into the bloodstream by adipocytes, and also through the conversion of ketogenic amino acids (leucine and lysine). After 3-5 days of fasting, the liver produces ketone bodies (beta-hydroxybutyrate and acetoacetate) from fatty acids through ketogenesis, which become the main energy source for the brain and muscles. At the same time, the use of protein as an energy source decreases. After 5 days without food, the brain almost completely switches to ketone bodies as an energy source, thus protecting muscle mass. Minimal gluconeogenesis still occurs, approximately 80 grams daily, with glucose being produced only in amounts necessary for cells that cannot use ketone bodies (e.g., erythrocytes and some parts of the brain) [7]. Depending on body weight and composition, ketone bodies, free fatty acids, and gluconeogenesis allow most people to survive for 30 or more days in conditions of food scarcity, and allow certain species, such as royal penguins, to survive without food for more than 5 months [8].

Metabolic Adaptations to Intermittent Fasting

In humans, the three most studied intermittent fasting regimens are alternate-day fasting (one day without food, the next day food ad libitum), 5:2 intermittent fasting (fasting for 2 days each week), and daily time-restricted feeding. Diets that significantly reduce caloric intake for 1 day or more each week (e.g., reducing to 500–700 calories per day) lead to increased levels of ketone bodies on those days [9, 10].

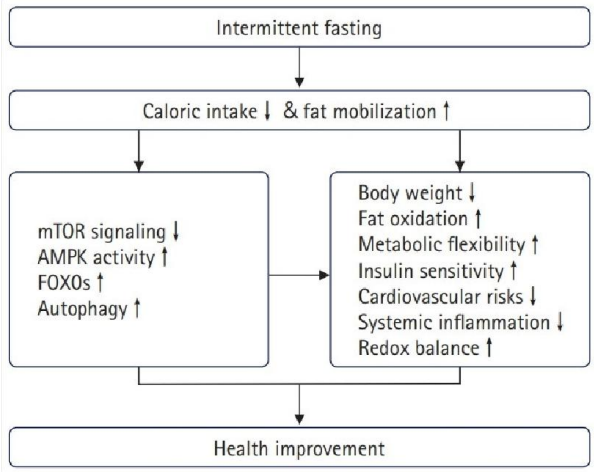
The metabolic shift from using glucose as a fuel source to using fatty acids and ketone bodies ("metabolic switch") results in a decreased respiratory quotient (the ratio of carbon dioxide produced to oxygen consumed), indicating greater metabolic flexibility and efficiency in energy production from fatty acids and ketone bodies [11].

Ketone bodies are not only fuels used during fasting periods; they are powerful signaling molecules with significant effects on cellular and organ functions. Ketone bodies act as metabolic signals that regulate epigenetics through beta-hydroxybutyrate (BHB), which inhibits histone deacetylase (HDAC). This inhibition then results in an antioxidant response and lifespan extension. They increase the activity of sirtuins (especially SIRT1 and SIRT3), which reduces oxidative stress. Ketones also modulate inflammatory and antioxidant pathways by promoting the activation of Nrf2 (Nuclear factor erythroid 2-related factor 2), the primary regulator of the antioxidant response, and by reducing the activity of NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells), a key factor in inflammatory processes. Additionally, ketones increase stress resistance and promote autophagy through AMPK (AMP-activated protein kinase), which stimulates autophagy and mitochondrial biogenesis, contributing to cellular health and stress resilience. Ketone bodies indirectly inhibit mTORC1 activity (the mechanistic/mammalian target of rapamycin complex), the major regulator of cellular growth and protein synthesis. Mechanistically, mTOR is a key regulator of autophagy and cellular metabolism in mammals. Reduced mTOR activity shifts cellular resources from non-essential anabolic reactions toward catabolic processes, including activation of complexes important for autophagy. Reduced mTOR activity is linked to extended lifespan and protection from age-related diseases [12].

By affecting these key cellular pathways, ketone bodies produced during fasting have profound effects on systemic metabolism. Furthermore, ketone bodies stimulate the expression of genes for brain-derived neurotrophic factor, with implications for brain health and psychiatric and neurodegenerative disorders [13]. Many studies have shown that some of the benefits of intermittent fasting are separate from its effects on weight loss. These benefits include: improvements in glucose regulation, regulation of blood pressure, reduction in heart rate, increased endurance training efficiency, and loss of abdominal fat [14].].

Picture 1. POSSIBLE MECHANISMS OF INTERMITTENT FASTING ON HEALTH IMPROVEMENT

Source (25.02.2025): *Song DK, Kim YW. Beneficial effects of intermittent fasting: a narrative review. J Yeungnam Med Sci. 2023 Jan;40(1):4-11. https://pmc.ncbi.nlm.nih.gov/articles/PMC9946909/*



The Effects of Intermittent Fasting on Health and Aging

After nearly a century of research on caloric restriction in animal models, the general conclusion was that reduced food intake significantly extends the lifespan of the animals studied. In one of the earliest studies on intermittent fasting, Goodrick and colleagues showed that the average lifespan of rats was extended by up to 80% when maintained on an alternate day feeding regimen, starting when they were young adults. However, the magnitude of the effects of caloric restriction on healthspan and lifespan varies and can be influenced by gender, diet, age, and genetic factors [2]. A meta-analysis of data available from 1934 to 2012 showed that caloric restriction in rats extended the average lifespan by 14 to 45%, but only by 4 to 27% in mice [15].

Conflicting results from two significant studies on monkeys raised doubts about the relationship between improved health status and extended lifespan through caloric restriction. One study on rhesus monkeys showed a positive effect of caloric restriction on both health and survival [16], while another study, also on rhesus monkeys, did not show a significant reduction in mortality with caloric restriction, despite clear improvements in overall health [17]. A subsequent study showed that differences in daily caloric intake, the timing of the intervention, food composition, feeding protocols, gender, and genetic background could explain the varying effects of caloric restriction on lifespan in the two previous studies [18].

Intermittent fasting in humans alleviates obesity, insulin resistance, dyslipidemia, hypertension, and inflammation. It seems that intermittent fasting provides more health benefits than can be attributed solely to a reduction in caloric intake. In one study, 16 healthy participants who underwent an alternate-day fasting regimen for 22 days lost 2.5% of their initial body weight and 4% of body fat, along with a 57% reduction in fasting insulin levels [19]. In two other studies, approximately 100 overweight women in each study were divided into two groups: one following a 5:2 intermittent fasting regimen, and the other reducing their daily caloric intake by 25%. Participants in both groups lost the same amount of weight during the 6-month period, but those in the 5:2 intermittent fasting group had a greater increase in insulin sensitivity and a larger reduction in waist circumference [20].

Benefits of Intermittent Fasting for the Aged and Diseased Vasculature

Vascular aging involves arterial stiffness and the formation of fibrolipid lesions in the arterial wall, leading to atherosclerosis. The main clinical manifestations of atherosclerosis include coronary artery disease, ischemic stroke, and peripheral artery disease, which are caused by hyperlipoproteinemia (low-density lipoprotein LDL cholesterol), inflammation, vascular remodeling, and plaque formation [21]. Intermittent fasting (IF) is associated with a reduction in LDL cholesterol levels [22]. In rats, both in the absence and presence of various stressors (e.g., swimming), intermittent fasting reduces resting blood pressure and heart rate. The reduction in blood pressure may be partially due to enhanced endothelial cell-dependent vasodilation [23,24].

Furthermore, intermittent fasting activates the parasympathetic nervous system by stimulating brain cells. During fasting, neurotrophic factors are released, and acetylcholine is secreted, which, via the vagus nerve, leads to a decrease in heart rate and blood pressure [25].

Risks of Intermittent Fasting for the Aged and Diseased Heart and Vasculature

Despite the numerous health benefits of intermittent fasting (IF), some risks have been reported in various models of cardiovascular diseases. For example, rats subjected to alternate-day fasting for 6 months showed reduced diastolic compliance of the left ventricle and diminished cardiac reserve [26].

The efficacy of activating autophagy in senescent cells remains a subject of ongoing debate, as autophagy has also been reported to promote cellular aging by facilitating the synthesis of aging-associated proteins. Furthermore, excessive stimulation of autophagy can lead to several pathological outcomes, including inhibition of angiogenesis [27]. Therefore, reduced regenerative capacity of the endothelium and the accumulation of senescent cells in older individuals may

potentially limit the beneficial effects of intermittent fasting on vascular health.

In older adults, particularly those with hypertension or other cardiovascular diseases, potential fluctuations in blood pressure during intermittent fasting periods may raise concerns regarding cardiovascular risks, orthostasis, and fall-related injuries [28]. Another risk associated with intermittent fasting arises from metabolic changes, such as electrolyte imbalances or activation of the sympathetic nervous system, which can predispose older individuals to dehydration and cardiac arrhythmias, especially in the presence of pre-existing heart conditions.

In summary, due to the lack of data, the implementation of intermittent fasting in older individuals or patients with cardiovascular diseases requires careful consideration due to potential risks, which depend on the specific fasting regimen, cardiac condition, comorbidities, gender, and age [29].

Effect of Intermittent Fasting on Cardiometabolic Health

The weight loss induced by intermittent fasting is primarily attributed to a reduction in fat mass. Studies have documented reductions in subcutaneous and visceral fat, with the latter being particularly beneficial due to its association with metabolic dysregulation and increased cardiovascular risk [30].

Waist circumference, a key anthropometric marker of cardiovascular risk used to assess abdominal adiposity, is strongly associated with all-cause mortality and cardiovascular mortality. It has been shown that waist circumference significantly decreases in individuals practicing intermittent fasting. This reduction in waist circumference is directly correlated with a lower risk of coronary artery disease and other cardiovascular pathologies [31].

Moreover, intermittent fasting improves several cardiovascular risk factors, including blood pressure, lipid profile, resting pulse, glucose and insulin levels, and insulin resistance. Furthermore, intermittent fasting can alleviate chronic inflammation associated with aging by reducing systemic inflammatory markers and oxidative stress linked to atherosclerosis in humans [29].

Aging is a critical factor in the pathogenesis and progression of heart failure (HF), increasing the incidence and severity of HF. Several studies have suggested that intermittent fasting may improve risk factors associated with the development of HF in both healthy individuals and those with obesity and ischemic heart disease [32].

For instance, in one study, participants who reported routinely practicing intermittent fasting at least once a month for a minimum of 5 years experienced a 71% reduction in the risk of heart failure compared to those who did not fast [33]. Another prospective observational study found that later periods of the first and last meals were associated with a greater risk of cardiovascular events, consistent with randomized studies reporting that late evening meals may exacerbate cardiovascular risk factors [34]. These inconsistent findings require further research into the relationship between intermittent fasting and heart failure through large randomized controlled trials investigating the effect of fasting at different times of the day.

The effect of intermittent fasting on muscle health is a topic of debate as it remains unclear whether intermittent fasting preserves lean muscle mass during weight loss or exacerbates the breakdown of muscle proteins and net catabolism. While some earlier studies suggested a reduction in lean mass with dieting, the general consensus is that intermittent fasting does not have a detrimental effect on lean mass, even with weight loss in otherwise healthy individuals, as well as in insulin-treated diabetic patients [35].

Physical and Cognitive Effects of Intermittent Fasting

In both animals and humans, physical function improves with intermittent fasting. For example, despite having similar body weights, mice maintained on an intermittent fasting regimen exhibit better running endurance than mice with unlimited access to food [2]. Balance and coordination are also improved in animals following time-restricted daily feeding or alternate-day fasting regimens [36]. Juveniles who fast for 16 hours daily lose fat while maintaining muscle mass over 2 months of intense training [37]. Animal studies show that intermittent fasting improves cognition across various domains, including spatial memory, associative memory, and working memory [38]. Alternate-day fasting and daily caloric restriction counteract the harmful effects of obesity, diabetes, and neuroinflammation on

spatial learning and memory. In a clinical trial, older adults on a short-term caloric restriction regimen experienced improved verbal memory. In a study involving overweight adults with mild cognitive impairment, 12 months of caloric restriction led to improvements in verbal memory, executive function, and global cognition [39, 40]. A large, multicenter, randomized clinical trial demonstrated that 2 years of daily caloric restriction resulted in significant improvements in working memory [41]. Further research is needed to explore the relationship between intermittent fasting and cognition in older adults, especially considering the absence of pharmacological therapies affecting brain aging and the progression of neurodegenerative diseases.

DISCUSSION

An increasing body of evidence supports intermittent fasting (IF) in all its variations as a potentially safe and feasible dietary intervention for improving human health. IF can improve physiological and molecular markers of aging and provide benefits for cardiovascular and metabolic health in patients with obesity, type 2 diabetes, metabolic syndrome, and heart failure [29]. Significant weight loss and other health benefits have been associated with two types of intermittent fasting: modified alternate-day fasting (alternating between a day of normal food intake and a day consuming up to 600 calories) and the "5:2 diet" (2 days of no caloric intake per week) [42].

While clinical evidence is mostly of a research nature, these studies provide a solid rationale for investigating the efficacy of IF in improving cardiovascular health, particularly in the elderly population at risk for or already experiencing cardiovascular diseases. Future randomized trials with larger sample sizes and longer durations will be necessary to assess the long-term outcomes, adherence, and safety of IF, especially in older participants.

Despite the health benefits of intermittent fasting and its applicability to many diseases, there are barriers to widespread adoption of these dietary patterns in the community and by patients. First, the traditional three-meal-a-day pattern with snacks is so ingrained in our culture that patients or physicians rarely consider changing this eating pattern. The abundance of food and extensive marketing in developed countries also pose significant barriers that must be overcome. Second, when transitioning to an intermittent fasting regimen, many people experience hunger, irritability, and reduced concentration during periods of food restriction. However, these initial side effects usually subside within a month, and patients should be informed of this [2].

Given the limitations and risks outlined above, patients should be cautioned that eating patterns involving extended periods without food could pose risks for people with diabetes who are on insulin or otherwise prone to hypoglycemia [42]. Physician education is also recommended for patients with a range of chronic conditions or at risk of such conditions, particularly those associated with overeating and a sedentary lifestyle, on how to implement intermittent fasting for prevention or as part of early treatment for these conditions.

Another important aspect to consider is that intermittent fasting alters the gastrointestinal microbiome [43]. Fasting regimens appear to have a positive impact on gut microbiota. Future studies characterizing the health effects of fasting regimens on the human microbiome have the potential to make an important contribution to this field. Therefore, it will also be crucial to investigate changes in metabolites produced by gut bacteria, focusing on the molecular mechanisms underlying the effects of intermittent fasting on cellular aging.

CONCLUSION

Intermittent fasting relies on the concept of a "metabolic switch," which involves a shift from glucose-dependent metabolism during a typical diet to ketones derived from fat cells during fasting. This "metabolic switch" may improve glucose regulation and reduce inflammation. The stress of fasting also increases autophagy, which removes damaged molecules. Given these physiological changes, intermittent fasting can offer significant long-term health benefits. Animal models of intermittent fasting show that this dietary pattern improves the health of the animals throughout their lifespan. Clinical studies in human models have also demonstrated significant health benefits, although these studies have mostly involved relatively short-term interventions lasting several months. Preclinical studies and clinical trials have shown

that intermittent fasting offers a broad range of advantages for many health conditions, such as obesity, diabetes, cardiovascular diseases, certain cancers, and neurological disorders. Numerous studies suggest that intermittent fasting regimens may be a promising approach for weight loss and improving metabolic health in people who can tolerate periods without food or consume very little at certain times of the day or on specific days of the week. For healthy, normal-weight, or obese adults, there is little evidence that intermittent fasting regimens are harmful physically or mentally. Future studies should determine whether the benefits observed in animal models can be sustained over long-term intermittent fasting in humans of various ages and health statuses. Further understanding of the processes linking intermittent fasting to many health benefits may allow us to develop targeted pharmacological therapies, including interventions on the gut microbiome, that mimic the effects of intermittent fasting without requiring fundamental changes to eating habits.

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MEDICATION ADHERENCE IN OLDER PEOPLE: PREDICTORS AND STRATEGIES FOR IMPROVEMENT

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Abstract: Medication adherence represents a complex and multidimensional issue in healthcare. Analyzing the factors influencing medication adherence in elderly individuals identifies three main groups: patient-related, medication-related, and environmental factors. Patients facing physical, cognitive, or sensory limitations may struggle with proper medication intake, while a lack of health literacy can contribute to an insufficient understanding of the therapy. The complexity of treatment regimens, medication side effects, and financial factors can also influence adherence to therapy. The consequences of non-adherence to drug therapy can be severe, including inadequate disease control, worsening symptoms and conditions, increased healthcare costs, and reduced quality of life. Therefore, interventions aimed at improving therapy adherence are crucial. These interventions include simplifying dosing regimens, using reminders, enhancing communication between patients and healthcare providers, and utilizing modern technologies. Clear and supportive communication between patients and healthcare providers can improve therapy adherence in elderly individuals.

Keywords: medication adherence, older adults, communication

Introduction

Population aging is a global phenomenon that significantly impacts health systems and the provision of health care. The increase in life expectancy leads to a larger number ofolder adults who require long-term medical therapy to maintain health and quality of life [1,2]. However, adherence to prescribed therapy in the elderly is often problematic and may lead to suboptimal treatment results [2,3]. Adherence to drug therapy, that is, taking drugs by the prescribed dose and schedule, is vital for achieving the desired health outcomes [4]. Research shows that older adults often have low adherence rates, which can result in complications, worsening of the disease, and increased health care costs [5]. Depending on the study design, nonadherence rates in the literature range from 16% to 76% [6,7]. Nonadherence to prescribed drug therapy can have severe consequences for the health of patients [4,8]. Improper intake or skipping doses can reduce the effectiveness of the treatment and lead to insufficient control of the disease [7]. Then, lack of adherence can lead to worsening symptoms and disease, which can result in complications or adverse effects and worse outcomes [8]. In this regard, poor adherence to therapy may require additional medical interventions, a change in medication, or an extension of the duration of therapy [4]. In addition, healthcare costs may increase due to the need for additional treatment or hospitalization [9]. Deteriorating health conditions can affect the patient's quality of life and ability to perform daily activities. Because of all the above, it is essential that patients, especially the elderly, follow their drug therapy according to the doctor's instructions to achieve optimal disease control and reduce possible complications [8].

Understanding the factors influencing medication adherence in the elderly is critical to developing effective interventions to improve adherence and health outcomes [5,7]. This paper presents the most important factors influencing adherence to therapy in the elderly and potential strategies to improve adherence.

Definition of terms

Medication nonadherence is a complex and multidimensional healthcare problem [5]. Adherence is the degree to which patients can

follow recommendations for prescribed treatments [10]. Compliance, adherence, persistence, and concordance are terms used in connection with suboptimal taking of prescribed drug therapy [2]. Although often used synonymously, they provide different perspectives on the patient-healthcare professional relationship and appropriate medication administration. Compliance is the patient following the doctor's recommendations, while adherence is behavioral compliance. Compliance refers to the agreement between the doctor and the patient about the purpose and use of the drug. Persistence measures the time between the first and last drug intake in cases where the patient stops therapy relatively soon after starting the treatment [2,5].

Awareness of intentional and unintentional non-adherence is crucial for developing effective interventions to improve drug therapy adherence [10]. Intentional non-adherence can be considered a process in which a patient actively chooses not to use treatment or to follow treatment recommendations [2]. Unintentional non-adherence refers to unplanned behavior and is less related to beliefs and level of cognition than intentional non-adherence. Unintentional adherence can result from forgetting and not knowing the correct way to use medications [2].

Factors affecting adherence to drug therapy in the elderly

Many factors can affect adherence to drug therapy in olderpeople [1,5]. They can generally be divided into three broad groups: patient-related, drug-related, and social and economic factors.

Patient-related factors

Elderly patients, especially those with physical, cognitive, or sensory limitations, may have difficulty taking medications properly [1,9, 10]. For example, people with arthritis may have difficulty opening medication bottles, while people with dementia may forget to take their medication or take it at the wrong dose [10].
Lack of understanding of the importance of adherence to therapy can lead to incorrect medication intake, such as skipping doses or incorrect dosing [11]. Then, a lack of understanding about the consequences of non-adherence to therapy can lead to an underestimation of the severity of the disease or a lack of awareness of potential complications [12]. In addition, the risk of medication errors may increase, which may reduce the effectiveness of therapy and lead to poor health outcomes. Older adults who lack an understanding of the importance of adherence may need additional education and support from healthcare providers to improve adherence and achieve better health outcomes [2,7].

Older patients with a higher level of health literacy are usually better informed about their medications and understand the importance of proper medication intake and possible side effects [9]. They can better understand the medication instructions given to them by a healthcare professional, including the dosage, method of administration, and time of taking the medication [7]. Next, they are more likely to ask relevant questions about their medications, which can improve their understanding and reduce the risk of medication errors. In addition, they better assess the accuracy of drug information they find on the Internet or other sources, thereby reducing the risk of accepting inaccurate or unreliable information [9]. Considering these factors, improving health literacy among older adults may be crucial to improving medication adherence and their health and quality of life [10].

Drug-related factors

The complexity of treatment regimens significantly impacts adherence in olderpeople for several reasons. First, older people often have chronic diseases that require multiple drug therapy [1,13]. With the increase in the number of drugs, the complexity of the therapeutic regimen also increases, which can make it difficult to follow and take the prescribed medications in the correct schedule [5]. Second, the treatment regimen's complexity can manifest through different ways of administering medications, such as oral tablets, drops, injections, and patches. The variety of drug administration methods can further complicate adherence, especially if the patient is unable to self-administer certain forms of medication or if side effects occur because of a particular administration method [10]. Third,

different medication instructions, such as different dosing schedules, specific conditions of administration [e.g., before meals or after meals], or dietary requirements [e.g., drinking more water], may further complicate adherence to therapy [13]. A meta-analysis of 76 studies showed that 72% of patients on a once-daily regimen were adherent, 69% on a twice-daily regimen, 65% on a three-times-daily regimen, and 51% on a four-times-daily regimen [14]

The presence of unpleasant side effects of drugs can significantly affect adherence to drug therapy in olderpeople [7]. Undesirable side effects of medications can make treatment adherence difficult for older people, reducing quality of life and motivation to take medications. Fear of side effects can lead to non-adherence to therapy, even if they are rare or mild. In addition, they can stop therapy on theirinitiative if they feel unpleasant side effects, which can lead to a lack of treatment effectiveness. Elderly patients with side effects may require the support of healthcare professionals to continue therapy and treatment effectiveness. Managing adverse drug reactions and providing support may be vital in improving adherence in older adults [12].

Social and economic factors

Social factors can have a significant impact on adherence to drug therapy in older people [5]. People living alone or without the support of family and friends may feel lonely and depressed, which may lead to a lack of motivation to adhere to therapy [7]. Limited access to health services, such as difficulties with transportation to doctors or pharmacies, can make it difficult for older people to collect their medications regularly. Also, financial factors can be an obstacle to taking medicines properly because some drugs can be expensive or not covered by health insurance [1,15]. High treatment costs for older people may limit access to specific therapies or force patients to choose different medications, affecting adherence [5,15].

INTERVENTIONS AIMED AT IMPROVING ADHERENCE TO MEDICATION THERAPY

Interventions aimed at unintentional non-adherence include simplifying dosing regimens, reminders, improved patient-physician communication, an individualized approach to each patient, and introducing or improving patient counseling [7,14,16–18].

Attempts to increase adherence are increasingly using modern technologies [2,4,7]. Currently, the Internet and the mobile phone are often used in interventions to improve adherence [18]. Short message service [SMS] is increasingly used to remind patients to take their medication. SMS enables instant delivery of short text messages to individuals at any time, place, and environment. As such, SMS reminders are a straightforward method with low intrusiveness and relatively low cost [2,4].

Communication between patient and doctor is of utmost importance, especially regarding adherence to therapy [11,16,18]. Healthcare professionals should never assume a patient is adhering to treatment[19]. Questioning patients about medication habits is also recommended [2]. In the study by Van Dulmen and Van Bijnen, GPs were shown videos of their consultations. Afterward, they were asked why they did not ask specific questions or why some of the patients' questions were ignored. GPs often cited lack of time as a reason for this, but there was also an element of presumption of patient adherence to therapy [19]. Through clear communication, the physician can provide detailed information about the importance of treatment, its goals, dosage, method of administration, and possible side effects, which can improve patient understanding and motivate them to adhere to therapy [19]. In addition, effective communication can help set realistic therapy expectations, reduce frustration, and increase patient motivation to adhere to treatment[18]. Through empathic and supportive communication, the physician can provide emotional support and motivate elderly patients to adhere to treatment despite side effects or difficulties. In this way, the doctor allows patients to ask questions and express their concerns or doubts regarding the therapy, contributing to better understanding and cooperation [11].

CONCLUSION

Adherence to therapy in older people has a more profound impact than is commonly assumed. In addition to directly affecting health, adherence to therapy can significantly impact emotional well-being and social interaction. Older people who adhere to their treatment plans often have greater independence and a sense of control over their lives, which can increase their quality of life. In addition, adherence to therapy can help maintain stable physical conditions, prevent complications, and reduce the risk of emergency medical interventions. This is extremely important in older people, whose bodies can become increasingly sensitive to changes and deficiencies in the therapeutic approach. Understanding the importance of adherence can help older adults maintain a more active and independent lifestyle, which is critical to their well-being. By identifying and addressing the specific needs of this population, healthcare providers can improve patient outcomes, reduce healthcare costs, and improve the overall quality of life of older adults.

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MENINGEAL SYNDROME

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Summary: Meningitis is an inflammation of the soft tissues of the brain and spinal cord, which are characterized by the presence of polymorphonuclear leukocytes in the cerebrospinal fluid, and are caused by various bacteria, viruses, parasites, etc. The term meningeal syndrome means that it is an irritation of the meninges (meningism) or an inflammatory process on them (meningitis) and is an indication for a cerebrospinal fluid puncture, which is the only way to distinguish meningism from meningitis. Meningism and meningitis cannot be distinguished from each other based on the clinical picture, because there is no: singular sign that occurs in meningitis, but not in meningism, and vice versa, difference in the intensity of meningeal symptoms in meningitis from that in meningism, condition that can be accompanied by meningitis that cannot be accompanied by meningism.
Key words: meningitis, inflammatory process, brain tumors, meningeal syndrome

INTRODUCTION

Meningitis represents inflammation of the meninges and, more rarely, the brain (meningoencephalitis), characterized by the presence of polymorphonuclear leukocytes in the cerebrospinal fluid (CSF). It is caused by various bacteria, viruses, parasites, and other agents.

The term *meningeal syndrome* refers to irritation of the meninges (*meningism*) or an inflammatory process affecting them (*meningitis*) and indicates the need for cerebrospinal fluid puncture, which is the only method to distinguish meningism from meningitis.

Meningism and meningitis cannot be differentiated based on clinical presentation alone because:

There is no sign present in meningitis that does not occur in meningism, and vice versa,

There is no difference in the intensity of meningeal symptoms in meningitis compared to meningism,

There is no condition that could be accompanied by meningitis but not by meningism.

ETIOLOGY OF MENINGEAL SYNDROME

Meningitis can be caused by infectious agents, allergic reactions, toxic, physical, and chemical noxae.

Bacterial meningitis is caused by pyogenic bacteria: *Neisseria meningitidis* (meningococcus), *Streptococcus pneumoniae* (pneumococcus), *Staphylococcus*, *Streptococcus*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Proteus*, etc.

Viral meningitis is caused by poliovirus, ECHO virus, Coxsackie virus, Armstrong virus, mumps virus, herpes zoster, influenza virus, mononucleosis, adenoviruses, and arboviruses.

Spirochetal and rickettsial meningitis are caused by *Leptospira*, *Treponema pallidum* (pale spirochete), and all rickettsial species.

Fungal meningitis is typically caused by *Candida*.

Parasitic meningitis is caused by *Ascaris*, *Trichinella*, and tapeworms.

Meningitis caused by chemical agents occurs due to endogenous toxins (e.g., urea) or inhalation of toxic gases [1].

Bacterial meningitis is the most common form of infectious process affecting the central nervous system (CNS). The incidence ranges from 0.13 to 0.4 per 1,000 live births and is higher in preterm infants, at 1.36–2.5 per 1,000 live births. Predisposing factors include low gestational age, premature rupture of membranes, cesarean section, catheterization, and prolonged rehydration. Meningocele and spina bifida can lead to meningitis through direct infection of the meninges [2].

Scheme 1. Classification of Meningitis Causes [3]

Classification:
Microbial meningitis Viral meningitis Rickettsial meningitis Pararickettsial meningitis Bacterial meningitis Fungal meningitis
Concomitant meningitis Para- and post-infectious meningitis Post-vaccinal meningitis
Toxic-allergic meningitis Meningitis collateralis s. sympathica Meningitis occurring during systemic infections Meningitis toxica (in a strict sense) Meningitis allergica
Irritative meningitis Meningitis after cerebrospinal fluid (CSF) puncture Meningitis following the introduction of heterogeneous substances Meningitis after meningeal hemorrhage Meningitis due to sunstroke Meningitis caused by cerebral foci

The most common causes of neonatal meningitis are Gram-negative bacteria, with *Escherichia coli* (E. coli) being the most significant. Neonatal meningitis occurs in two forms: early neonatal meningitis, caused by Gram-positive cocci, affects 1/3 of affected neonates. *E. coli* may occur sporadically or occasionally as an epidemic in neonatal wards [3]. Other causative agents include *Proteus*, *Pseudomonas aeruginosa*, *Klebsiella*, *Salmonella*, *Streptococcus pneumoniae* (pneumococcus), and *Staphylococcus*, while *Neisseria meningitidis* (meningococcus) and *Listeria monocytogenes* are less frequently isolated. Other bacteria such as *Citrobacter* and *Campylobacter* are rarely encountered [3,4].

PATHOANATOMICAL CHANGES IN MENINGEAL SYNDROME

In purulent meningitis, changes occur in the meninges with the accumulation of purulent exudate in the subarachnoid space and ventricles. This leads to increased intracranial pressure and sometimes to ventricular occlusion, which may cause pyocéphaly. Purulent exudate accumulates at the base of the brain and on the convexities, commonly in pneumococcal meningitis. Inflammation can affect cranial nerves, causing blindness, deafness, or paralysis.

Endotoxin from meningococcus causes thrombosis, hemorrhages, and perivascular infiltrates, leading to degenerative changes in organs and tissues, particularly in the skin, brain, and adrenal glands. Brain edema may occur due to decreased cerebrospinal fluid pH and bacterial toxic factors, resulting in ischemia and altered consciousness. The exudate may organize, forming adhesions that can cause hydrocephalus [5].

PATHOGENESIS OF MENINGEAL SYNDROME

Bacteria such as *Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *E. coli* evade the body's defense mechanisms by adhering to mucosal cells. The bacterial capsular polysaccharide prevents phagocytosis, allowing bacteria to avoid the complement system. After surviving in the intravascular space, bacteria enter the subarachnoid space, where the body's defenses are insufficient.

Inflammation in the subarachnoid space leads to increased complement levels in the cerebrospinal fluid, while immunoglobulin concentrations remain low, contributing to the immune deficiency in this space during bacterial meningitis [5].

PATHOPHYSIOLOGY OF MENINGEAL SYNDROME

In experimentally induced infections, subcapsular components of bacteria (cell wall and lipopolysaccharide or endotoxin) are significant determinants of pathogenicity compared to surface components. For example, in the cell wall of *Streptococcus pneumoniae*, two main polymers are present: peptidoglycan and ribitol-phosphate teichoic acid. The former causes inflammation within 24 hours, while the latter does so within 5 hours [5].

Blood-Brain Barrier (BBB) Damage

The blood-brain barrier (BBB) separates cerebrospinal fluid and brain tissue from the intravascular space. The main sites are the arachnoid membrane, the epithelial layer of the choroid plexus, and the endothelium of cerebral capillaries. These capillaries are the primary sites of damage due to the endothelium's unique ultrastructural properties—sparse plasmalemmal vesicles and continuous

intracellular tight junctions, which make them resistant [5,6].

Interaction Between Leukocytes and Endothelial Cells

An essential component of the inflammatory response during bacterial meningitis is the migration of circulating leukocytes, primarily neutrophils, from the bloodstream into the cerebrospinal fluid. This process depends on interactions between endothelial cells and leukocytes.

During acute inflammation, circulating leukocytes are activated by various inflammatory mediators, such as complement components, cytokines, and bacterial lipopolysaccharide. This activation leads to leukocyte sequestration in the microcirculation, partly due to reduced deformability and increased endothelial adhesiveness [5].

Changes in Intracranial Pressure and Cerebral Blood Flow

Intracranial pressure (ICP) is often elevated during bacterial meningitis and may cause cerebral herniation, which is life-threatening. During the early hours of infection, cerebral blood flow (CBF) increases by 100–200%, which, along with brain edema, leads to intracranial hypertension.

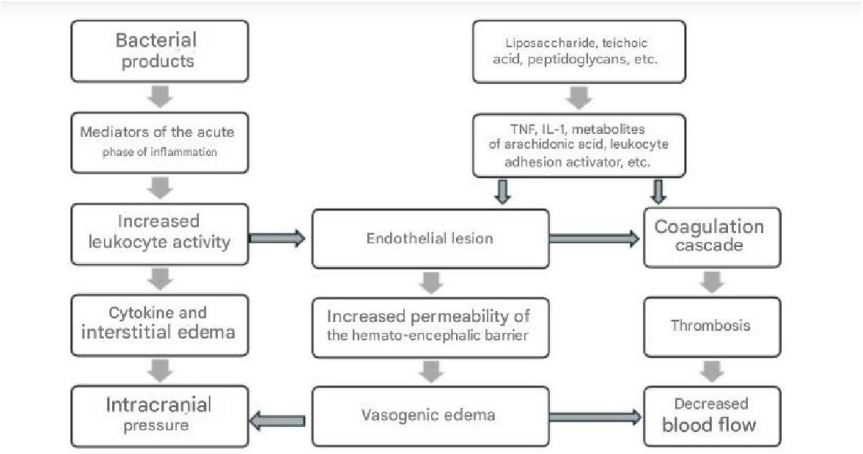
As the infection progresses, cerebral blood flow decreases while ICP continues to rise, and vasculitis develops. In approximately 30% of infants and children with bacterial meningitis, cerebral blood flow is reduced by 30–70%. Factors explaining the association between reduced cerebral blood flow and poor outcomes include inadequate delivery of energy substrates, increased metabolic demands, or inefficient substrate utilization.

Metabolic encephalopathy is believed to result from free radicals, endotoxins, prostaglandins, or other neurotoxins released during infection. Brain edema correlates with the degree of protein in cerebrospinal fluid (proteinorachia) but may also occur due to hyponatremia, which results from inappropriate antidiuretic hormone secretion [5].

Outcome of Bacterial Meningitis

The outcome of bacterial meningitis depends on cerebral perfusion pressure (CPP). The highest morbidity and mortality are observed in children with CPP below 30–50 mmHg.

Image 1. Pathophysiology of Bacterial Meningitis [3]



CLINICAL PICTURE

Meningitis cerebrospinalis epidemica

The clinical manifestations of bacterial meningitis in newborns are not characteristic.

Scheme 2. Symptomatology of Meningitis [2]

Symptomatology
Headache
Signs of irritation of spinal roots Stiff neck Vujić's phenomena: Rotational phenomena of the legs and pronation phenomena of the arms Neck phenomenon (upper Brudzinski's sign) Kernig's sign Collateral phenomenon of the legs (lower Brudzinski's sign)
Signs of irritation of bulbar centers Vomiting Bradycardia Respiratory disturbances
Signs of irritation of the brainstem at the base of the brain (basilar signs) Motor nerve injuries: III - Strabismus, miosis V - Trismus VII - Rictus sardonicus Neuritis of the optic nerve Papilledema
General neurological signs Vasomotor disturbances: Increased dermographism Sensory disturbances: Hyperesthesia Sensory disturbances: Photophobia

Symptomatology of meningitis encompasses three main syndromes: infectious, meningeal, and cerebrospinal fluid (CSF) syndromes.

INFECTIOUS SYNDROME

Initial symptoms include fatigue, general weakness, and anorexia.

MENINGEAL SYNDROME

This syndrome arises due to increased intracranial pressure and develops rapidly (within 1-3 days). Clinical manifestations include:

Headache – Intense and persistent, unrelieved by analgesics. In children, manifests as restlessness, crying, and constant head movement.

Vomiting – No relief after vomiting; referred to as "central vomiting."

Fontanelle tension – Increased intracranial pressure in infants with an open fontanelle.

Meningeal signs – Neck stiffness, Kernig's sign, Brudzinski's sign; reflexes due to pressure on the brain.

Increased sensitivity – Photophobia, hyperacusis, painful palpation of muscles.

Neurovegetative disorders – Cerebral vomiting, bradycardia, constipation, pronounced dermographism.

Altered consciousness – Ranges from drowsiness to coma, caused by fever, inflammation, edema, and intracranial pressure.

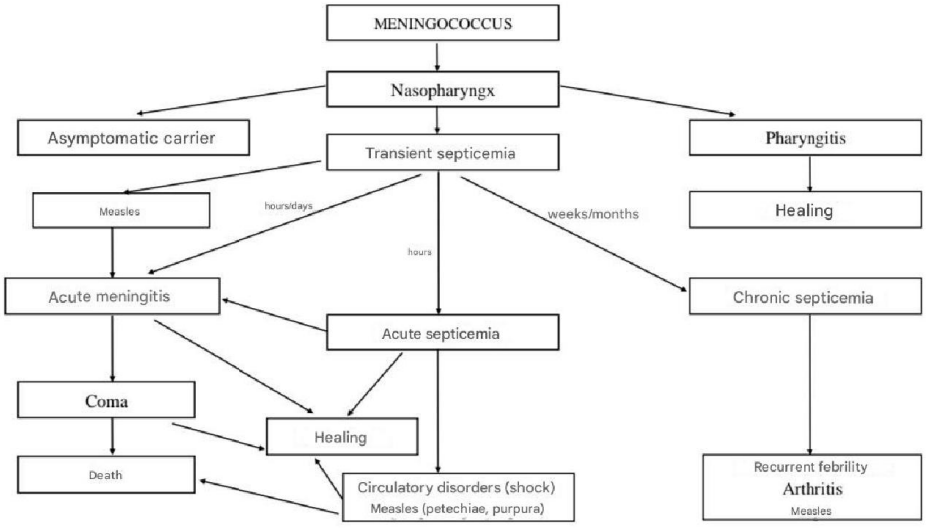
CEREBROSPINAL FLUID (CSF) SYNDROME

This includes changes in CSF accompanying acute leptomeningeal inflammation:

Clear CSF – Normal, as in serous meningitis, with a positive Pandy's reaction.

Cloudy CSF – Indicates purulent meningitis.

Figure 2. Course of Meningococcal Infection [1]



DIAGNOSIS OF MENINGEAL SYNDROME

The diagnosis of neonatal meningitis is established through medical history, clinical examination, and laboratory tests, primarily lumbar puncture. The cerebrospinal fluid (CSF) analysis includes:
White blood cell count in CSF,
Differentiation of cellular elements,
Preliminary protein level determination using Pandy's reagent,
Microscopic examination of Gram-stained CSF,
Microscopic examination of CSF sediment,
Glucose levels in CSF and blood,
Quantitative protein analysis in CSF,
CSF culture.
Other laboratory tests include:
Fundoscopic examination,
EEG,
Brain ultrasound (ECHO),
Stool culture,
Urine culture,
Blood culture,
Throat swab,
Complete blood count,
Erythrocyte sedimentation rate,
Ionogram,
C-reactive protein.
Additional methods such as immunoelectrophoresis, latex agglutination, ELISA test, and Limulus test can also be used. The diagnosis is based on the clinical presentation and CSF findings from lumbar puncture, where the CSF is typically cloudy. The primary method for bacterial detection is the microscopic examination of Gram-stained CSF sediment.

Table 1. Characteristics of Normal Cerebrospinal Fluid and Cerebrospinal Fluid from Patients with Different Types of Meningitis [3]

TYPES OF MENINGITIS				
Characteristics of cerebrospinal fluid	Normal	Bacterial	Viral Leptospirosis	Tuberculous
Appearance	clear	cloudy/purulent	Clear opalescent	Clear opalescent
Leukocyte count in mm3	(<10)	(10-3000)	(10-1000)	(10-1000)
Normal count	0-5	>1000	<200	<200
Type of leukocyte	lymphocytes	polymorphonuclear and (PMN)	lymphocyte (in the initial 10% PMN)	lymphocyte (in the initial 20-30%)
Proteins g/l	0.15-0.4	0,5-5,0+	0.5-1,0	1,0-6,0+
Glucose in mmol/l	2.55-5.5 or 55-60% blood glucose	Very low level (as low as 0)	normal	low level
Gram staining of sediments	no bacteria	+(80%)	no bacteria	+(80%) Ziehl Nielson staining-
Bacterial culture	negative	+ (90%)	negative	+ (85%)

Differential Diagnosis

In the differential diagnosis of bacterial meningitis, the following diseases are considered:
Viral meningitis
Tuberculous meningitis
Leptospirosis meningitis
Fungal meningitis
Parasitic meningitis
Brain abscess
Brain tumor
Ruptured blood vessel
Febrile convulsions, and others

I8. Complications of Meningeal Syndrome

Complications of meningitis may include:
Subdural effusion (fluid accumulation in the subdural space, manifesting with fever, convulsions, somnolence, agitation, tense fontanelle, etc.)
Ventriculitis
Abscess formation or hydrocephalus
Damage to cranial and/or spinal nerves

Prognosis of Bacterial Meningitis

The prognosis of acute bacterial meningitis depends on six key factors: the child's age, type of bacteria, speed of diagnosis, consciousness

level, presence of convulsions, and serious mechanical complications. Pneumococcal meningitis has a higher chance of complications and a higher mortality rate (20%) compared to meningococcal and Haemophilus influenzae meningitis (5-10%). The mortality rate is 40-60% in neonates, while neurological consequences (hydrocephalus, convulsions, psychomotor retardation, etc.) are registered in 31-56% of surviving children.

Viral Meningitis

Etiology

Viral meningitis is most commonly caused by enteroviruses (ECHO and Coxsackie viruses), mumps virus, and less commonly by viruses such as lymphocytic choriomeningitis (LCM), herpes virus, adenovirus, cytomegalovirus, Epstein-Barr virus, Herpes-zoster virus, influenza virus, measles, rubella, and arboviruses. In our country, the most common pathogens are enteroviruses and the mumps virus. Viral meningitis accounts for 60-70% of all meningitis cases. Enteroviruses are transmitted fecal-orally, usually during the summer months, and primarily affect children up to 10 years old. The mumps virus is transmitted by droplets, causing epidemics every 3-4 years, most commonly in children between 5-12 years. Lymphocytic choriomeningitis virus occurs sporadically, mostly in winter months, and is transmitted from rodents. Chronic serous meningitis can also be caused by pale treponema, fungi, parasites, and neoplasms.

2. Pathogenesis and Pathoanatomic Changes

Enteroviruses reach the meninges via viremia, while the mumps virus enters the body through the nasopharyngeal mucosa and then spreads through the bloodstream to the CNS. Pathohistological changes in organs are not well known due to the good prognosis of viral meningitis.

3. Clinical Picture of Viral Meningitis

Symptoms are often milder than those of bacterial meningitis, and the incubation period depends on the virus type. The disease may begin abruptly with symptoms such as headache, chills, malaise, abdominal pain, leg and back pain, vomiting, and fever. Meningeal symptoms like neck stiffness and a positive Kernig's sign are present but less pronounced than in bacterial meningitis. Additionally, enteroviral meningitis may cause lymphadenitis, pharyngitis, conjunctivitis, and rash in children under 3 years old. Mumps meningitis is typically associated with parotitis. In rare cases, convulsions or meningoencephalitis may occur during viral meningitis. Recovery is usually complete, though symptoms may last several weeks.

4. Diagnosis of Viral Meningitis

The diagnosis is based on the clinical picture, epidemiological data, and cerebrospinal fluid (CSF) analysis. The CSF is clear, with leukocyte counts ranging from 100 to 1000 per mm^3, and elevated protein levels are present along with normal glucose levels. Specific findings may include the presence of lymphocytes in the CSF. For etiology diagnosis, virus isolation from CSF, throat swab, or stool, or a rise in antibody titers may be used. Peripheral blood may show leukocytosis with lymphocytosis.

5. Treatment of Viral Meningitis

The treatment is primarily symptomatic, including analgesics, antipyretics, antiemetics, and infusions. Main therapeutic measures include:

Fluid intake: Initial fluid intake should be 800-1000 mL/m^2 body surface area, and it should be gradually increased. If sodium levels are low, diuretics and sodium chloride are used.

Intracranial hypertension treatment: This includes general and specific measures, such as raising the head by 30°, and using mannitol (0.5-2.0 g/kg) to reduce pressure.

Seizure treatment: Diazepam (0.25-0.5 mg/kg i.v.) is used to stop seizures, along with phenytoin or phenobarbital for anticonvulsant effects.

Infants, Toddlers, Preschool and School-Age Children

Etiology and Pathogenesis

Purulent meningitis in children of this age group is usually caused by *Neisseria meningitidis* (meningococcus), *Streptococcus pneumoniae* (pneumococcus), and *Haemophilus influenzae*. Less common pathogens include *Staphylococcus aureus*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Listeria monocytogenes*, *Klebsiella*, and others. Meningitis may result from the direct spread of bacteria from nearby inflamed sites, such as otitis, sinusitis, or otitis media. Meningococcus most commonly enters the body via droplets through the nasopharynx, where it may remain latent or cause nasopharyngitis, which spontaneously resolves after a few weeks. In some cases, meningococcus enters the bloodstream and causes bacteremia, which may

progress to meningitis by crossing the blood-brain barrier.

Clinical Picture

Infants: Meningitis may start abruptly with convulsions or coma, although it often begins gradually. The child becomes febrile, lethargic, irritable, refuses to feed, vomits, has diarrhea, and often becomes dehydrated. Neck stiffness may be mild, and hypotonia is common, with the head often falling backward. The key sign is a "tense fontanelle," indicating increased intracranial pressure. Other signs may include vasomotor disturbances like pale or flushed face, spleen swelling, joint swelling, and petechiae.

Preschool and school-age children: Meningitis often begins abruptly with high fever (39-40°C), headache, and vomiting. The headache becomes severe and worsens with head movements. Vomiting is frequent, and the patient complains of malaise, muscle, and joint pain. As the disease progresses, meningeal symptoms appear: neck stiffness, increased sensitivity to light (photophobia), hyperacusia, irritability, and the presence of reflexes such as Kernig's and Brudzinski's signs. In some cases, somnolence, stupor, or coma may develop. Bradycardia, dermographism, and hyperactive tendon reflexes may also be present. If the condition worsens, cranial nerve paralysis or a positive Babinski sign may occur. In 20-30% of cases, febrile herpes appears, which has diagnostic significance in epidemic meningitis.

Diagnosis and Treatment

The diagnosis and treatment of meningitis in this age group depend on the exact identification of the pathogen and prompt initiation of therapy.

1. Therapy for Infants Aged 29 to 60 Days

Due to the unpredictability of bacterial meningitis pathogens in infants of this age, treatment should start with a three-component therapy before the pathogen is identified. The recommended drug combination includes:

Ampicillin – for controlling infections caused by *Listeria monocytogenes* and *Streptococcus agalactiae*

Amikacin – for its effectiveness against gram-negative bacteria

Chloramphenicol – which covers many bacteria, including *Haemophilus influenzae* and *Streptococcus pneumoniae*

This combination provides broad-spectrum protection until the specific pathogen is identified.

Therapy for Infants Over 2 Months, Preschool, and School-Age Children

For children older than 2 months, a combination of penicillin and chloramphenicol is commonly used, while newer cephalosporins are indicated in cases where bacterial resistance is identified (particularly against *Haemophilus influenzae* and *Streptococcus pneumoniae*).

Benzylpenicillin G: 400,000 IU/kg or 10,000,000 IU/m daily, divided into 8-12 doses or continuously via infusion.

Chloramphenicol succinate: 2.5 g/m^2 daily, divided into 4-6 doses.

2. Therapy for Purulent Meningitis

Treatment for purulent meningitis requires immediate administration of antibiotics and symptomatic therapy. Antibiotic therapy should begin immediately after blood and CSF samples are taken.

Meningococcal meningitis: The drug of choice is **Penicillin G**, administered intravenously in infusions, in a dose of 300,000 IU/kg/day divided into 6 doses over 7 days. If resistance or hypersensitivity to penicillin exists, third-generation cephalosporins (e.g., cefotaxime) or chloramphenicol should be used.

Haemophilus influenzae: The preferred treatment for purulent meningitis caused by *H. influenzae* is chloramphenicol, which can be used alone or in combination with ampicillin, at doses of 300-400 mg/kg/day, divided into 4-6 doses for 10-14 days.

Gram-negative bacteria: For meningitis caused by gram-negative bacteria, second-generation cephalosporins are more effective than aminoglycosides or ampicillin.

Symptomatic therapy includes:

Fluid and electrolyte replacement via saline and

Table 2. Antibiotics Most Commonly Used in the Treatment of Neonatal Meningitis [3]

Name of the medicine	T.M.	<2000	T.M.	>2000
	Age from 0-7 days	7 days	0-7 days	7 days
Amikacin	15mg/kg (2)	15-22,5mg/kg (2)	20mg/kg (2)	30mg/kg (3)
Gentamicin	5mg/kg (2)	7,5mg/kg (3)	5mg/kg (2)	7,5mg/kg (3)
Ampicillin	100mg/kg (2)	150mg/kg (3)	150mg/kg (2)	200mg/kg (4)
Penicillin G	100.000ij/kg (2)	150.000ij/kg (3)	150.000ij/kg (3)	200.000ij/kg (4)
Cefotaxime	100mg/kg (2)	150mg/kg (3)	100mg/kg (2)	150mg/kg (3)
Methicillin	100mg/kg (2)	159mg/kg (2)	150mg/kg (3)	200mg/kg (4)
Chloramphenicol	25mg/kg (2)	25-59mg/kg (2)	25mg/kg (1)	50mg/kg (2)

CONCLUSION

Based on the presented facts and data, we can conclude the following:

Purulent meningitis is a disease that is widespread worldwide, occurring sporadically, except when caused by meningococcus, which can appear endemically and epidemically.

Epidemics are usually caused by meningococcus group A, and they most commonly occur at the end of winter and the beginning of spring.

The source of infection is more often a healthy carrier (about 10% of the general population are healthy carriers, and among those who have been in contact with individuals suffering from meningeal meningitis, this percentage is higher, around 25%), and less frequently a patient.

Viral meningitis is usually a disease of school-age children and younger individuals.

Serous meningitis is usually a disease of school-age children and younger individuals.

Tuberculous meningitis always ends in death if treatment is delayed.

Clinical study results have shown that early adjuvant therapy with dexamethasone significantly reduces the frequency of neurological sequelae in affected children.

The most commonly used therapy is penicillin, followed by third-generation cephalosporins or chloramphenicol.

The fatal outcome occurs in 40 to 60% of affected neonates, while neurological sequelae are observed in 31 to 56% of surviving children.

Based on all the above, we can conclude that meningeal syndrome represents a significant practical and theoretical problem that requires extensive epidemiological and clinical investigations.

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MYOCARDIAL INFARCTION WITH NON-OBSTRUCTIVE CORONARY ARTERY DISEASE (MINOCA) - CASE REPORT

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Summary:Introduction: Acute coronary syndrome type myocardial infarction with non-obstructive coronary artery disease (MINOCA) represents a myocardial infarction without coronary artery stenosis or with stenosis less than 50%. The aim of this paper is to highlight MINOCA as a relatively new entity in cardiology, the importance of early diagnosis and timely treatment, as well as the application of primary and secondary prevention of cardiovascular diseases along with the modification of risk factors for these conditions. Case presentation: A 60-year-old female patient presents with chest pain described as tightness and pressure. The physical examination is normal, while the electrocardiogram shows ST-segment depressions in leads V4-V6 ranging from 0.5 mm to 1 mm. The patient was treated according to the protocol for non-ST-elevation myocardial infarction (NSTEMI). Coronary angiography was immediately performed and found to be normal. Treatment was continued with medical therapy. Conclusion: MINOCA encompasses a heterogeneous group of patients who experience myocardial infarction but do not have significant coronary artery obstruction on angiogram. Our patient had a typical presentation of non-ST-elevation infarction and was treated with medical therapy to reduce cardiovascular risk for future events and improve outcomes.

Key words: Acute coronary syndrome (ACS), Myocardial infarction without persistent ST elevation (NSTEMI), Prevention, Myocardial infarction with non-obstructive coronary artery disease (MINOCA), Treatment, Prevention

INTRODUCTION

Acute coronary syndrome (ACS) accounted for 48.3% of all deaths from ischemic heart diseases in Serbia in 2022. According to data from the population registry for ACS, in 2022, the diagnosis of acute coronary syndrome was made in 19,701 cases in Serbia. During 2022, 4,564 people in Serbia died from this syndrome. Myocardial infarction with non-occlusive coronary arteries (MINOCA) refers to a clinical situation in which a patient exhibits symptoms suggestive of acute coronary syndrome (ACS), with elevated troponin levels, but coronary angiography shows no significant obstruction of the coronary arteries (defined as stenosis <50% in any major epicardial artery). The reported prevalence of MINOCA significantly varies in different studies, ranging from approximately 1% to 14% of ACS patients undergoing angiography [1].

Acute coronary syndrome can present as unstable angina pectoris, acute myocardial infarction with or without ST elevation, or de novo left bundle branch block, as well as sudden cardiac death [2,3]. The definition of acute myocardial infarction (MI) involves myocardial cell necrosis with a clinical picture consistent with acute myocardial ischemia. Acute myocardial damage, associated with an increase and/or decrease in high-sensitivity troponin (hs-cTnI) levels and caused by myocardial ischemia, is referred to as acute myocardial infarction. If a patient experiences symptoms along with newly elevated ST segments in two contiguous leads or a newly developed bundle branch block, this is classified as STEMI (ST-Elevation Myocardial Infarction). In contrast, if no persistent ST segment elevation is observed, it is classified as NSTEMI (Non-ST-Elevation Myocardial Infarction) [4,5,6].

MINOCA can be considered a COMMON term that encompasses a heterogeneous group of underlying causes: coronary and non-coronary, which may include both cardiac and extracardiac disorders (Figure 1.).

Figure 1. MINOCA - a common term encompassing a heterogeneous group of coronary and non-coronary causes.
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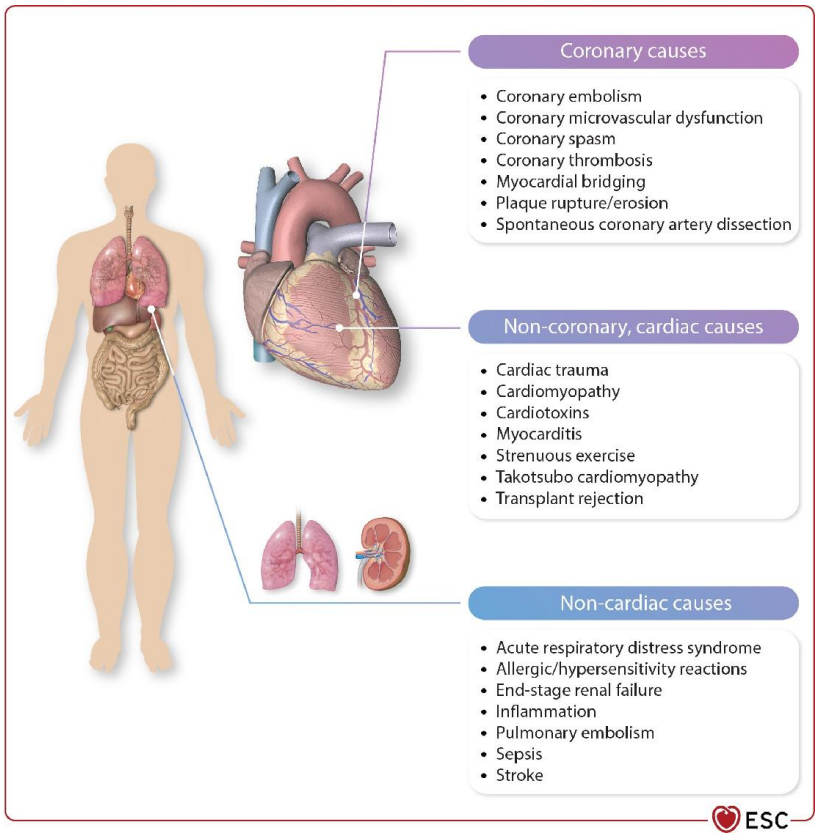

When the diagnosis is not clearly established after coronary angiography, MINOCA represents a working, rather than a final, diagnosis. It is crucial that clinicians conduct additional assessments and investigations to identify the underlying cause of MINOCA, which will enable a definitive diagnosis and appropriate treatment for the patient. Failure to identify the underlying cause of MINOCA may lead to inadequate or inappropriate therapy [1]. If the underlying cause of MINOCA cannot be determined solely through invasive coronary angiography (ICA), further assessments of microvascular function and coronary artery reactivity, as well as intravascular imaging, should follow. The term "functional coronary angiography" refers to the combination of standard coronary angiography with additional tests (e.g., testing for coronary microcirculation dysfunction and vasoreactivity) (Figure 2).

Figure 2. MINOCA diagnostic algorithm. Evaluation of patients with a working diagnosis of MINOCA.
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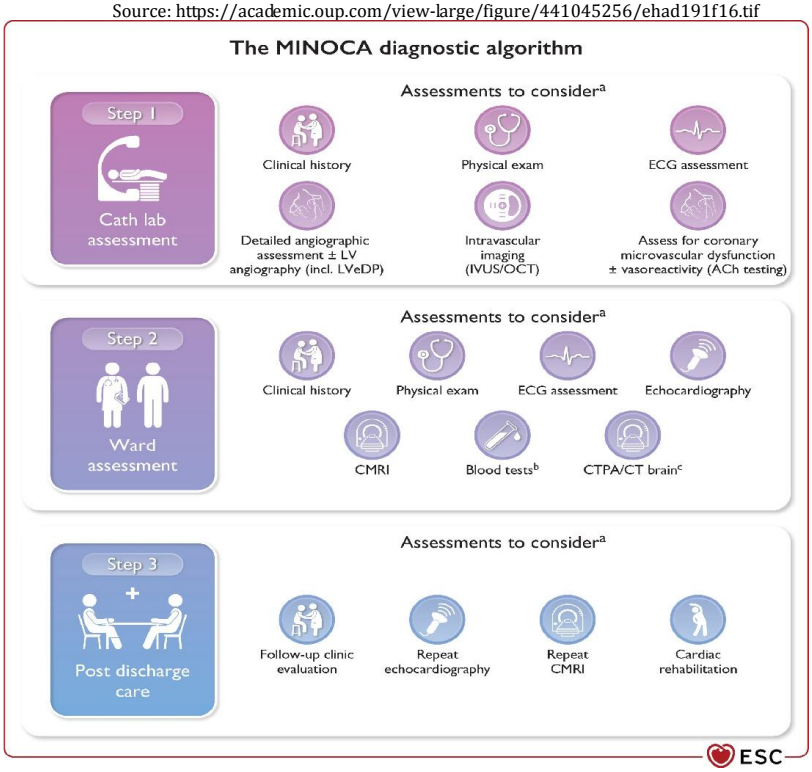


If the underlying cause of MINOCA cannot be determined through functional coronary angiography, non-invasive imaging is recommended (e.g., echocardiography, CMR, CT angiography, CT heart), according to the clinical indication. Cardiac magnetic resonance (CMR) is one of the key diagnostic tools for determining the underlying cause of MINOCA [7–11]. CMR can identify the underlying cause in up to 87% of patients with a working diagnosis of MINOCA and should be performed as soon as possible after patient admission, ideally during the initial hospitalization [12]. (Table 1)

Table 1. Recommendations for myocardial infarction with non-occlusive coronary arteries (MINOCA)
Source: https://academic.oup.com/view-large/441045259

Recommendations	Class[a]	Level[b]
In patients with a working diagnosis of MINOCA, CMR imaging is recommended after invasive angiography if the final diagnosis is not clear.	I	B
Management of MINOCA according to the final established underlying diagnosis is recommended, consistent with the appropriate disease-specific guidelines.	I	B
In all patients with an initial working diagnosis of MINOCA, it is recommended to follow a diagnostic algorithm to determine the underlying final diagnosis.	I	C

CMR, cardiac magnetic resonance; MINOCA, myocardial infarction with non-obstructive coronary arteries.
[a]Class of recommendation.
[b]Level of evidence.

Determining the underlying cause of MINOCA enables the initiation of appropriate therapy in accordance with the final diagnosis. Secondary preventive therapy should be considered for patients with evidence of coronary atherosclerotic disease and for the control of risk factors.

Treatment of Takotsubo syndrome is not based on prospective randomized controlled trials, so therapy is mainly based on supportive and empirical strategies [13,14]. Treatment of patients with myocarditis is carried out according to the recommendations of the working group for myocardial diseases of the European Society of Cardiology (ESC) [15,16].

Ischemia without infarction with non-occlusive coronary arteries (INOCA) has been described in the context of chronic coronary syndromes (CCS) [17,18].

CASE REPORT

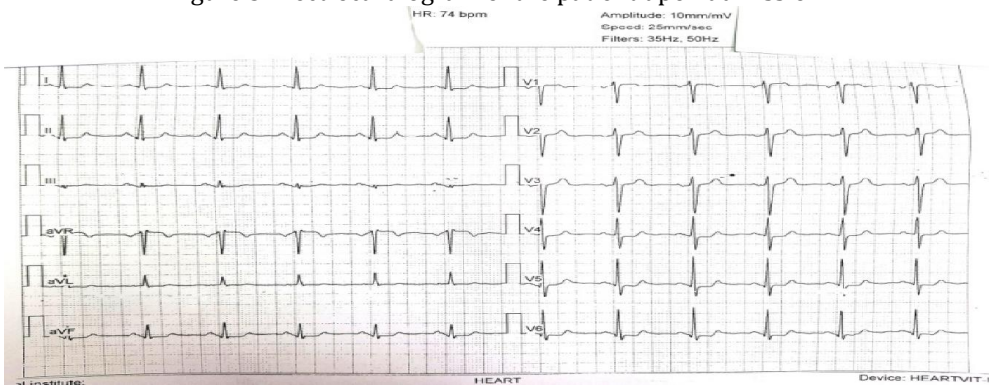
A 60-year-old female patient presents with chest pain described as tightness and pressure at rest. She reports that the day before seeing the doctor, she felt chest pain resembling tightness and pressure. The pain occurs with exertion, most often when walking uphill, lasts longer than half an hour, radiates through the left side of the chest, and decreases with cessation of exertion, which corresponds to the clinical picture of unstable angina pectoris. She had no similar symptoms previously.

The family history was unremarkable. From the personal history, we learn that she is being treated for arterial hypertension and dyslipidemia and is a non-smoker.

Physical examination: Inspection revealed that the patient is conscious, oriented, mobile, of medium osteomuscular build and nutritional status, afebrile, eupneic, and with normal heart sounds. She appears to be moderately ill. The auscultatory findings on the heart and lungs are normal. Blood pressure is 160/90 mmHg. Heart rate is 75/min.

The electrocardiogram shows sinus rhythm, normal axis, a heart rate of 75/min, with ST segment depression in the anterolateral leads V4-V6 of 0.5 to 1 mm (Figure 3).

Figure 3. Electrocardiogram of the patient upon admission



The patient was admitted with a diagnosis of acute coronary syndrome type unstable angina, and during hospitalization, the first cardiac biomarker, high-sensitivity troponin (hs-cTnI), was 4.3 ng/l, which was normal. The following day, hs-cTnI was repeated and found to be 79.2 ng/l, showing an increase of approximately 20 times from the first value, and 7 times higher than the upper reference limit (reference range 0.0-11.6 ng/l), which led to the definitive diagnosis of non-ST-elevation myocardial infarction.

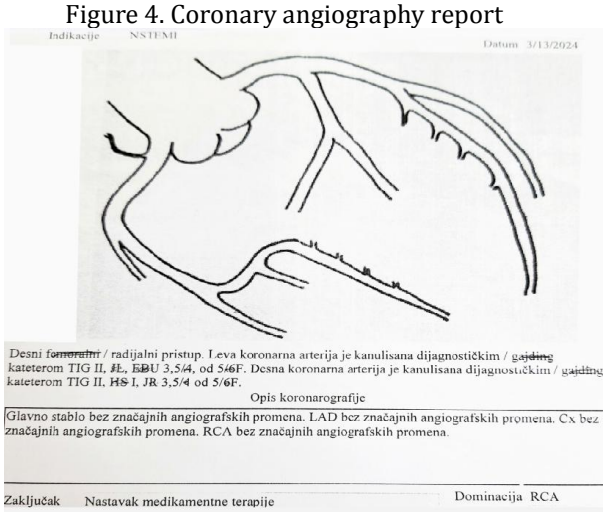
Laboratory tests were performed:

Analysis	Result	Comment
Glycemia	4,6 mmol/l	*Normal*
Creatinine	74,7 umol/l	*Normal*
Cholesterol	8,1 mmol/l	*Elevated*
Triglycerides	1,3 mmol/l	*Normal*
CRP	4,4 mg/l	*Normal*
AST	45 IU/l	*Slightly elevated*
ALT	23 IU/l	*Normal*
CK	150 IU/l	*Normal*
LDH	921 IU/l	*Elevated*
Complete blood count within reference range		
BNP	*17 pg/l*	*Normal (ref. range 0,0-100,0 pg/l)*

Treated according to the NSTEMI protocol. The therapy included low-molecular-weight heparin, dual antiplatelet therapy (DAPT), the beta-blocker nebivolol, ACE inhibitor, calcium channel blocker, diuretic, proton pump inhibitor, and nitroglycerin as needed.

According to the NSTEMI criteria and the significant increase in serum troponin levels, coronary angiography was performed, which showed no significant angiographic changes in the main stem, LAD, Cx, and RCA (Figure 4

Figure 4. Coronary angiography report


Indikacije NSTEMI

Datum 3/13/2024

Desni ~~femoralni~~ / radijalni pristup. Leva koronarna arterija je kanulisana dijagnostičkim / ~~gajding~~ kateterom TIG II, ~~JL~~, ~~EBU~~ 3,5/4, od 5/6F. Desna koronarna arterija je kanulisana dijagnostičkim / ~~gajding~~ kateterom TIG II, ~~HS~~ I, JR 3,5/4 od 5/6F.

Opis koronarografije

Glavno stablo bez značajnih angiografskih promena. LAD bez značajnih angiografskih promena. Cx bez značajnih angiografskih promena. RCA bez značajnih angiografskih promena.

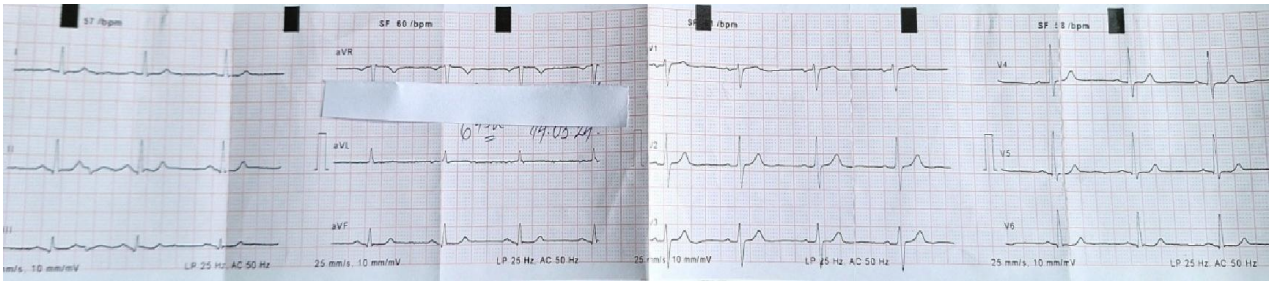
Zaključak Nastavak medikamentne terapije Dominacija RCA

Given the absence of significant stenosis, medical and pharmacological therapy was continued. During the further course of hospitalization, to determine the cause of MINOCA, an echocardiogram was performed: concentric hypertrophy of the left ventricular walls, with normal systolic function, ejection fraction (EF) = 60%, without clear segmental abnormalities in contractility, which excludes a large infarction and supports the possibility of a subendocardial infarction in the presence of myocardial hypertrophy.

Throughout the course, the patient remained stable and cardially compensated. Further investigation of the definitive cause of non-occlusive infarction is recommended according to the MINOCA algorithm: stress echo test and cardiac magnetic resonance imaging (CMRI), and in the event of worsening symptoms, functional coronary angiography with intravascular ultrasound (IVUS) and optical coherence tomography (OCT), as well as microvascular dysfunction and coronary vasospasm tests [1].

At discharge, the patient was without chest pain, with a normal blood pressure value of 130/90 mmHg, and a normalized ECG: sinus rhythm, normal axis, heart rate 70/min, without ST-T changes (Figure 5).

Figure 5. ECG of the patient at discharge



Therapy at Discharge: DAPT, beta blocker nebivolol; ACE inhibitor, calcium channel blocker and diuretic as a fixed combination, proton pump inhibitor, and nitroglycerin as needed.

DISCUSSION

According to the fourth universal definition of myocardial infarction, there are several subtypes of myocardial infarction. There is a group of patients with MI without angiographically obstructive coronary artery disease (without stenosis of 50% or more in a large epicardial vessel), and the term myocardial infarction without coronary artery obstruction (MINOCA) has been adopted for this entity. Prevalence is estimated at 6-8% [4], but it is heterogeneous and varies from 1% to 14% of patients with ACS [1]. MINOCA is more common

in women, as well as in patients presenting as NSTEMI [4]. The criteria for diagnosing MINOCA are:

1. *Criteria for diagnosing acute myocardial infarction:*
   a) Positive cardiac biomarkers (preferably cardiac troponin);
   b) Clinical evidence of myocardial infarction, including: ischemic symptoms, new or presumed new significant ST-T changes or new left bundle branch block (LBBB), development of pathological Q waves, evidence by imaging method of newly developed myocardial viability loss and impaired regional wall motion, identification of coronary thrombus on angiography or autopsy,
2. *Absence of coronary artery obstruction,*
3. *Absence of a clear clinical cause for the AMI presentation* [19, 20].

The causes of troponin elevation, as the most sensitive markers, can be divided into coronary and non-coronary causes. Coronary causes include: vasospastic angina, coronary microvascular dysfunction, rupture/erosion of an atherosclerotic plaque, spontaneous coronary thrombosis or embolism, and overlooked obstructive CAD. Non-coronary causes can be cardiac disorders: myocarditis, Takotsubo cardiomyopathy, other cardiomyopathies (dilated, hypertrophic), and non-cardiac disorders such as pulmonary embolism, renal insufficiency, and sepsis [21, 22]. An individualized approach to therapy is essential.

Our patient presented with new-onset chest pain and was observed to have shallow ST depressions on the ECG. She was hospitalized in the intensive care unit and treated according to the non-STEMI acute coronary syndrome protocol. Coronary angiography was performed, after which she was diagnosed with MINOCA. Throughout the course, she had no recurrent angina and no dynamic electrocardiographic changes. She was discharged with recommendations for hygiene-dietary regime measures and pharmacological therapy. Patient education was provided on the importance of maintaining an ideal body mass index, a diet rich in fruits and vegetables, the significance of daily moderate physical activity, and achieving target blood pressure and cholesterol levels.

CONCLUSION

Myocardial infarction with non-obstructive coronary artery disease (MINOCA) is a relatively new entity in cardiology and encompasses a heterogeneous group of patients who do not have significant coronary artery obstruction on angiography. The aim of this paper is to highlight MINOCA as a relatively new entity in cardiology, the importance of early diagnosis and timely treatment, as well as the application of primary and secondary prevention of cardiovascular diseases with modification of risk factors. The presented patient, based on the symptoms of angina and ST segment depression on the ECG, was initially diagnosed as a classic acute coronary syndrome without persistent ST elevation but with significantly elevated troponin levels, as a myocardial infarction with probable severe coronary stenosis or occlusion. However, the normal coronary angiography result classified her into the relatively rare MINOCA group. The patient was treated according to the acute coronary syndrome protocol, and during the course of hospitalization, there were no complications. She was discharged for further home treatment with pharmacological therapy, including dual antiplatelet therapy, and advice on hygiene-dietary measures to modify risk factors. The patient was advised to have regular check-ups and was referred for cardiac magnetic resonance imaging, which, according to the MINOCA algorithm, would clarify the cause of the infarction.

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CEREBRAL VENOUS SINUS THROMBOSIS AS A COMPLICATION OF MASTOIDITIS – A CASE REPORT WITH LITERATURE REVIEW

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Abstract: Introduction: Mastoiditis is the inflammation of the mastoid part of the temporal bone, specifically the mastoid air cells. It most commonly occurs as a complication of middle ear infection. Mastoiditis is a clinical diagnosis, and antibiotics play a central role in its treatment. Cerebral venous sinus thrombosis is a rare intracranial complication of acute mastoiditis. Case Presentation: A 49-year-old patient presented with tinnitus in the left ear, vertigo accompanied by nausea and vomiting, and stiffness on the left side of the neck. A general clinical and neurological examination was performed, which was normal at that time. Otoscopic examination of both ears was also normal. The patient was afebrile. Symptomatic treatment was prescribed, including analgesics, muscle relaxants, Betahistine, and a B-complex vitamin. Two days later, the patient returned with worsened symptoms, including a feeling of fullness and pain in the left ear, occasional discharge from the same ear, and severe pain and stiffness in the left side of the neck. Due to significant pain, the clinical examination was limited. Inspection revealed retroauricular swelling in the area of the left mastoid and the left side of the neck. The patient was urgently referred for consultation with an otorhinolaryngologist and neurologist at a regional hospital, who indicated an urgent non-contrast CT of the endocranium and laboratory tests. A contrast-enhanced CT of the endocranium confirmed the presence of venous sinus thrombosis along with inflammation of the left mastoid air cells. Radical trepanation of the temporal bone/mastoidectomy on the left side was performed. During hospitalization, parenteral antibiotic, anticoagulant, and supportive therapy were administered. The patient reported subjective improvement with the treatment, and follow-up clinical, laboratory, and CT findings indicated regression of the inflammatory process. Conclusion: In patients with ear pain, the most common symptom of middle or outer ear infection, it is important during the examination to identify typical signs of retroauricular inflammation (swelling, redness, and tenderness) as an indication of mastoiditis. Mastoiditis is the second most common complication of acute otitis media. Timely diagnosis and appropriate treatment of mastoiditis reduce the risk of complications, such as cerebral venous sinus thrombosis.

Keywords: otitis media, cerebral veins, otalgia

UVOD

Mastoiditis is an inflammation of the mastoid part of the temporal bone, specifically the mastoid air cells. Since children are more susceptible to middle ear infections, they are at an increased risk of developing acute mastoiditis compared to adults. Most commonly, acute mastoiditis is a complication of acute otitis media (middle ear infection). Subacute middle ear infections cause subacute mastoiditis. Although rare, other causes of mastoiditis lead to an infection of only the mastoid air cells, which is called early mastoiditis.

Mastoiditis can be divided into three categories based on the mechanism of infection:

- Early Mastoiditis: Involves infection of only the mastoid air cells without spreading into the middle ear cavity.
- Acute Mastoiditis (the most common form): Infection of the epithelial mucosa with erosion through the bony septations of the mastoid air cells. This erosion can progress to the formation of an intracavitary abscess, which may further spread to adjacent structures.
- Subacute Mastoiditis: Occurs after a persistent middle ear infection or repeated episodes of acute otitis media with inadequate antimicrobial therapy, leading to a persistent infection and

erosion of the bony septations between the mastoid air cells. [1].

With the advent of antibiotics, the development of acute mastoiditis and progression to dangerous complications is unlikely. However, if left untreated, mastoiditis can lead to life-threatening complications, including meningitis, intracranial abscess, and venous sinus thrombosis [2].

The most common pathogen in mastoiditis is Streptococcus pneumoniae. Other common pathogens include Staphylococcus aureus, Streptococcus pyogenes, and Haemophilus influenzae. Risk factors for mastoiditis include age under two years, immunocompromised conditions, recurrent acute otitis media, or incomplete pneumatization of the mastoid process [3].

In adults, the most common symptoms of mastoiditis are otalgia (ear pain), otorrhea (ear discharge), and hearing loss, with typical retroauricular signs of mastoiditis usually present (i.e., swelling, erythema, tenderness in the retroauricular area).

Otoscopy will reveal bulging of the posterior superior wall of the external auditory canal and bulging with pus behind the tympanic membrane. The tympanic membrane is often perforated, with drainage of purulent material. A normal tympanic membrane generally, but not always, rules out acute mastoiditis [4].

Mastoiditis is a clinical diagnosis. Laboratory tests and radiological imaging methods are used as adjuncts when the diagnosis is uncertain or when complications of acute mastoiditis are being considered. Laboratory analyses include a complete blood count (CBC) with leukocyte formula, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Typically, an elevated white blood cell count and increased inflammatory markers (ESR, CRP) are observed. Radiological assessment of acute mastoiditis involves CT and MRI imaging [5].

Antibiotics play a central role in the treatment of mastoiditis. Additional invasive therapeutic measures, including myringotomy, tympanostomy, and mastoidectomy, may be indicated depending on the severity of the infection [5].

Complications of mastoiditis occur when the infection spreads outward toward the periphery or inward toward the brain. Depending on the direction, extracranial complications may include subperiosteal abscess, facial nerve paralysis, labyrinthitis, petrositis, and Bezold's abscess, while intracranial complications include meningitis, intracranial abscesses, and cerebral venous sinus thrombosis [6,7]. These patients often present clinically with seizures, neck stiffness, headache, and altered mental status.

Cerebral Venous Sinus Thrombosis (CVST) is a rare complication of acute mastoiditis, with a declining incidence in the post-antibiotic era [8]. It involves partial or complete occlusion of a sinus or cerebral vein. The earliest description dates back to the first half of the 19th century. Since then, it has become increasingly recognized due to the widespread availability of advanced imaging techniques, such as CT venography, MR venography, and digital subtraction angiography [9].

The most common sites of occlusion are the transverse sinuses (44–73%), superior sagittal sinus (39–62%), sigmoid sinus (40–47%), deep venous system (10.9%), and cortical veins (3.7–17.1%) [10].

The clinical presentation of CVST is variable. Headache is typically the most common symptom (88.8%), followed by seizures (39.3%) and paresis (37.2%). It may also present with other focal neurological deficits or altered mental status. Intracranial hemorrhage occurs in 30–40% of patients [11].

CASE REPOST

A 49-year-old patient presented to a general practice clinic complaining of tinnitus in the left ear for the past 7 days, vertigo accompanied by nausea and a single episode of vomiting, as well as stiffness in the left side of the neck. Upon reviewing the patient's medical records, it was noted that he had been treated for left middle ear infection on several occasions over the past year. He has arterial hypertension, which is well-controlled with regular antihypertensive therapy. He has no other known medical conditions.

A general clinical and neurological examination was performed, both of which were unremarkable at that time. Otoscopy of both ears was also normal. The patient was afebrile. Symptomatic treatment was prescribed, including analgesics, muscle relaxants, betahistine, and a vitamin B complex.

Two days later, the patient returned with worsening of the described symptoms, including a feeling of fullness and pain in the left ear, as well as intermittent discharge from the same ear. There was also severe pain and stiffness in the left side of the neck. Due to the patient's intense pain and poor cooperation, the clinical examination was limited. Inspection revealed swelling in the area of the left mastoid and left side of the neck. The patient was urgently referred for consultation with an otorhinolaryngologist (ENT specialist) and a neurologist at the regional hospital. They recommended an urgent non-contrast CT of the endocranium and laboratory tests, which showed: CRP: 224.5 mg/L; Leukocytes: 15 x 10^9/L; Platelets: 41 x 10^9/L; Erythrocytes: 3.6 x 10^{12}/L; Hemoglobin: 120 g/L; Hematocrit: 0.33 L/L. The CT scan revealed the presence of gas inclusions tracking in the region of the jugular canal and the lumen of the left jugular vein, indicating venous sinus thrombosis. The left mastoid air cells and inner ear were filled with hypodense material, most likely inflammatory in nature, consistent with mastoiditis.

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The patient was transported on the same day to the Emergency Center of UKCV, where laboratory tests were repeated: CRP: 231.6 mg/L; PCT: 135.58 ng/mL; Leukocytes: 9.47 x 10^9/L; Erythrocytes: 3.7 x 10^{12}/L; Hemoglobin: 119 g/L; Hematocrit: 0.34 L/L; Platelets: 42 x 10^9/L. A contrast-enhanced CT of the endocranium was also repeated. The scan showed complete opacification of the left mastoid air cells, primarily of inflammatory etiology. Post-contrast delayed studies revealed that the sigmoid sinus, along with the adjacent bony structures, did not opacify, unlike the contralateral side, with visible gas particles within the sinus—indicative of left venous sinus thrombosis. Additionally, in continuity with the left sigmoid sinus, the left transverse sinus was observed to be partially thrombosed with visible gas particles.

An urgent admission to the ENT Clinic and Head and Neck Surgery was indicated. Upon clinical examination at admission, it was noted that the left mastoid was slightly swollen and painful on palpation. Otomicroscopic examination of the left external auditory canal revealed it to be filled with a large amount of purulent material, which was irrigated. The skin of the ear canal showed no changes. Whitish deposits were present pre-tympanically, and the tympanic membrane displayed pronounced vascularization with a diffuse light reflex. A paracentesis was performed, yielding a small amount of purulent material. An urgent radical mastoidectomy (trepanation of the temporal bone) was performed on the left side, and the surgical material was sent for pathohistological verification. The findings were: Inflammatio phlegmonosopurulenta acuta mucosae (acute phlegmonous-purulent inflammation of the mucosa). Additionally, cholesteatomatous debris was found in the examined material. Intraoperatively, a swab of the purulent material was taken, and Actinomyces spp. was isolated. During hospitalization, the patient received parenteral antibiotic therapy, anticoagulant therapy (LMWH), and supportive care. Laboratory parameters and CT scans of the endocranium (native and with contrast) were regularly monitored. The patient reported subjective improvement with the applied therapy, and follow-up clinical, laboratory, and CT findings indicated regression of the inflammatory process. Upon completion of hospitalization, the patient was advised to continue treatment with oral antibiotics and LMWH, with a transition to oral anticoagulants (Acenocoumarol). The LMWH was overlapped with Acenocoumarol for about five days to achieve a PT/INR ratio of 2.0–3.0, with INR monitored in the therapeutic range. On follow-up visits over the next six months after hospitalization, the patient reported feeling well, with normal clinical and laboratory findings.

DISCUSSION

Since ear pain is the most common sign of middle or external ear inflammation, patients often first present to their primary care physician or the on-duty doctor at the emergency service. It is crucial that during the examination, the presence of typical signs of retroauricular inflammation (swelling, redness, and retroauricular tenderness) is recognized, as these may indicate the presence of mastoiditis. This is important because mastoiditis is the second most common complication of acute otitis media, after tympanic membrane perforation. Timely diagnosis and appropriate treatment of mastoiditis reduce the risk of developing potentially fatal complications. Palma et al., in a retrospective study of 62 patients with mastoiditis, reported that out of

the total number of patients, 48.4% exhibited typical retroauricular signs of inflammation and bulging of the posterior-superior wall of the external auditory canal. In 51.6% of patients, signs of retroauricular inflammation were not observed, and the diagnosis was based on CT findings.

Typical signs of retroauricular inflammation were observed in 53.4% of cases where mastoiditis developed as part of acute otitis media, and in 36.8% of cases where mastoiditis occurred with subacute otitis media. Of the total number of patients, 50% had a fever upon admission, and 21% had a temperature of 38°C [12]. This study supports the notion that in a significant number of patients, mastoiditis can be easily overlooked, even with a careful clinical examination.

If a patient presents with clinical signs and symptoms of acute mastoiditis, they should be referred for an urgent ENT consultation, as the patient will likely require hospital admission for parenteral antibiotics, myringotomy, tympanostomy tube placement, and possibly mastoidectomy. For patients who present with frequent episodes of acute otitis or chronic otitis media who are otherwise stable and show no signs of mastoiditis, an outpatient ENT consultation is recommended to discuss the risk and prevention of mastoiditis [13].

Most patients with uncomplicated acute mastoiditis resolve their symptoms with conservative measures, including antibiotics, corticosteroids, and myringotomy (tympanic membrane incision, paracentesis), without the need for mastoidectomy. It is crucial to monitor patients closely, especially in the first 48 hours of treatment. If the patient's clinical status does not improve or worsens after admission, mastoidectomy is indicated [14]. There is ongoing debate among physicians regarding the treatment of otitis media, specifically the use of antibiotics and the consequences of untreated infections. As mentioned, otitis media can progress to mastoiditis, which may lead to fatal complications.

Many cases of otitis media are viral, yet patients are often prescribed antibiotics. From a physician's perspective, it is extremely difficult to determine whether a patient's infection is bacterial or viral based on physical examination alone. Patient history can aid in diagnosis, but it remains a significant challenge. This uncertainty may lead to the overprescription of antibiotics and subsequent antibiotic misuse, contributing to the development of antibiotic-resistant infections. On the other hand, physicians must consider the consequences of untreated infections. Ultimately, to improve patient outcomes, physicians must:

Take a detailed medical history,

Perform an adequate physical examination,

Consult an ENT specialist in unclear cases, as even a seemingly simple ear infection can result in a fatal outcome.

To enhance the overall healthcare system's performance, further studies should investigate the outpatient management of uncomplicated acute mastoiditis. Avoiding hospital admission can prevent iatrogenic complications, improve patient satisfaction, and reduce healthcare costs [13].

Cerebral venous sinus thrombosis (CVST) is a rare form of venous thromboembolism (VTE) in the adult population, with an incidence of 3–4 per 1,000,000, and it is more common in women, with a 3:1 ratio compared to men [15].

Acute otitis and mastoiditis are significant risk factors for CVST due to the spread of infection from small venules draining the mastoid air cells into the sigmoid sinus, leading to the direct spread of inflammation. This process can cause occlusion of cerebral veins and dural venous sinuses, delaying cerebrospinal fluid (CSF) absorption, which in turn increases venous pressure, resulting in elevated intracranial pressure, also known as intracranial hypertension [16].

Other risk factors include: Oral contraceptive use, Puerperium, Head trauma, Direct injury during neurosurgical procedures. Women on oral contraceptives and patients with active cancer are in a prothrombotic state, further increasing the risk of cerebral sinus thrombosis [17].

Clinical manifestations of CVST vary: 30% present acutely within 48 hours of blockage, 50% present subacutely (between 48 hours and 30 days), 20% may present anytime between 30 days and six months [15]. Ipsilateral headache is present in nearly 90% of adult patients diagnosed with CVST [15,17]. In addition to headache, CVST patients may exhibit: Edema and tenderness over the mastoid process (Griesinger's sign), Nausea and vomiting, Altered mental status, Seizures, Focal motor deficit, Diplopia, Otalgia [15–17].

Reports indicate that 13.2% of patients may experience visual deficits, likely due to papilledema from increased intracranial pressure [15,16,18]. Ophthalmoplegia may also occur due to paralysis of the oculomotor, abducens, or trochlear nerves, often associated with eye pain [15–17]. If untreated, elevated intracranial pressure can lead to life-threatening complications, including: Permanent blindness, Status epilepticus, Coma, Death from cerebral herniation [17]..

When clinical suspicion is high, a definitive diagnosis requires neuroimaging. Brain MRI combined with MR venography (MRV) is the most sensitive and best modality for diagnosis [17,19]. Computed Tomography Venography (CTV) and MRV both have a sensitivity of 95% [15]. Interestingly, a study in the literature describes the use of ultrasound in identifying complications of mastoiditis. In a population of 10 patients, ultrasound identified complications in 9 cases. Currently, CT scanning is the standard of care; however, given the promising results of this study, further research into using ultrasound to identify mastoiditis complications should be considered.

This is especially important for the pediatric population, as it may prevent unnecessary radiation exposure from CT scans. Even if ultrasound serves only as an adjunct for screening patients who eventually undergo CT scanning, the benefit is significant for both the pediatric population and overall healthcare costs [20]. When a diagnosis of cerebral venous sinus thrombosis (CVST) is made, it is imperative to initiate anticoagulation (AC) with heparin. A meta-analysis showed that starting heparin is associated with an absolute reduction in mortality of 13% [15,17].

The most commonly used anticoagulants are unfractionated heparin (UFH) or low molecular weight heparin (LMWH). Due to practical advantages, LMWH is recommended over UFH [15]. There is insufficient evidence regarding the use of new anticoagulants.

For individuals with transient risk factors, such as infection, trauma, or pregnancy, the duration of anticoagulation therapy is typically three months, or three to six months [15]. For those with predisposing prothrombotic conditions, such as active cancer, the duration is longer—approximately six to twelve months [15].

Endovascular thrombolysis for rapid recanalization and decompressive craniotomy may be considered in life-threatening cases that do not respond to anticoagulant therapy [15].

Historically, CVST was associated with a high mortality rate due to life-threatening complications. However, with advances in neuroimaging and early treatment, mortality rates have decreased to less than 3% [16]. The prognosis for CVST is generally favorable.

Preter et al. conducted a retrospective study examining the long-term outcomes in 77 patients diagnosed with CVST. The study reports that 85% of patients did not experience long-term neurological sequelae during a 77.8-month follow-up. Additionally, the study found that 14.5% of patients with neurological impairment suffered from seizures, cognitive deficits, and focal neurological deficits [21].

CONCLUSION

In patients presenting with ear pain, the most common symptom of middle or outer ear infection, it is crucial during examination to identify the presence of typical signs of retroauricular inflammation (swelling, redness, and tenderness behind the ear) as an indication of mastoiditis. This is important because mastoiditis is the second most common complication of acute otitis media.

Timely diagnosis and appropriate treatment of mastoiditis significantly reduce the risk of complications, such as cerebral venous sinus thrombosis (CVST).

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DOCTOR JOVAN STEJIĆ – THE FIRST SERBIAN DOCTOR OF MEDICINE

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Summary: Doctor Jovan Stejić was born in Arad on November 24, 1803. He was the first Serbian to hold the title of Doctor of Medicine and worked in the renewed Serbia. He was the creator of Serbian medical terminology, the first Serbian anthropologist, and the Chief of Sanitation for the Principality of Serbia. Additionally, he served as the Chief Secretary of the State Council, a fighter for the reform of the Serbian language and orthography, a great enlightener, and an advocate for the rights of individuals and citizens. Doctor Stejić was also one of the founders of the Society of Serbian Letters and the Serbian Academy of Sciences and Arts. His arrival in Serbia as the personal physician of Prince Miloš Obrenović marked the beginning of organized healthcare services in the country. He succeeded in bringing advanced medical ideas to Serbia, modeled after the country where he studied. He belonged to the first generation of Serbian intellectuals who invested their knowledge and efforts into the cultural enlightenment of the Serbian people and the building of the modern Serbian state in the 19th century. Some of the key messages of his works include natural rights, the right to freedom and equality, the right to honor and good name, and the right to property and acquired goods. His stance was that the state should be organized according to the law, and the law should be equal for all. He spoke about freedom and people's right to express their opinions. Significantly, he emphasized the educational role for younger generations. As a pioneer in many areas, through his literary work, he sought to highlight the foundations of moral values and the importance of a clear and peaceful conscience, thereby laying the foundations of medical ethics.
One of his notable contributions was the book he translated and supplemented as a student according to the needs of the Serbian people, "Macrobiotics, or the Science of Prolonging Human Life," which was the first medical book in Serbia. By translating this book, he initiated pioneering work on Serbian medical terminology. Doctor Stejić died of tuberculosis in 1853 in Belgrade. He left behind his son, Pavle Stejić, a renowned Belgrade surgeon.
Doctor Jovan Stejić distinguished himself through his diverse cultural, healthcare, and social work as a physician, writer, great scientist, and enlightener.
Key words: Jovan Stejić, prvi srpski doktor medicine, prva srpska medicinska knjiga

INTRODUCTION

Doctor Jovan Stejić, originally from Arad, was the first Serbian Doctor of Medicine in the renewed Serbia during the 19th century. He received his medical education in Pest and Vienna. Coming from the Habsburg Monarchy, he arrived in the renewed Serbia to serve as the personal physician of Prince Miloš Obrenović. His arrival marked the beginning of organized healthcare services in Serbia.

He was the creator of Serbian medical terminology, the first Serbian anthropologist, Chief Secretary of the State Council, and an advocate for the reform of the Serbian language and orthography. Doctor Jovan Stejić, together with Doctor Karlo Pacek, was a founder of the Serbian sanitary service. He was also one of the founders of the Society of Serbian Letters and the Serbian Academy of Sciences and Arts.

Doctor Stejić laid the foundations of medical ethics and transfusion practices. The book he translated and supplemented according to the needs of the Serbian people, "Macrobiotics, or the Science of Prolonging Human Life," was the first medical book in Serbia. By translating this book, he initiated pioneering work on Serbian medical terminology.

As a writer, through his works, he fought for citizens' rights. Inspired by Kant's ideas, he preached morality, modesty, diligence, and a sense of duty, thereby influencing younger generations through education. Doctor Jovan Stejić successfully introduced modern and

advanced healthcare ideas to Serbia, modeled after the healthcare system of the country where he studied.

Doctor Jovan belonged to the first generation of Serbian intellectuals who dedicated their knowledge and efforts to the cultural enlightenment of the Serbian people and the construction of a modern Serbian state.

The aim of this work is to explore the life, education, career, and contributions to medicine of the first Doctor of Medicine in renewed Serbia, Doctor Jovan Stejić.

BIOGRAPHY

Doctor Jovan Stejić was born in Arad on November 24, 1803. He completed his primary education in Arad, and after receiving a scholarship from Sava Tekelija, he studied in Szeged, where he finished his secondary education and began studying philosophy.

He studied medicine at the Faculty of Medicine in Pest and earned his doctorate in Vienna in 1829.

Picture1. Doctor Jovan Stejić
taken from: https://www.sanu.ac.rs/clan/stejic-jovan/

In that period, Serbia lacked qualified educational personnel, so in 1828, Jevrem Obrenović awarded Jovan Stejić a scholarship. In 1829, Stejić began working in Šabac. From 1830 to 1832, he moved to Kragujevac after Prince Miloš Obrenović appointed him as his personal physician and tutor for his sons, Milan and Mihailo. Prince Miloš highly valued Doctor Jovan both as a physician and as an advisor.

In 1832, a conflict arose between Prince Miloš and Doctor Stejić. One reason was that Doctor Stejić refused to let the Prince review the manuscript of his book, "Assembly of Truth and Science," before printing in the newly established State Printing House. This refusal angered Prince Miloš, who halted the printing process. In this book, Doctor Stejić discussed natural rights, the right to freedom and equality, the right to honor and good reputation, and the right to property and acquired goods. His stance was that the state should be organized by law, and the law must be equal for all. He advocated for freedom and people's right to express their opinions and addressed reforms in Vuk Karadžić's orthography, with which he partially disagreed.

After the first original text was printed, Doctor Jovan abandoned the newly accepted Vuk's orthographic reform. Due to this conflict, he left Serbia in 1832 and moved to Zemun, where he practiced private medicine for eight years. He occasionally returned to assist Doctor Kunibert in treating Prince Miloš's family.

In 1833, Doctor Stejić recommended introducing mandatory practical internships for young doctors. While living in Zemun, in 1837, he contributed to the Tyrolean calendar "Urania."

Doctor Jovan returned to Serbia in 1840. He was appointed Chief of Civil Sanitation and initiated efforts to open the first psychiatric hospital in Serbia. He also drafted the first regulations for burials.

In 1841, he became Chief Secretary of the State Council. He was one of the founders of the Society of Serbian Letters in 1842, which

later became the Serbian Learned Society in 1862, evolving into the Serbian Royal Academy and finally the Serbian Academy of Sciences and Arts.

In September 1842, the government dismissed him from public service, but he was allowed to remain in Belgrade as a private physician.

In 1843, he resumed his role as Chief of Civil Sanitation. During this tenure, he ordered vaccination for children against smallpox, issued guidelines to prevent dysentery, and organized efforts to combat syphilis.

On June 25, 1845, he was appointed Chief Secretary of the State Council. Doctor Stejić initiated efforts to document and preserve historical documents and monuments of Serbian history. He served in this role until his death in 1853.

In addition to medicine, Doctor Jovan Stejić was involved in literature and became a member of the German Enlightenment movement.

As a writer, through his works, he fought for citizens' rights. He wrote about natural rights, the right to freedom and equality, the right to honor and good reputation, and the right to property and acquired goods. His belief was that the state must be organized by law and that the law should apply equally to all. He advocated for freedom and the right to express opinions and discussed reforms to Vuk Karadžić's orthography. Inspired by Kant's ideas, he preached morality, modesty, diligence, and a sense of duty, thereby influencing younger generations.

In 1826, Doctor Stejić translated the book "Macrobiotics, or the Science of Prolonging Human Life" from German, which was printed in Vienna. This book is considered his most significant work. The book is a Serbian adaptation of an encyclopedic manual by German clinician Johann Peter Hufeland. In "Macrobiotics," Doctor Jovan Stejić explored what would happen if young blood were transfused into an elderly person's body. The book is regarded as a precursor to transfusion therapy, which became widely practiced during World War I. It was the first book to mention hygiene in sexual relations in Serbian. The book was dedicated to Sava Tekelija, his benefactor.

Doctor Jovan Stejić's literary works in the field of physical and spiritual hygiene include titles such as:

"Reflections on Diversity"

"What to Eat and Drink"

"On the State from Weber's Democritus"

"Europe from the State Dictionary of Rothe and Welker"

"Critique of Vuk's Translation of the New Testament"

"Anthropology, or the Science of Man"

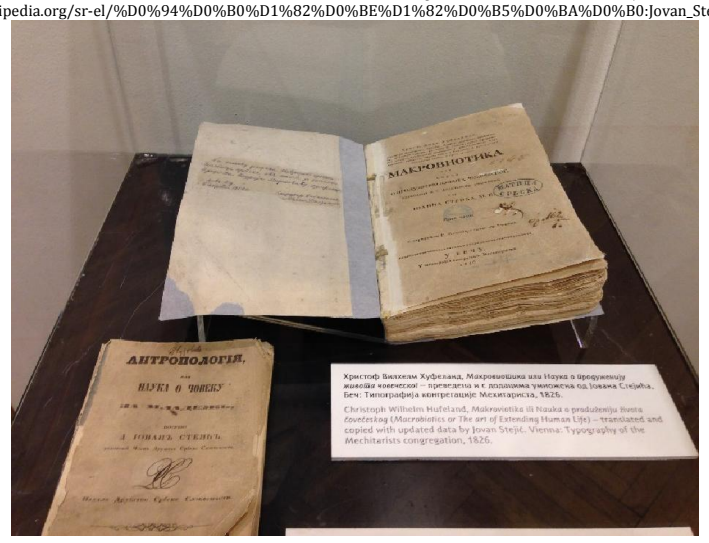
"Proposal for a Serbian Dictionary and Serbian Grammar"

"Entertainment for Mind and Heart"

"Macrobiotics, or the Science of Prolonging Human Life".

Picture 2. Book: "Macrobiotics" by Doctor Jovan Stejić

Taken from: https://sr.m.wikipedia.org/sr-el/%D0%94%D0%B0%D1%82%D0%BE%D1%82%D0%B5%D0%BA%D0%B0:Jovan_Steji%C4%87_MD.IMG_2057.jpg



He often collaborated with the Glasnik of the DSS and served as its editor-in-chief for a time. He also contributed to the publications Dnevnik and Srpski narodni list. Among his published works, the most notable is Makroviotika ili nauka o produženju života čovekova (1826, Vienna). This is a Serbian-adapted translation in the form of a textbook, an encyclopedic handbook of the German clinician Johann Peter Huferland. In this work, hygiene of sexual relations and the idea of blood transfusion were mentioned for the first time in the Serbian language.

Pijanstvo (1827) provides a vivid depiction of the causes and consequences of alcoholism, as well as methods for treating alcoholics. Zabava za razum i srce is a collection of texts with health messages, published in five volumes (Vienna, 1828; Buda, 1831; Zemun, 1834; Buda, 1836; and Novi Sad, 1839). The third book consists of translations of texts by other authors under the title Mudra izrečenija iz raznih pisaca (Wise Sayings from Various Authors), while the fourth book, titled Ogledi umne nauke (Essays on Intellectual Science), was written for a general audience.

Antropologija ili nauka o čoveku za mladež (Anthropology or the Science of Man for Youth) was published in 1850. In Srpski pravopis (Serbian Orthography) from 1852, he expressed his views on the need to adopt new terms and expressions in various scientific fields. His Predlog za srpski rečnik i srpsku gramatiku (Proposal for a Serbian Dictionary and Grammar) was published in 1853 as vice president of the Društvo srpske slovesnosti (Society of Serbian Letters) and represents a continuation of the debate started in 1832 regarding Vuk Karadžić's spelling reform.

To this day, his marital status remains unknown, but it is known that he had a family and that his son was named Pavle Stejić, a renowned Belgrade surgeon. Dr. Jovan established his family home in the center of Belgrade, on Makedonska Street, in 1845, where he lived with his family. Dr. Jovan Stejić passed away in Belgrade on November 21, 1853, from tuberculosis and was buried in the cemetery near the Church of Saint Mark, which existed at the time.

CONCLUSION

Dr. Jovan Stejić was a significant figure in Serbian culture and medical history. He was considered one of the most respected intellectuals in shaping Serbian culture, particularly its medical history. He was a pioneer of preventive medical care in Serbian territories and one of the founders of civil healthcare services. Dr. Stejić was a physician, author of numerous articles and other literary works, especially in medical and health education, a translator, and a political and cultural activist. Dr. Stejić's most significant achievement is that he created Serbian medical literature and medical terminology and founded the civil healthcare system in Serbia.

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CHARLES BINGHAM PENROSE – A VISION FOR THE FUTURE

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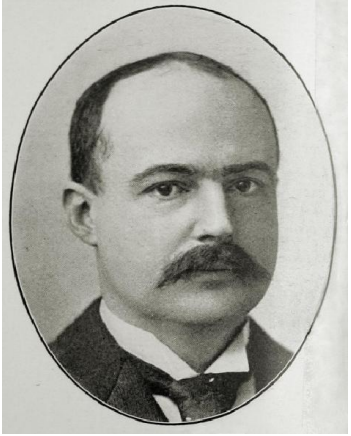
Summary: Charles Bingham Penrose (1862–1925) was a renowned American surgeon and physicist who secured his place in the history of surgery with the invention of a drain named after him. Penrose attended Harvard College, where he graduated at the age of 19 with highest honors in physics. At 22, he earned his Doctor of Medicine degree from the University of Pennsylvania. Following his graduation, he worked as an ambulatory surgeon, participated in various research projects, and ran a medical practice specializing in gynecology. In 1887, he founded the first hospital in Philadelphia dedicated exclusively to gynecological issues. For his contributions to this field, he was awarded the title of Professor of Gynecology at the University of Pennsylvania in 1893. In the late 19th century, Penrose focused primarily on surgical drainage and the education of surgeons in this field, encouraging them to use this procedure more frequently. He described a rubber drain used for abdominal cavity drainage, which remained in use until the mid-20th century. This drain came to be known as the Penrose drain. Penrose contracted tuberculosis at a young age, and due to the advanced form of the disease, he had to withdraw from medical practice at the age of 38. He was married and a father to three children. Charles Bingham Penrose passed away on February 28, 1925, at the age of 64, while on a train near Washington, D.C..
Key words: Charles Bingham Penrose – Surgeon, Drain

In the history of medicine, there have been widely used therapies that may seem almost laughable in light of modern knowledge about physiology and medical practice, yet they play an important role in the education of physicians. The past provides a lesson for the present and a direction for the future. However, we must persistently engage in critical examination of the past. We still do not have all the answers, but we can affirm that answers exist. One goal remains always important – believe in yourself and your ideas. And that is what defines exceptional people.

One of the exceptional doctors who believed in himself and his ideas was Charles Bingham Penrose, the father of modern surgical drainage. For this reason, this article was written in memory of the discovery of the drain named after him.

Picture 1. Charles Bingham Penrose
taken from :https://commons.wikimedia.org/wiki/Category:Charles_Bingham_Penrose#/media/File:CharlesBinghamPenrose.jpg/2



Charles Bingham Penrose – Surgeon, Physicist, Naturalist, Adventurer. Charles Bingham Penrose was born in Philadelphia on February 1, 1862. Charles's father, Richard Allen Fullerton Penrose Sr., was a physician and a professor of obstetrics at the University of Pennsylvania, while Charles's mother, Sarah Hanna Boies Penrose, hailed from Maryland and was adopted by a wealthy Boston merchant. Shortly after marrying Richard, Sarah withdrew from high society and focused on educating her seven sons. Richard Allen Fullerton Penrose came from a prestigious Philadelphia family. One brother was a United States senator, and another was president of the National Academy of Sciences [1,2].

Charles initially received his education from private tutors. The proximity to the Delaware and Schuylkill rivers also allowed Penrose to enjoy fishing, ice skating, and swimming. His first school was the Episcopal Academy, located at Newton Square in Pennsylvania, which he graduated from with top honors [2].

Penrose attended Harvard College, where he graduated at the age of 19 with an AB degree and the highest honors in physics, just two months after his mother passed away from tuberculosis. Shortly thereafter, his articles on magnetism and electricity appeared in scientific journals [1].

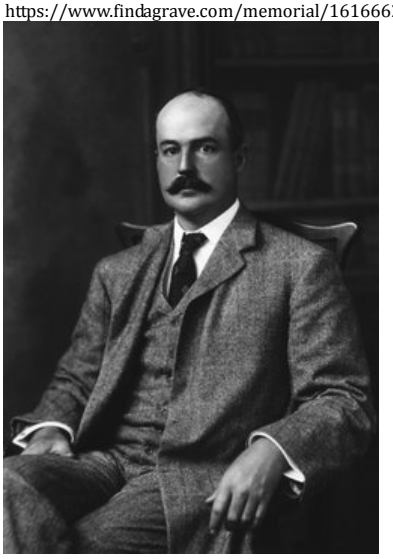
In 1882, Penrose published his significant work, "The Relation Between Surface Energy and Thermoelectricity," where he stated that a thermodynamic equation could be derived in an entirely different way if the energy of thermoelectric current is considered as part of the energy present on a different surface [3].

Penrose enrolled in the University of Pennsylvania's medical school while simultaneously continuing his studies in mathematics and physics at Harvard University as a doctoral candidate. This study arrangement was allowed by the University Council on the condition that Penrose spent two months each semester at Harvard. In the spring of 1884, at the age of 22, he received his Doctor of Medicine (MD) degree from the University of Pennsylvania and a Doctor of Philosophy (PhD) in physics from Harvard University. His physics doctoral thesis was titled "Mathematical Theory of Thermoelectricity and the Relation Between Thermoelectricity and Surface Energy" [2,4].

After completing his physics doctorate, Penrose devoted himself to medicine. He served as a staff physician and ambulatory surgeon at a Pennsylvania hospital from 1885 to 1886 and at the Philadelphia Dispensary from 1888 to 1893 [2].

During his residency, Penrose participated in research on the diuretic effects of injected cocaine. The article, "Observations on the Diuretic Effect of Cocaine," was published in the local medical journal The College and Clinical Record and suggested that the diuretic effect of injected cocaine was apparent [5].

Slika 2. Penrose as a Professor of Gynecology at the University of Pennsylvania
taken from: https://www.findagrave.com/memorial/16166622/flower

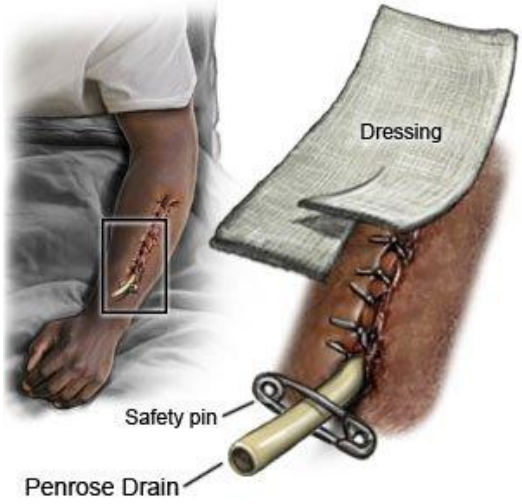


As a physician, Penrose ran a medical practice specializing in gynecology. This led him to establish the Gynecean Hospital in 1887, the first medical institution in Philadelphia dedicated exclusively to gynecological issues. After contracting tuberculosis in 1891, Penrose temporarily left his medical practice and moved to Wyoming for recovery. There, he fully committed to physical activity: in the mornings, he worked with a pickaxe and shovel, and in the afternoons, he rode horses. By early the following year, his health had significantly improved. Returning to Philadelphia in 1893, he was appointed Professor of Gynecology at the University of Pennsylvania. Colleagues regarded Penrose as a skilled and competent surgeon [1,6].

In 1889, Penrose presented his views defending drainage in abdominal surgery to the American Medical Association. In the late 19th century, surgeons were divided over whether drainage tubes in abdominal surgery should be used rarely or frequently. At that time, most surgical drains were made of glass tubes or gauze. These types of drains could damage surrounding tissue or become embedded in it, leading to infection. Additionally, bowel damage often occurred during drain removal [7].

Penrose acknowledged that many surgeons feared using drainage tubes and explained that, with proper handling and careful cleaning, such fears were unfounded. He described a rubber drain inserted directly through the wound into the abdominal cavity, forming a channel through which blood and other fluids could exit the abdomen. In his book "Textbook of Women's Diseases," published in 1897, he illustrated a drain made from tubular rubber sheeting and filled with gauze. His famous advice to surgeons was: "When in doubt, drain!" [1,2].

Picture 3. Principle of Operation of the Penrose Drain
taken from: https://www.drugs.com/cg/penrose-drain.html



An interesting fact is that the first rubber drain designed by Penrose was made from a condom with its tip cut off. Another fact is that the Penrose drain became the dominant method of surgical drainage until the introduction of the Jackson-Pratt (suction) drain in the 1950s [8].

Penrose's physical appearance and impressive stature matched his intellectual and professional impeccability. In the summer of 1882, at the age of 20, he rode a horse from Philadelphia to Niagara Falls and back. At 28, he swam 15 miles (24 km) in the ocean in 5 hours [1]. A few years later, while hunting in Montana, Penrose shot a silver bear (grizzly) cub. After the bear's mother discovered this, she severely injured Charles. Penrose saved his own life by shooting the bear in the neck during the struggle [9].

Although he was one of seven brothers, Penrose was the only one to have children. He married Catherine Drexel in 1892. They had a

daughter named Sarah in 1896, and four years later, a son named Charles, who unfortunately died in 1901. Their third child, Boys Penrose, became a writer and historian [2,10].

Due to the advanced form of pulmonary tuberculosis, in 1899, at the age of 38, Penrose retired from medical practice for the rest of his life. He occasionally traveled west, hoping that the air, altitude, sunlight, and exercise would cure him [9].

In his final years, Charles's health deteriorated significantly. He spent the winter of 1924/25 in South Carolina, trying to recover from tuberculosis. Penrose planned to return to Philadelphia by train to visit relatives, accompanied by two nurses and his cousin Sarah. He was found dead in his train compartment near Washington, D.C., on February 28, 1925, at the age of 64. A heart attack was suspected to be the cause of death [9].].

Picture 4. The Family Tomb of Charles Bingham Penrose
taken from: https://www.findagrave.com/memorial/16166622/charles-bingham-penrose

He was buried at Laurel Hill Cemetery in Philadelphia. The majority of his fortune was left to his children, and $100,000 was bequeathed to the nurse who cared for him until his death [1].

Conflict of Interest: The authors declare no conflict of interest.

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The summary must not contain any claims that are not contained in the text of the article. It must be written in such a way that even an educated nonexpert can understand the content of the article. After the summary, write 3 to 8 keywords. The words in the title should not be repeated and the keywords should be relevant or descriptive and in accordance with MESH rules (available at https://www.nlm.nih.gov/mesh).

The next part of all the papers is an **INTRODUCTION** (with a subtitle of the same name), which must be brief, with a brief overview of the literature on the problem in question, and with a clear statement of **the purpose of the article** in a separate paragraph at the end of the introduction.

MATERIALS AND METHODS (with the same subtitle) must contain sufficient information to enable other researchers to repeat similar research without further information. Patient names and medical history numbers should not be used nor other details to help identify patients. The names of the apparatuses, software and statistical methods used must be indicated.

Show the **results** (with the subtitle of the same name in BOLD) clearly and concisely. You should not display the same data both in tables and charts.

DISCUSSION (with the subtitle of the same name) should discuss the interpretation of the results, their meaning in comparison with other, similar research and in accordance with the hypotheses of the research. The results already written should not be repeated.

CONCLUSION (with the subtitle of the same name) should be given in a separate chapter.

Each table, chart, or illustration must be self-explanatory, i.e. even without reading the text in the manuscript. Above the table, chart, orimage,there should be a serial number and a title. Put the legend in a footnote below the table, chart, or image and explain any non-standard abbreviations there. Illustrations (images) should be sharp and contrasting, no larger than 1024x768 pixels. The number of images should be limited to the most necessary (generally no more than 4-5). If the image, table, or chart is downloaded from the Internet or another source, the source must be indicated.

REFERENCES

LITERATURE. At the end of the paper, write a list of cited literature, which should be as current as possible and most references should not be older than 5 years. References are numbered in the order they appear in the text. Mark the references in the text with an Arabic number in square brackets [...]. The literature lists the first 3 to 6 authors of the article cited, followed by "et al". Journal titles can only be abbreviated as in Index Medicus. The journal abbreviation can be found at: http://www.nlm.nih.gov/. If the abbreviation is not known, give the name of the journal as a whole. The literature is cited as follows:

Journal articles

Standard journal article:

Gao SR, McGarry M, Ferrier TL, Pallante B, Gasparrini B, Fletcher JR, et al. Effect of cell confluence on production of cloned mice using an inbred embryonic stem cell line. Biol Reprod. 2003; 68 (2): 595-603.

Organization as author:

WHO collaborative study team on the role of breastfeeding on the prevention of infant mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. Lancet. 2000; 355: 451–5.

No authors listed:
Coffe drinking and cancer of the pancreas [editorial]. BMJ. 1981; 283 628.

A volume with a supplement:
Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig heart anaphylaxis. Pharmacol Res Commun. 1988; 20 Suppl 5: 75–8.

Books and other monographs

The author is a person (s):
Carlson BM. Human embryology and developmental biology. 3rd ed. St. Louis: Mosby; 2004.

Editor (s) as authors:
Brown AM, Stubbs DW, editors. Medical physiology. New York: Wiley; 1983.

Chapter in a book:
Blaxter PS, Farnsworth TP. Social health and class inequalities. In: Carter C, Peel JR, editors. Equalities and inequalities in health. 2nd ed. London: Academic Press; 1976. p. 165–78.

Meeting announcements: Harris AH, editor. Economics and Health: 1997: Proceedings of the 19th Australian Conference of Health Economists; 1997 Sep 13-14; Sydney, Australia. Kensington, N.S.W.: School of Health Services Management, University of New South Wales; 1998.

Conference Articles:
Anderson JC. Current status of chorion villus biopsy. In: Tudenhope D, Chenoweth J, editors. Proceedings of the 4th Congress of the Australian Perinatal Society; 1986: Brisbane, Queensland: Australian Perinatal Society; 1987. p. 190-6.

Dissertation:
Cairns RB. Infrared spectroscopy studies of solid oxygen. Dissertation. Berkley, California: University of California, 1965.

Electronic material

Article in aninternetmagazine:
Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs. 2002; 102 (6). Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Article published electronically before the printed version:
Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. Blood. 2002-Nov-15; 100 (10): 3828-31. Epub 2002 Jul 5.

CD-ROM:
Anderson SC, Poulsen KB. Anderson's Electronic Atlas of Hematology [CD-ROM]. Philadelphia: Lippincott Williams & Wilkins; 2002.

Online monograph:
Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: http://www.nap.edu/books/0309074029/html/.

Website:
Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/.

Part of awebsite:
American Medical Association [homepage on the Internet]. Chicago: The Association; c1995-2002 [updated 2001 Aug 23; cited 2002 Aug 12]. AMA Office of Group Practice Liaison; [about 2screens]. Available from: http: //www.ama-assn.org/ama/pub/category/1736.html

NOTE. A paper that does not meet the requirements of this guide cannot be referred for review and will be returned to the authors for completion and correction. Adhering to the preparation instructions will significantly shorten the time of the entire process until the paper is published, which will positively affect the quality of the articles and the regularity of the publication of the journal.

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