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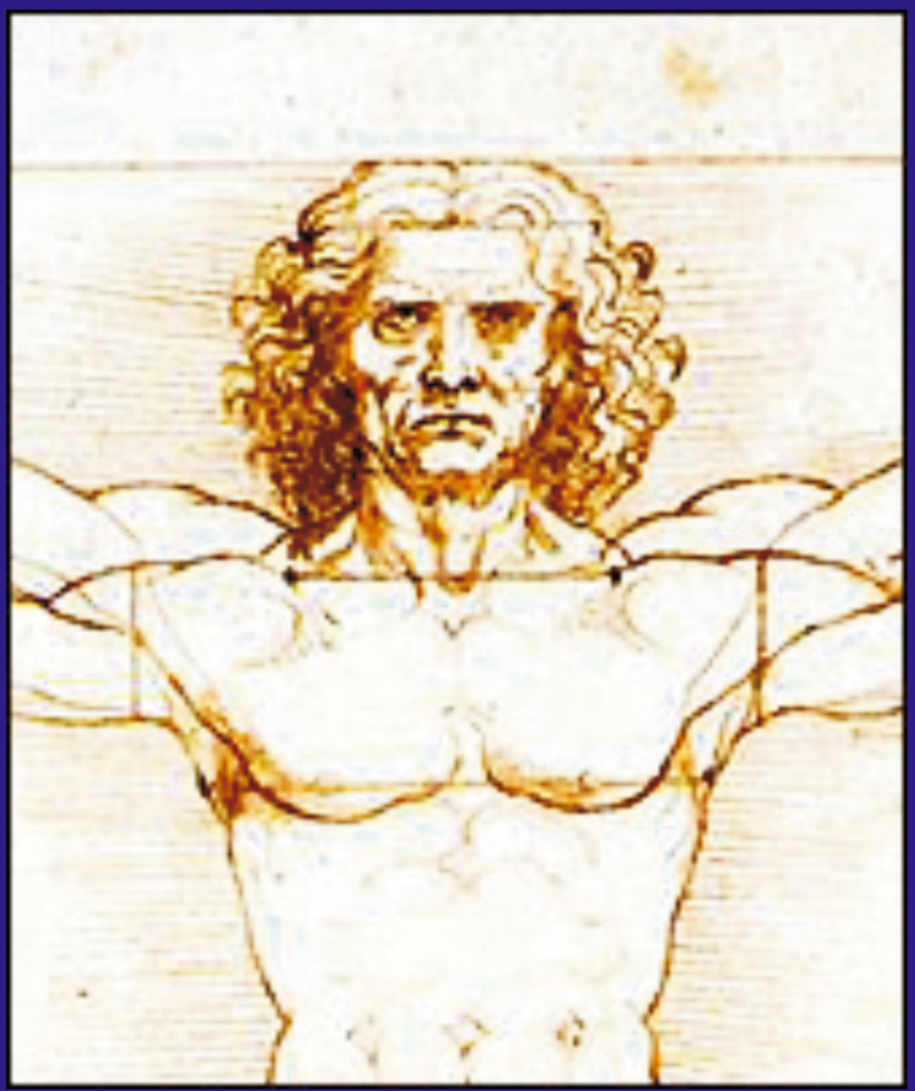

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Original article

QUALITY OF LIFE OF PATIENTS AFTER TOTAL KNEE ARTHROPLASTY

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Abstract: **Introduction:** Diseases of the musculoskeletal system are common in the general population. They significantly contribute to increased morbidity, more frequent use of healthcare services, reduced working capacity, increased professional absences, and the occurrence of disability.

Methodology: This study involved patients who underwent knee replacement surgery at the Clinical Center of Montenegro, Podgorica. We employed the SF-36, a widely used universal standard questionnaire, which has been applied in over 4,000 published studies.

Results: Statistically significant improvements in quality of life were observed in all examined domains: physical functioning (p = 0.0001), role limitations due to physical problems (p = 0.0001), role limitations due to emotional problems (p = 0.0001), vitality/energy (p = 0.0002), mental health (p = 0.0004), social functioning (p = 0.0001), physical pain (p = 0.0001), and perception of general health (p = 0.0001) following knee endoprosthesis implantation.

Conclusion: Statistically significant differences were observed in all quality of life domains before and after knee endoprosthesis surgery, confirming the improvement in patients' quality of life after the procedure.

Keywordsjesus: knee endoprosthesis, quality of life, disability, working ability.

INTRODUCTION

Knee osteoarthritis is one of the most common joint diseases worldwide, particularly in the elderly population, who often have multiple comorbidities. This condition leads to disability and impairs the mobility of patients, disrupting their normal functioning (1-4). The World Health Organization (WHO) defines quality of life as an individual's personal perception of their objective reality. This includes how the environment affects them in the context of their personal, family, and work environments, the culture and value system in which they live, and in relation to their own goals, needs, expectations, standards, and interests (5, 6, 7). In 2001, the WHO also defined disability as an impairment of body structure and organ function (5). In many countries, the concept of disability has been redefined with the goal of improving quality of life (8, 9, 10).

The human body represents a harmonious, essential entity composed of numerous parts with different functions that interact and complement each other. All living beings share a universal need for movement, as life cannot exist without it. A lack of movement in modern humans leads to various health problems and reduces quality of life (9, 10).

Degenerative, inflammatory, metabolic changes, and post-traumatic conditions can occur in the knee joint. Degenerative changes, particularly in bones and soft tissues, take center stage, leading to changes in mechanical relationships. Excessive cartilage wear has multiple causes, with some of the most significant being knee joint overload, congenital joint deformities, excessive weight, constant strain due to work, and micro-injuries from recreational sports or improper engagement in sports without professional supervision (10).

The most well-known types of osteoarthritis are coxarthrosis (hip joint osteoarthritis) and gonarthrosis (knee osteoarthritis), but osteoarthritis can also affect small joints in the fingers and spine, leading to painful syndromes in the back (9, 11, 12). The knee joint is

particularly vulnerable to osteoarthritis, which can be very unpleasant as it causes pain, limited joint mobility, and significant limitations in daily activities (10, 13).

Quality of life is a concept studied across many scientific disciplines (medicine, physiology, psychology, sociology, etc.). There are numerous definitions of quality of life in medical literature, all emphasizing physical, psychological, and social dimensions. General quality of life provides insights into human aspirations, while health-related quality of life (HRQoL) focuses only on aspects directly related to health. "Health-related quality of life encompasses the physical, psychological, and social domains of health, influenced by human experiences, beliefs, expectations, and perceptions" (14). Reduced quality of life is particularly evident in older individuals, as previously published studies show a strong association with the prevalence of psychosomatic and motor disorders (15).

When considering the determinants of quality of life, physical activity often ranks low on the priority list. However, insufficient physical activity can lead to muscle atrophy, sarcopenia, osteoporosis, and chronic non-communicable diseases, including type 2 diabetes, arterial hypertension, coronary heart disease, obesity, and certain types of cancer. Engaging in properly dosed physical activity and adhering to a balanced diet can help older working-age people maintain their physical and mental fitness, effectively performing their social and professional duties (16).

Aim

To assess the quality of life in patients before and after knee endoprosthesis implantation.

PATIENTS AND METHODS

This study included patients who underwent total knee replacement at the Clinical Center of Montenegro in Podgorica. The research was conducted from April to August 2022 and focused on patients with knee joint disease who were treated surgically. The patients were surveyed about their general and socio-demographic characteristics, as well as their quality of life before surgery and after the implantation of the total knee replacement.

The SF-36 universal standard questionnaire was used in this study, which is widely applied in over 4,000 published studies to assess quality of life in specific populations. This questionnaire collects data on the impact of impaired health on patients' daily lives. It consists of 36 items, each addressing different health aspects. It measures health multidimensionally, including: physical functioning, role limitations due to physical health, bodily pain, social functioning, role limitations due to emotional difficulties, vitality, mental health, and overall self-assessment of health status. A higher score reflects a better self-assessment of health in these areas.

The physical health profile (PCS, Physical Component Summary Measure) includes four of the eight dimensions: physical functioning, role limitations due to physical difficulties, bodily pain, and perception of overall health. The mental health profile (MCS, Mental Component Summary Measure) includes vitality/energy, social functioning, role limitations due to emotional difficulties, and mental health. The SF-36 questionnaire represents an empirically validated operationalization of two general health concepts—physical health and mental health—and their manifestations in functioning and well-being.

Statistical analysis will be performed in collaboration with a statistician, utilizing descriptive and inferential statistics through both parametric and non-parametric tests. The study was approved by the Ethics Committee of KCCG/2021. Participation in the research was voluntary and anonymous, with patients providing informed consent. All procedures were in accordance with institutional and national research ethics standards, as well as the 1964 Helsinki Declaration and its later amendments.

RESULTS

For this study, participants with gonarthrosis of the knee and injuries leading to knee replacement surgery were intentionally selected. Since every patient had an equal chance of participating, this sample is considered a simple random sample. Some general and sociodemographic characteristics of the participants are presented in Table 1. Out of 32 participants, the majority were women (24, or 75%), while 8 were men

Table 1. *Sociodemographic and general characteristics of the respondents*

		N	%
Gender	**Men**	8	25.0
	Women	24	75.0
Year categories	**36-47 year**	3	9.4
	48-60 year	7	21.9
	61-73 year	11	34.4
	74-85 year	11	34.4
A type of trauma	**Gonarhtrosis**	29	90.6
	Injury	3	9.4
Localization of trauma	**Right knee**	15	46.9
	Left knee	17	53.1

Table 2. *Average values of the quality of life domains before and after surgery*

	Surgery	N	Mean	Std. Deviation	Std. Error Mean	p
Physical functioning	before surgery	**32**	25.56	17.91	4.93	**p = 0.0001**
	after surgery	**32**	53.76	7.37	3.07	
Role limitation due to physical disabilities	before surgery	**32**	40.07	9.53	1.13	**p = 0.0001**
	after surgery	**32**	65.61	14.80	2.62	
Body pains	before surgery	**32**	63.20	10.55	1.91	**p = 0.004**
	after surgery	**32**	55.81	9.92	1.78	
Perception of general health	before surgery	**32**	53.24	17.68	3.13	**p = 0.0001**
	after surgery	**32**	64.76	9.98	1.76	
Energy and vitality	before surgery	**32**	38.64	21.94	3.88	**p = 0.002**
	after surgery	**32**	54.16	16.45	2.91	
Social functioning	before surgery	**32**	38.28	11.76	2.08	**p = 0.0001**
	after surgery	**32**	72.13	10.16	1.80	
Limitations due to emotional difficulties	before surgery	**32**	48.11	5.92	1.71	**p = 0.0001**
	after surgery	**32**	31.93	11.76	1.05	
Mental health	before surgery	**32**	54.35	20.97	3.83	**p = 0.004**
	after surgery	**32**	67.50	16.64	3.04	

(25%). The majority of participants were in the age groups of 61-73 and 74-85 years (11 participants each, 34.4%), while the fewest were in the 36-47 years group (3 participants, 9.3%), and 7 participants (21.9%) were in the 48-60 years group. Regarding the type of trauma, most participants (29, or 90.6%) had gonarthrosis, while 3 had an injury. Out of the 32 participants, 17 (53.1%) had trauma in the left knee, and 15 (46.9%) had trauma in the right knee.

Analysis of the SF-36 Questionnaire

For the purpose of researching quality of life before and after knee replacement surgery, with corresponding healthcare, the standardized SF-36 questionnaire was used. It consists of 36 questions, 35 of which are grouped into 8 different domains: physical functioning, role limitation due to physical difficulties, bodily pain, perception of general health, energy and vitality, social functioning, role limitation due to emotional difficulties, and mental health (38, 39). Within this questionnaire, respondents were given the opportunity to self-assess their health compared to the previous year, both for the period before and after knee surgery.

In the health assessment before surgery compared to the previous year, most respondents (15, or 46.9%) defined their health as the same, 12 (37.5%) characterized it as somewhat worse, while only 5 (15.6%) indicated that it was much worse than a year ago. After surgery, 19 (59.4%) respondents stated that their health was much better compared to the previous year, while the remaining 13 (40.6%) rated their health as somewhat better compared to the previous year. For the period after surgery, there were no negative responses.

In Table 2, the average values of all quality of life domains before and after knee surgery for the total number of respondents (n = 32) are presented. To determine potential differences in all domains of health and quality of life before and after surgery, the paired sample t-test method was used. It is evident that the average health score in the physical functioning domain before surgery (M = 25.56) was significantly lower compared to the period after surgery (M = 53.76). This difference was statistically significant (p = 0.0001).

We tested differences in the role limitation component due to physical difficulties before and after knee surgery using the paired t-test. The results showed that there was also a statistically significant difference in

this domain (p = 0.0001). Before surgery, the average health in the role functioning domain was M = 40.07, and after surgery, there was significant improvement, with an average of M = 65.61, ranging from a minimum of zero to a maximum of 100 on the health scale.

The level of bodily pain before surgery (M = 63.2) was higher compared to the level of bodily pain after surgery (M = 55.81). The paired sample t-test showed that these differences were also statistically significant (p = 0.004).

Regarding the perception of general health, it is evident that respondents perceived their health as much better after surgery (M = 64.76) compared to the period before surgery (M = 53.24). The differences, based on the results of the paired t-test, also proved to be statistically significant in this case (p = 0.0001).

The application of the paired sample t-test confirmed a statistically significant difference in the domain of energy and vitality (p = 0.002). The results show that energy and vitality in the sample patients increased after surgery (M = 54.16), while before surgery, the values in these domains were much lower (M = 38.64).

The level of social functioning also significantly improved in the subjects after surgery (M = 72.13), whereas before the surgery, it was significantly lower (M = 38.28). Differences measured by the paired t-test in this domain also proved to be statistically significant (p = 0.0001).

Limitations due to emotional difficulties were much greater in the subjects before surgery (M = 48.11), while they visibly decreased after surgery (M = 31.93). The observed difference, according to the analysis of the paired sample t-test results, proved to be statistically significant (p = 0.0001).

In the domain of mental health, the results were significantly better after surgery (M = 67.5) compared to the period before surgery (M = 54.35). The differences determined by the paired sample t-test were statistically significant in this domain as well (p = 0.003).

DISCUSSION

The quality of life is influenced by personal development (14). Based on the results of our study, we assessed the quality of life of a sample of patients across eight different domains: physical functioning, role limitation due to physical difficulties, general health perception, bodily pain, energy and vitality, social functioning, role limitation due to emotional difficulties, and mental health. According to previous research, the prevalence of women with an average age of 62-72 who have undergone total knee replacement is higher compared to men. Therefore, our findings align with those results, as the majority of our sample consisted of women (24, or 75%), most of whom were aged 61-73 and 74-85 years (14-19).

In terms of self-assessed health before surgery, compared to the previous year, most respondents defined their health as the same, while after surgery, 19 (59.4%) respondents reported that their health was much better compared to the previous year. Mobility limitations and the development of flexion contractures are cited as some of the most common effects of pathological knee processes, making range of motion an important measure of postoperative outcomes (19).

The study by Walid Kamal M. and associates, as well as many studies before it, found that regular physical activity, especially in the elderly population, significantly improves health, mobility, and quality of life (20, 21). Furthermore, according to the research of Legović A. (22), a significant increase in quality of life was observed in respondents three, six, and twelve months after surgery. Similarly, our research results show that the average health score in the domain of physical functioning before surgery was significantly lower, with health in the domain of physical role functioning showing significant improvement after surgery.

A study that included 41 patients who underwent total knee replacement found that the comparison of preoperative and postoperative quality of life assessments using the SF-36 form showed significant differences at the 5% level in the categories of “somatic pain” and “psychological well-being.” The parameter “somatic functionality” showed almost significant improvement with a p-value of 0.0616. The study concluded that after total knee replacement, an improvement in quality of life could be documented (23).

According to the findings of certain authors (19), pain is an essential measure of postoperative outcomes. Alleviating pain significantly improves a patient’s quality of life and their ability to perform functional activities. In line with these findings, the results of the same authors’ research showed significant improvement in terms of pain reduction, as measured by the Visual Analog Scale (VAS). Our research results follow the same trend, with the level of bodily pain before surgery being higher than the level of bodily pain after surgery.

It is evident that our respondents perceived their health as much better after surgery compared to the period before surgery, and energy and vitality in these patients increased after surgery. The relationship between impairment and limitations in participation in activities is largely determined by the type of illness, but contextual factors such as social support and/or work demands also play a crucial role. Accordingly, the level of social functioning also significantly im-

proved in respondents after surgery, whereas it was significantly lower before surgery (19).

According to various literature sources, pain from osteoarthritis can significantly reduce mobility and participation in daily activities, becoming a major source of stress, affecting both the body and mind, and manifesting as panic attacks and deteriorating general health. The findings of the mentioned research have proven that psychological conditions such as anxiety and depression correlate with pain intensity and lower functional ability in people suffering from hip and knee osteoarthritis (24).

In the research results of Šantić V. et al., statistically significant improvements were evident after surgery, measured in terms of physical function, role limitations due to physical problems, social function, energy and vitality, pain, general health, and role limitations due to emotional problems, except in the domain of mental health, where statistically significant improvement was not found. If we summarize our research, it is evident that it correlates with the aforementioned study, where statistically significant improvements were found in the same domains, including mental health (25).

Considering that quality of life is a subjective assessment, differences in coping with illness, fears, and emotional control strategies are to be expected. Women over the age of 60 have worse physical functioning than younger women. Additionally, older women have greater limitations in performing their roles due to emotional problems, vitality, mental health, and social functioning. High stress levels, memory issues, and fear of illness are factors that can potentially affect mental health and usually occur alongside treatment (26).

Accordingly, the results showed that limitations due to emotional difficulties were much greater in respondents before surgery, while in the domain of mental health, results were significantly better after surgery. Based on the obtained results, statistical significance was achieved in all domains of quality of life, indicating that the quality of life of patients improved after total knee replacement surgery compared to the preoperative period.

The limitation of our study lies in the sample of patients who were operated on in the Clinical Centre of Montenegro without considering patients who were not operated on and who underwent alternative therapeutic methods and rehabilitation.

Further research should focus on early recognition of patients with knee diseases, as these individuals experience limitations in both their quality of life and ability to work. It is especially important to emphasize early disease detection and rehabilitation to prevent future adverse health and economic consequences for patients with knee conditions. Additionally, it is essential to design preventive programs at the primary level of healthcare**.**

CONCLUSION

According to the criteria of the instrument used in this research, it is evident that before surgery, respondents experienced difficulties in all domains of patient quality of life covered by this survey instrument. When providing quality healthcare, attention should be focused on the patient and their needs to maintain and improve their safety, satisfaction, independence, and recovery. At the forefront of recovery through proper healthcare, patients need guidance and education on potential limitations, the risks of not following instructions, the use of assistive devices, and the implementation of physical exercises to improve health. Healthcare facilitates the patient's recovery as quickly as possible and allows for the gradual increase of daily activities according to their capabilities. Along with medical-technological advances and established treatment standards, healthcare ensures comprehensive quality, safety, and continuity of healthcare procedures to protect health. Accordingly, the analysis of patients' quality of life after total knee replacement surgery, with adequate healthcare, in our study demonstrated significant improvements in quality of life across various domains compared to the preoperative period.

Abbreviations

HRQoL - Health-related quality of life
PCS - Physical Component Summary Measure
MCS - Mental Component Summary Measure
VAS - Visual Analog Scale
WHO - World Health Organization

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Sažetak

KVALITET ŽIVOTA PACIJENATA NAKON UGRADNJE TOTALNE ENDOPROTEZE KOLENA

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Uvod: Bolesti sistema za kretanje česte su bolesti u opštoj populaciji. One značajno utiču na porast morbiditeta, češće korišćenje zdravstvene zaštite, smanjenje radne sposobnosti, porast profesionalnog apsentizma i nastanak invalidnosti.

Metodologija: U ovom istraživanju su učestvovali ispitanici (pacijenti) sa ugrađenom endopretezom kolena u Kliničkom Centru Crne Gore – Podgorica. Koristili smo istraživačku metodu univerzalnog standardnog upitnika SF 36 koji je najšire primenjivan na više od 4 000 objavljenih publikacija.

Rezultati: Poboljšanje kvaliteta života pacijenta, u svim ispitivanim domenima (fizičko funkcionisanje p = 0,0001; ograničenje funkcije pokreta zbog fizičkih problema p = 0,0001; ograničenja funkcionisanja zbog emocionalnih problema p = 0,0001; vitalnost/energija p = 0,0002; mentalno zdravlje p = 0,0004 socijalno funkcionisanje p = 0,0001; opšte zdravlje p = 0,0001), identifikovano je nakon ugradnje endoproteze kolena.

Zaključak: Budući da su u svim domenima kvaliteta života dobijene statistički značajne razlike u rezultatima pre i nakon operacije ugradnje endoproteze kolena, potvrđeno je da se kvalitet života pacijenata nakon ugradnje endoproteze kolena poboljšao.

Ključne reči: endoproteza kolena, kvalitet života, invaliditet, radna sposobnost.

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Original article

TALC PLEURODESIS IN MANAGING BREAST CANCER-CAUSED MALIGNANT PLEURAL EFFUSIONS

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Abstract: **Introduction**: Breast cancer (BC) is the most common malignant tumor and the leading cause of cancer-related deaths among women in Serbia. Malignant pleural effusion (MPE) is a common manifestation of metastatic BC. Among solid tumors, BC accounts for the second-highest prevalence of MPE, occurring in 25% of cases. Current guidelines identify talc pleurodesis (TP) as one of the most effective treatments for MPE in most patients. This study aims to evaluate the effectiveness of TP in managing breast cancer-caused MPE.

Patients and Methods: This retrospective study included 21 patients with metastatic BC and MPE who were hospitalized at the Clinic for Thoracic Surgery, University Clinical Center Niš, during 2023. The success of TP was assessed using predefined clinical and radiographic criteria.

Results: TP was successful in 15 patients (71.4%). Luminal B BC was the most common subtype (42.9%). In the majority of cases, MPE was serous (71.4%) and ipsilateral (61.9%) to the primary breast tumor. Pleural cytology was positive in 28.6% of cases.

Conclusion: TP is an effective treatment for breast cancer-caused MPE. MPE is predominantly associated with Luminal B BC, and patients typically present with ipsilateral, serous MPE.

Keywords*:* malignant pleural effusion, breast cancer, thoracic drainage, talc pleurodesis.

INTRODUCTION

MPE is the pathological accumulation of free fluid in the pleural space, caused either by a malignant tumor originating in the pleura or by a metastatic tumor affecting the pleura (1). It occurs in approximately 15% of oncology patients and is often a manifestation of terminal disease (2, 3).

In developed countries, MPE is the third most common cause of pleural effusion, following congestive heart failure and parapneumonic effusion (1). Among malignant tumors, breast cancer (BC) is the second leading cause of MPE, accounting for 25% of cases, while lung cancer ranks first, with a prevalence exceeding 40% (1).

The primary goal of MPE treatment is to improve quality of life and prolong survival (4, 5). Treatment options include thoracocentesis, tube thoracostomy, drainage and pleurodesis, indwelling pleural catheter, pleuroperitoneal shunt, pleurectomy, and, in rare cases, extrapleural pneumonectomy (1, 6). Chemical pleurodesis, categorized as a secondary treatment option for MPE according to the 2023 BTS guidelines, is the focus of our research. Our study specifically evaluates BC patients undergoing this treatment (4).

The term "pleurodesis" originates from "pleura" (the lining of the lung) and "desis" (binding), reflecting its purpose: to obliterate the pleural space and prevent fluid accumulation (7). This effect is achieved by introducing an appropriate chemical agent (e.g., talc slurry, doxycycline, bleomycin, povidone iodine) into a previously well-drained pleural space, inducing iatrogenic pleurisy that results in pleural membrane adhesion and fibrosis (8).

This research aims to evaluate the success of TP in patients with breast cancer-caused MPE. Additionally, it examines the characteristics of the study subjects, including gender, age, immunohistological subtype of BC, macroscopic appearance and cytological features of pleural effusion, and the side of the effusion relative to the primary BC.

PATIENTS AND METHODS

This study was designed as a retrospective, monocentric study. It included 21 patients with metastatic

Table 1. *Inclusion and exclusion criteria for study*

Inclusion criteria	Exclusion criteria
1) patients with histologically verified BC and radiograph-confirmed pleural effusion	1) MPE patients with histologically verified malignancy elsewhere
2) data on the performed TP with a minimum of 4g of medical talc	2) patients treated using thoracentesis or thoracic drainage without TP
	3) record of previous chemical pleurodesis with less than 4g of medical talc or using another chemical agent
	4) other medical conditions associated with pleural effusion (pneumonia, heart / kidney / liver failure, etc.)

BC and MPE, comprising 20 females and one male, with an average age of 53.6 ± 10.9 years. All patients were hospitalized at the Clinic for Thoracic Surgery, University Clinical Center Niš, between January 1, 2023, and December 31, 2023. The youngest subject was 29 years old, and the oldest was 78. Disease-related data were obtained from the medical database.

Subjects were selected for the study based on predefined clinical and radiographic criteria (Table 1).

Therapeutic Procedure

For thoracic drainage, polyvinyl chloride chest tubes (size 24 Fr.) were used. Effusion was evacuated through an underwater or active drainage system (-20 cm H_2O) until complete lung re-expansion or for up to 48 hours. After achieving lung re-expansion, a previously prepared talc slurry was administered through the chest tube into the pleural space, which was then clamped for 4–6 hours. At the end of this period, the chest tube was returned to active drainage mode until secretion dropped to < 150 mL/24 h or for the next 48 hours.

The talc slurry was prepared by mixing 4 g of medical talc, 20 mL of 2% lidocaine-chloride solution (40 mg/2 mL), and 100 mL of 0.9% sodium chloride solution (NaCl).

TP success criteria

1) post-interventional secretion via chest tube < 150 ml/24h,

2) absence of respiratory problems within 7-10 days of drain removal, or

3) absence of clinically significant radiographic progression of MPE within 7-10 days of drain removal.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent from individuals was waived due to the retrospective nature of the study.

RESULTS

TP was successful in 71.4% of cases (Figure 1).

Luminal B BC was the most prevalent histological subtype of BC in the sample, accounting for 42.9%. In second place, in terms of frequency, was Luminal A BC (23.8%), followed by *triple-negative* BC (19%) and *HER2+* BC (4.8%). In 9.5% of cases (2 subjects), the histological subtype of BC was not defined (Figure 2a).

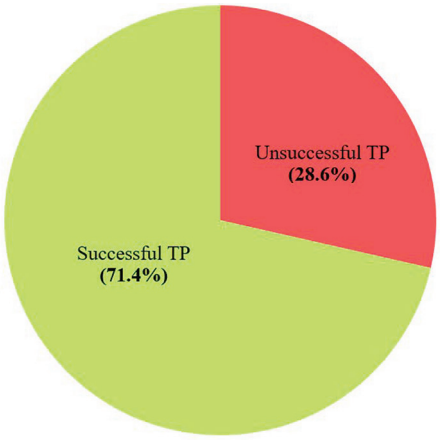

Figure 1. *Research results*

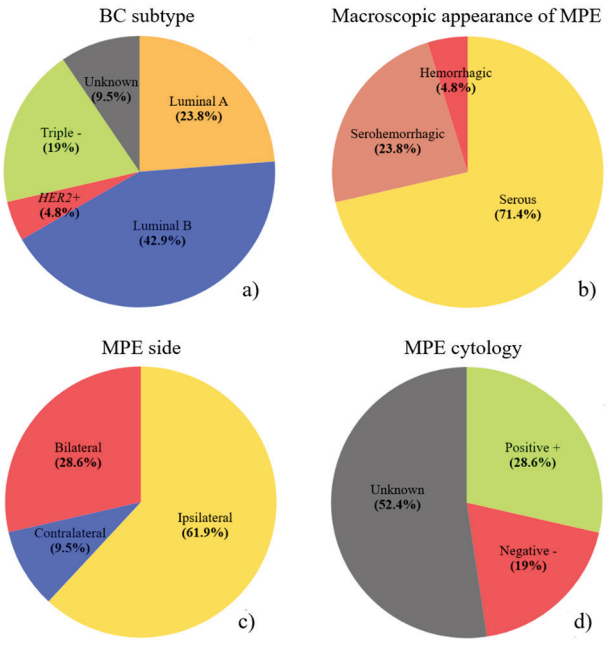

Figure 2. *Research results*

Regarding the macroscopic appearance of the pleural fluid, MPE was serous in 71.4%, serohemorrhagic in 23.8%, and hemorrhagic in 4.8% of cases (Figure 2b).

Relative to the side of the primary BC, MPE was ipsilateral in 61.9%, contralateral in 9.5%, and bilateral in 28.6% of cases (Figure 2c).

Cancer cells were identified in the pleural fluid in 28.6% of cases. In 19%, no cancer cells were present, while data on cytological examination were missing in 52.4% of cases (Figure 2d).

DISCUSSION

BC is the most common malignant tumor and the leading cause of cancer-related deaths in women in Serbia and globally (9). Thanks to organized screening programs, the disease is increasingly detected at an early stage, where treatment success is higher and prognosis more favorable. However, in some cases, BC can be insidious, presenting without obvious symptoms for extended periods, which leads to late-stage detection.

MPE can often be the first manifestation of advanced BC. It occurs in 7-11% of women at some stage of their illness, with over 15% of cases having MPE as the first sign (10). Among oncology patients with MPE, BC patients typically have a longer expected survival, ranging from 6.1 to 15.7 months, according to various studies (1, 10-16).

While BC in men is less common, with approximately one hundred times lower prevalence than in women (17), it is still notable. In men, MPE is present in about 7% of BC cases at the time of diagnosis (17).

The development of MPE is a complex, multifactorial pathological process. It is primarily caused by an imbalance between pleural fluid production and resorption. Pleural fluid hyperproduction can be driven by tumor cells and/or cytokines (e.g., interleukin-2, tumor necrosis factor, angiopoietin 1 and 2). Reduced resorption occurs due to obstruction of the parietal pleura pores and lymphatic capillaries, often as a result of direct invasion or lymphatic spread of the malignancy (6, 18). Most researchers believe that impaired pleural fluid resorption is the primary cause of MPE in BC patients (15, 19, 20).

Given these mechanisms, it is unsurprising that the majority of our patients had effusions on the ipsilateral side of the primary BC (61.9%), which aligns with findings in other studies (10, 13-15, 21-23). Only Chemow et al. reported differing results, with 64.7% of patients having bilateral MPE (16).

MPE can be serous, serohemorrhagic, or hemorrhagic in nature (2, 6), with the presence of hemorrhagic fluid often indicating metastatic invasion of the pleura (2). According to the Light criteria, an effusion containing > 100,000 erythrocytes/μL (in the absence of trauma) suggests an occult malignancy as the likely underlying cause (24). In our study, most patients had serous MPE (71.4%).

Cytological examination of pleural effusion revealed cancer cells in only 28.6% of cases, which is lower than the range of 47.5% to 78% reported in other studies (11, 13-15, 25, 26). The absence of cytological data for 52.4% of patients is due to the retrospective design of our study (whereas the aforementioned studies were prospective). Despite this, the presence of cancer cells was only one inclusion criterion, so the lack of cytological data did not affect the overall study results.

The classification of BC based on membrane receptor expression (ER, PR, HER2) plays a critical role in guiding treatment and determining prognosis. The disease is divided into four subtypes: Luminal A, Luminal B, HER2+, and triple-negative BC (27). Although some studies suggest MPE is more common in patients with triple-negative BC (28, 29), the majority of our subjects had Luminal B BC (42.9%), likely due to the small sample size.

According to the British Thoracic Society (BTS) and American Thoracic Society (ATS) guidelines, TP is one of the most effective treatments for MPE in patients who have achieved complete lung re-expansion through thoracic drainage, possess good performance status, and have a longer expected survival (> 1 month) (4, 30). As mentioned in the introduction, the goal of TP is to obliterate the pleural space and prevent fluid buildup, which has a long-term positive effect on the clinical course and prognosis of the disease (7, 31). While the precise mechanism of pleurodesis remains unclear, it is known that transforming growth factor-β plays a key role. This cytokine induces epithelial-mesenchymal transition and collagen production in mesothelial cells, leading to pleural space obliteration (2).

A meta-analysis published in 2020 confirmed the superiority of talc over other chemical agents (e.g., doxycycline, silver nitrate, bleomycin, povidone iodine, tetracycline, and mustin) in terms of effectiveness (7). Furthermore, talc is more cost-effective than other options (32, 33), and in 12-month survival analyses, bedside TP was found to be the least expensive treatment for MPE (32).

Our study is the first to evaluate the efficacy of TP specifically in the BC population. A 2024 meta-analysis by Rodrigues et al. (which included at least 117 BC patients treated with TP) found the overall effectiveness ranged from 54.2% to 96.5%, depending on the study

(34). In our study, TP was effective in 71.4% of cases, which is within the range reported in these studies.

CONCLUSION

From the results of our research, it can be concluded:

1) TP is an effective MPE treatment method,

2) MPE is most commonly associated with Luminal B BC, and

3) The majority of BC patients with MPE exhibit ipsilateral, serous effusions

Study limitations and future directions

The main limitations of our study include its retrospective design, small sample size (n = 21), and incomplete medical records in some cases (particularly the absence of data on cytological examination and BC subtypes). We attribute the small sample size to the fact that, prior to 2023, pleurodesis in our clinic was predominantly performed using less than 4g of talc or alternative chemical agents.

Future research should involve a prospective study with a larger sample size, conducted under controlled conditions, to assess the response of different BC subtypes to TP treatment.

Abbreviations

ATS – American Thoracic Society
BC – Breast cancer
BTS – British Thoracic Society
ER – Estrogen ceceptor
HER2 – Human epidermal growth factor 2 receptor
MPE – Malignant pleural effusion
PR – Progesterone receptor
TP – Talc pleurodesis

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Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

TALK PLEURODEZA U TERAPIJI MALIGNIH PLEURALNIH IZLIVA IZAZVANIH KARCINOMOM DOJKE

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Uvod: Karcinom dojke (*engl.* BC) je najčešći maligni tumor i vodeći uzrok smrti od malignih bolesti kod žena u Srbiji. Česta manifestacija metastatskog BC je MPE. Među solidnim tumorima, BC je drugi najčešći uzročnik MPE, sa prevalencom od 25%. Prema aktuelnim smernicama, TP je terapija izbora za većinu pacijenata sa MPE. Cilj našeg istraživanja je procena uspešnosti TP kod pacijenata sa MPE zbog BC.

Ispitanici i metode: Istraživanje je dizajnirano kao retrospektivna studija. Studijom je obuhvaćen ukupno 21 ispitanik sa metastatskim BC i MPE. Svi pacijenti uključeni u studiju bili su hospitalizovani na Klinici za grudnu hirurgiju Univerzitetskog kliničkog centra u Nišu, tokom 2023. godine. Efikasnost TP smo procenjivali na osnovu unapred definisanih kliničkih i radiografskih kriterijuma.

Rezultati: TP je bila uspešna kod 15 ispitanika (71,4%). Luminalni B BC je bio najzastupljeniji u uzorku (42,9%). U većini slučajeva MPE je bila serozna (71,4%) i ipsilateralna (61,9%) u odnosu na stranu primarnog tumora dojke. Citologija pleuralnog punktata je bila pozitivna u 28,6% slučajeva.

Zaključak: TP je uspešna metoda lečenja MPE izazvanih BC. U osnovi MPE uglavnom leži Luminalni B BC. Pacijenti najčešće imaju ipsilateralnu, seroznu MPE.

Ključne reči: maligna pleuralna efuzija, karcinom dojke, torakodrenaža, talk pleurodeza.

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Case report

PLEUROPULMONARY SALMONELLA INFECTION – A CASE REPORT

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Abstract: **Introduction:** Invasive nontyphoidal salmonellosis occurs in 5–10% of all nontyphoidal *Salmonella* infections, with an increasing trend, even in non-endemic areas. Extraintestinal manifestations may include inflammation or abscess formation in various organs, such as the lungs, meninges, kidneys, testes, muscles, and gallbladder.

Case report: We present the case of a 65-year-old female patient admitted for treatment due to fatigue, dyspnea, and weight loss. She did not report diarrhea or fever, and no epidemiological factors suggested a gastrointestinal infection. Her medical history included hypertension and long-term heavy cigarette smoking. A chest X-ray, followed by a CT scan, revealed a pleural effusion, and *Salmonella enteritidis* was isolated from the pleural fluid. Stool, blood, and urine cultures were negative. Further diagnostics revealed dilated bile ducts, mild thickening of the gallbladder wall, and chronic gastritis. Laboratory findings indicated an elevated erythrocyte sedimentation rate, leukocytosis with neutropenia, and increased levels of C-reactive protein and lactate dehydrogenase. The patient was treated with ceftriaxone. The clinical course was complicated by an ischemic cerebrovascular accident, but the overall outcome was favorable.

Conclusion: Pulmonary salmonellosis is rare but can occur in the absence of the typical gastrointestinal symptoms associated with *Salmonella* infection. Early diagnosis is crucial for successful treatment. In this context, prompt microbiological sampling and the initiation of broad-spectrum antibiotics are essential.

Keywords*:* Salmonella, pleural empyema, negative stool cultures, negative blood cultures.

INTRODUCTION

Salmonellosis is one of the leading gastrointestinal infections worldwide, with over 90 million cases and more than 155,000 deaths annually (1). These infections are classified into three main types: typhoidal, nontyphoidal invasive, and nontyphoidal noninvasive. Typhoidal forms are the most severe and are most commonly observed in endemic regions. Nontyphoidal invasive salmonellosis accounts for 5–10% of all *Salmonella* infections and remains a significant challenge in diagnosis and treatment (2). Nontyphoidal noninvasive salmonellosis is the mildest clinical form.

The most common clinical manifestations include fever and signs of enteritis, such as diarrhea accompanied by abdominal pain. The bacteria can spread from the intestines through the bloodstream or lymphatic system, causing inflammatory changes in various organs, including the meninges, bones, skeletal muscles, heart, lungs, kidneys, and testes. In affected organs, empyemas or abscess-like formations may develop (3, 4). *Salmonella* has also been isolated from cultures of patients with skin lesions, external auditory canal infections, or infections at the tip of a dialysis catheter (5).

The most common risk factors for *Salmonella* infection include residing in endemic areas such as sub-Saharan Africa, the Middle East, and Southeast Asia (6). Additional risk factors include male gender, advanced age, comorbidities, and the use of immunosuppressive medications (7).

CASE REPORT

A 65-year-old woman was admitted to General Hospital Užice in August 2024 due to fatigue and difficulty breathing. The fatigue had persisted for two months, and dyspnea had worsened over the past few days. During this period, she had lost 5–6 kg of body weight. She also reported nausea but no vomiting, fever, or diarrhea. Her medical history included hypertension and long-term heavy smoking.

A previous abdominal ultrasound revealed only one abnormal finding: the presence of free fluid in the Douglas pouch. A computed tomography (CT) scan of the abdomen showed a heterogeneous liver structure, a gallbladder wall thickness of 4 mm, dilation of the hepatic duct and common bile duct up to 12 mm, and suspected early dilation of the intrahepatic bile ducts in the left liver lobe. Numerous lymph nodes, measuring up to 8 mm, were observed in the hepatogastric and hepatoduodenal ligaments, as well as para-aortically and paracavally. Free fluid was also noted perihepatically and in the pelvic cavity. An esophagogastroduodenoscopy revealed chronic gastritis.

Magnetic resonance cholangiopancreatography (MRCP) showed mildly dilated intrahepatic bile ducts and dilated extrahepatic bile ducts extending to the major papilla. The common hepatic duct measured 8 mm, and the common bile duct measured 9 mm, with smooth contours up to the intrapancreatic section, where there was luminal narrowing and wall thickening of up to 4 mm.

Upon admission, the patient was afebrile, cachectic, and dyspneic. Peripheral oxygen saturation (SpO_2) on room air was 83%. On auscultation, breath sounds were absent in the right lower lung field. The heart rate was irregular. The abdomen was non-tender and non-distended, with no palpable hepatosplenomegaly.

The electrocardiogram showed atrial fibrillation with absolute ventricular arrhythmia, an average ventricular rate of 70–80 beats per minute, and micro R waves up to V3, indicating systolic overload of the left ventricle.

A chest X-ray revealed lung parenchymal opacity on the right side, suggestive of a pleural effusion (Figure 1).

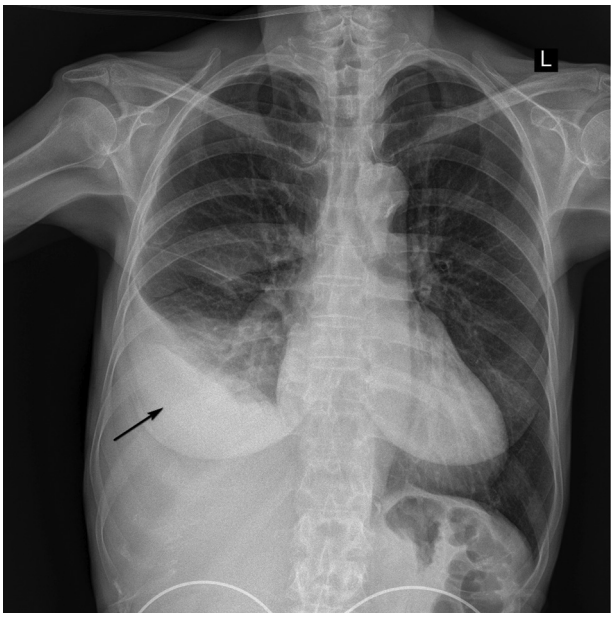

Figure 1. Chest X-ray
(*Source: image is from the author's archive)*

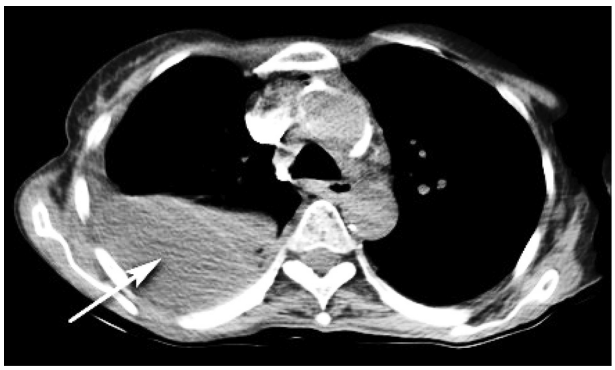

Figure 2. Computed tomography of the chest
(*Source: image is from the author's archive)*

A CT scan of the chest revealed early emphysematous changes of the centrilobular type bilaterally and an atypical pleural effusion on the right, measuring up to 50 mm in thickness. The effusion extended to the lung apex and interlobarly in the cranial part of the costal margin, with axial dimensions of 72 × 43 mm and caudal dimensions of 26 × 9 mm. There was associated compressive atelectasis and ground-glass opacities in the adjacent lung parenchyma (Figure 2).

Laboratory findings showed an elevated erythrocyte sedimentation rate (ESR), leukocytosis with neutrophilia, and increased levels of lactate dehydrogenase and C-reactive protein (Table 1). A pleural punc-

Table 1. *Laboratory analyses at the patient's admission*

Parameters (normal range)	Measured value
Erythrocite sedimentatiton rate (< 20 mm/hr)	98
Red blood cells (4-5.9 x 1012/L)	3.5
White blood cells (4–10 x 109/L)	13.9
Neutrophil count (1.9–8.0 x 109/L)	9.6
Platelet count (150.0–450.0 x 109/L)	263
Fibrinogen (2.0–4.0 g/L)	4.5
Blood sugar (4.1–5.9 mmol/L)	5.5
Blood urea nitrogen (2.8–7.2 mmol/L)	7.2
Serum creatinine (59.0–104. Umol/L)	34
Alanine aminotransferase (<45 U/L)	97
Aspartate aminotransferase (15.0-60.0 U/L)	48
Alkaline phosphatase (30–120 U/L)	64
Serum amylase (30–118 U/L)	54
Urine amylase (21–447 U/L)	142
Sodium (132–146 mmol/L)	136
Potassium (3.5–5.5 mmol/L)	4.1
Lactate dehydrogenase (208.0–378.0 U/L)	547
Creatne kinaze (32.0–294.0 U/L)	69
Creatine kinaza-MB (< 24 U/L)	9
C-reactive protein (< 5 mg/L)	104

ture evacuated 1400 mL of purulent fluid, and SpO_2on room air improved to 96%.

Salmonella enteritidis was identified in the puncture culture using the Vitek® 2 Advanced Expert System (bioMérieux). Antibiotic susceptibility testing, performed using the disk diffusion method, showed sensitivity to *Amoxicillin, Ceftriaxone, Ciprofloxacin*, and *Trimethoprim-sulfamethoxazole*. No isolates were found in the urine culture or repeated stool cultures.

Treatment included oxygen support, antibiotics (*Ceftriaxone*), cardiotonics, calcium channel blockers, diuretics, and antithrombotic therapy (acetylsalicylic acid).

On the fifth day of hospitalization, the patient developed right-sided weakness and difficulty speaking. A CT scan of the brain revealed a large area of hypodensity in the middle and, to a lesser extent, in the upper right frontal gyrus, consistent with an older ischemic lesion. In the upper left frontal gyrus, one relatively larger and one smaller area posterior to it appeared as more recent ischemic lesions.

Further neurological monitoring was conducted, followed by physical therapy.

The hospitalization lasted 12 days. The patient was discharged without respiratory or gastrointestinal complaints, with normal auscultatory findings and chest X-ray. The neurological examination revealed mild sensory dysphasia and moderate right-sided hemiparesis.

DISCUSSION

Pulmonary infections caused by gram-negative bacteria in community settings are rare (8). Extraintestinal salmonellosis is also uncommon and typically occurs in individuals with immunodeficiencies (9).

We present a case of a patient who acquired the infection in a community setting. She did not belong to the typical high-risk group—elderly men on immunosuppressants—and primarily presented with respiratory symptoms. Similar cases have been reported by other authors (10, 11).

Our patient had experienced fatigue but attributed it to the effects of smoking. The most common symptoms of non-typhoidal Salmonella infection are diarrhea and abdominal pain (12). However, in our case, as well as in other reported cases, these symptoms were absent (10, 11). Pulmonary Salmonella infection was also described by Kaur et al., who diagnosed a bronchogenic Salmonella cyst in their patient (13).

While investigating the source of the infection, it was suspected that Salmonella may have entered the bronchi through inhaled marijuana vapors. Our patient was a long-time smoker but denied marijuana use, although she occasionally rolled cigarettes with cut tobacco. Based on Kaur et al.'s reasoning, we cannot definitively exclude this route of pathogen entry.

As with previous reports, blood cultures in our case were sterile. The patient denied experiencing fever during the two months of her symptoms. Before hospitalization, she had been prescribed amoxicillin by a gastroenterologist, which she took for seven days. The Salmonella enteritidis strain isolated from the pleural puncture was sensitive to amoxicillin. It is possible that the antibiotic therapy partially affected the pathogen and limited early dissemination but was insufficient to fully eradicate the infection.

The clinical course and outcome of the infection depend on the serotype of the pathogen and the immune status of the host (14). Different Salmonella serotypes produce specific toxins that exert varying effects on organs (15). The first line of defense against enteropathogenic Salmonella is the intestinal immune system, which is activated by bacterial toxins (16). Macrophages in the intestinal mucosa are activated through receptors for the Salmonella flagellin antigen (17). In response, Salmonella polarizes macrophages, enabling immune evasion and long-term persistence in the intestines (18). Among various mechanisms of dissemination, Salmonella exploits host cell migration, primarily through dendritic cells (1). A key virulence factor of these bacteria is the type III secretion system, which initiates apoptosis in infected macrophages (19). Through this system, Salmonella modulates programmed cell death, a crucial host defense mechanism (20).

The complexity of these immune evasion strategies may explain the increasing prevalence of invasive non-typhoidal Salmonella infections (2), which have been associated with higher mortality rates and an increased need for intensive care (21). Immediately after the pleural puncture, we initiated *Ceftriaxone* treatment without anticipating the presence of gram-negative bacteria in the pleural culture. Since Salmonella enteritidis was found to be sensitive to *Ceftriaxone* and the patient's clinical condition improved, we continued this therapy. Other authors have also reported successful treatment of Salmonella-related pulmonary infections with *Ceftriaxone* (22). As in our case, antibiotic therapy was often preceded by surgical intervention to drain empyemas or abscesses whenever feasible (4, 22).

Recent studies have highlighted rising antibiotic resistance in Salmonella strains. However, in our case, the pathogen remained susceptible to multiple antibiotics, and the patient's symptoms resolved rapidly. Laboratory findings were consistent with a bacterial

infection, including elevated erythrocyte sedimentation rate (ESR), leukocytosis with neutrophilia, and increased levels of C-reactive protein and lactate dehydrogenase. Similar laboratory patterns have been reported by other authors (5).

The clinical course of our patient was unexpectedly complicated by an ischemic stroke. A CT scan revealed older ischemic changes, but the patient had no history of prior neurological symptoms. Long-standing hypertension may have contributed to vascular changes that weakened her immune defenses and increased susceptibility to infection.

Despite the cerebrovascular event, the patient's overall clinical course was favorable. However, the exact source of the Salmonella infection remains uncertain. Given the initial gastric symptoms and imaging findings of biliary tract abnormalities, we considered the biliary tract a potential source of infection, as described in previous literature (23, 24). A bile culture would have been necessary to confirm this, but the patient declined a repeat endoscopic retrograde cholangiopancreatography.

In conclusion, this case represents a rare presentation of invasive non-typhoidal Salmonella infection. Early suspicion of Salmonella infection is crucial for accurate diagnosis and treatment, especially in the absence of typical enteric symptoms.

Abbreviations

CT - computed tomography

MRCP - Magnetic resonance cholangiopancreatography

SpO_2 - Peripheral oxygen saturation

Author contributions: PS: Conceptualization, validation, data curation, writing—original draft..PA: Formal analysis, literature research, review, and editing.NA: Formal analysis, literature research, supervision.

Conflict of Interest: The authors declare no conflicts of interest related to this article.

NOTE: Artificial intelligence was not used as a tool in this study.

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Sažetak

PLEUROPULMONALNA INFEKCIJA SALMONELOM - PRIKAZ SLUČAJA

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Uvod: Invazivna netifoidna salmoneloza je prisutna kod 5-10% svih netifoidnih salmoneloza, sa tendencom rasta, čak i u neendemskim područjima. Ekstraintestinalni klinički oblici mogu biti upale ili apscesi u raznim organima, kao što su pluća, moždanice, bubrezi, testisi, mišici, žučna kesa.

Prikaz slučaja: Analizirali smo slučaj pacijentkinje starosti 65 godina primljene na lečenje zbog malaksalosti, otežanog disanja i gubitka u telesnoj težini. Nije imala dijareju, niti febrilnost. Nije bilo epidemioloških podataka za crevnu infekciju. Prethodna medicinska dokumentacija je ukazala na arterijsku hipertenziju i dugogodišnje intenzivno pušenje cigareta. Na radiografskom snimku, a zatim i skeneru grudnog koša viđen je pleuralni izliv, a u punktatu je izolovana Salmonella enteritidis. Koprokulture, hemokulture i urinokultura su bile negativne. Dijagnostikovano je proširenje žučnih puteva i lako zadebljanje žučne kese, kao i hronični gastritis. U laboratorijskim nalazima je imala ubrzanu sedimentaciju eritrocita, leukocitozu sa neutropenijom, povišene vrednosti c-reaktivnog proteina i laktat dehidrogenaze. Lečena je ceftriaksonom. Klinički tok se komplikovao ishemičnim cerebrovaskularnim insultom, ali je ishod lečenja bio povoljan.

Zaključak: Plućni oblik salmoneloze nije čest, ali je moguć bez prethodnih simptoma uobičajenih za crevnu salmoneloznu infekciju. Za uspešno izlečenje je važno rano postavljanje dijagnoze. U tom smislu je potrebno što ranije uzimanje uzorka za mikrobiološku dijagnostiku i uvođenje antibiotika širokog spektra dejstva.

Ključne reči: Salmonella, pleuralni empijem, negativne koprokulture, negativna hemokultura.

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Case report

ISOLATED CONGENITAL KNEE DISLOCATION: A CASE REPORT

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Abstract: **Introduction:** Congenital knee dislocation is a rare orthopedic condition characterized by abnormal positioning of the knee joint at birth, with an estimated incidence of approximately 1 in 100,000 live births. It is often associated with other congenital anomalies, necessitating prompt diagnosis and management.

Case Report: A male neonate delivered via cesarean section was referred for orthopedic evaluation due to a left lower extremity deformity. Initial examination revealed left knee hyperextension of approximately -45 degrees and restricted passive flexion limited to 90 degrees. Neurovascular assessment was normal. Radiographic imaging confirmed hyperextension without additional skeletal deformities. The treatment plan involved above-knee cast immobilization in maximal flexion, changed weekly for six weeks. By the end of the immobilization period, the patient exhibited significant improvement, achieving a full passive range of knee flexion and extension. Follow-up two weeks later confirmed normal passive and active ranges of motion, with no residual impairment.

Conclusion: Early intervention in congenital knee dislocation is crucial for achieving favorable functional outcomes, emphasizing the effectiveness of non-operative strategies in neonates.

Keywords: Knee dislocation, Congenital abnormalities, Conservative treatment, Neonatal orthopedics.

INTRODUCTION

Congenital knee dislocation (CKD) is a rare condition characterized by abnormal positioning of the knee joint at birth, with an estimated incidence of approximately 1 in 100,000 live births (1). It is frequently associated with other congenital anomalies, such as hip dislocation and clubfoot, with studies indicating that 60-88% of patients with CKD present with additional musculoskeletal abnormalities (2, 3, 4). The etiology of CKD is largely idiopathic; however, it has been associated with various factors, including muscle imbalance, ligamentous laxity, and other congenital abnormalities of lower extremities (2, 5). Diagnosis is typically made after physical examination and imaging studies, including X-rays, which reveal characteristic features such as anterior tibial translocation on the femur and hyperextension of the knee joint (1).

Management typically involves non-operative techniques such as closed reduction and immobilization, which have shown success in restoring normal knee function when initiated promptly (5, 6). Early intervention is crucial, as delayed treatment can lead to more complex surgical requirements and poorer functional outcomes (2, 3, 4). Therefore, while isolated congenital knee dislocation is uncommon, its implications for pediatric orthopedic practice are significant, necessitating awareness and appropriate management strategies.

CASE REPORT

A male neonate was delivered via cesarean section and referred for orthopedic evaluation on the same day due to a left lower extremity deformity. Upon initial examination, the left knee was hyperextended at an angle of approximately -45 degrees, with passive flexion restricted to 90 degrees (Figure 1). The neurovascular status of the limb was assessed and found to be normal.

Radiographic imaging was performed, and X-rays confirmed hyperextension of the knee; however, no additional skeletal deformities were identified (Figure 2).

Based on the clinical findings and imaging results, the patient was diagnosed with isolated congenital knee dislocation. The initial treatment plan involved above-knee cast immobilization, with the knee positioned in

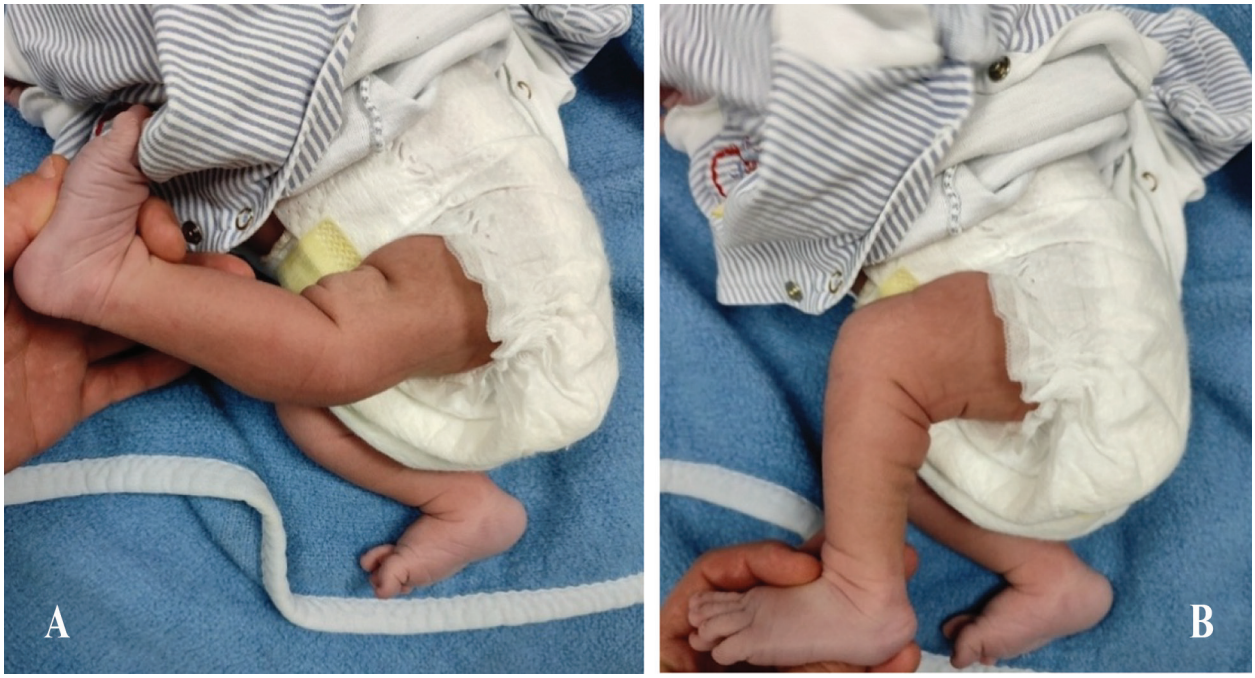

Figure 1. *Clinical images on the day of birth A. – Knee in maximal extension and B – knee in maximal flexion (from authors' archive)*

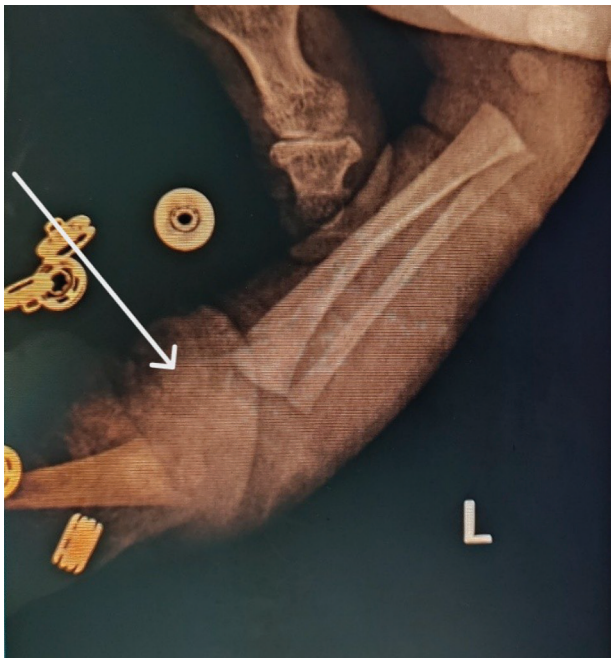

Figure 2. *X-rays of the knee in maximal passive extension show hyperextension of the knee joint (from authors' archive)*

Figure 3. *Above-knee cast immobilization in maximal flexion placed after the examination (from authors' archive)*

maximal flexion to promote proper alignment and facilitate correction of the dislocation (Figure 3).

The cast was changed weekly for a period of six weeks. During each follow-up examination, the cast was removed, and a regimen of passive range of motion exercises was implemented. Specifically, passive flexion and extension exercises were performed for a duration of five minutes before reapplying a new above-knee cast in maximal flexion. This approach aimed to enhance joint mobility while maintaining the necessary immobilization to correct the dislocation.

At the conclusion of the six-week immobilization period, the cast was removed, revealing a significant improvement in the knee's range of motion. The patient demonstrated full passive range of knee flexion with a loss of 10 degrees in passive knee extension

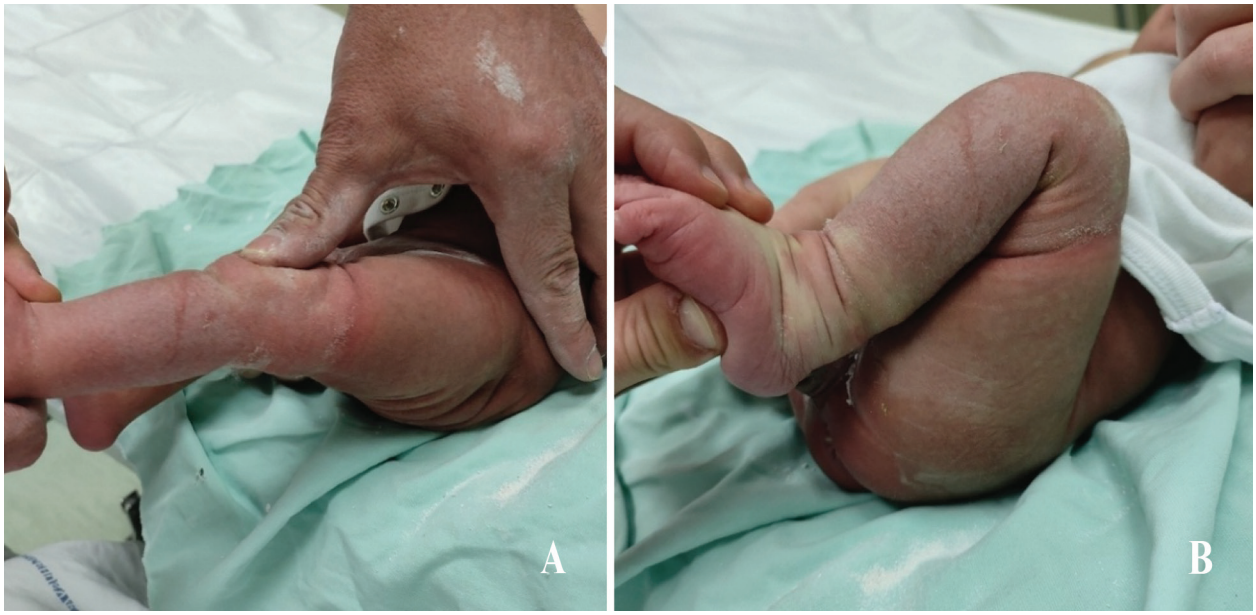

Figure 4. *Images at the end of 6 weeks of treatment A. – Knee in maximal extension and B – knee in maximal flexion (from authors' archive)*

(Figure 4). Following this examination, the parents were instructed to continue passive range of motion exercises several times per day to further promote joint function and prevent stiffness.

A follow-up examination conducted two weeks after the cast removal revealed that both passive and active ranges of motion had normalized, confirming the successful management of the congenital knee dislocation.

DISCUSSION

Congenital knee dislocation (CKD) is a rare condition that poses significant challenges in both diagnosis and management. The estimated incidence of CKD is approximately 1 in 100,000 live births, making it less common than other congenital musculoskeletal disorders, such as developmental dysplasia of the hip (1). In our case, the male neonate presented with a left knee hyperextension deformity, which was promptly identified and managed through conservative measures. This aligns with current literature that emphasizes the importance of early intervention in improving functional outcomes and preventing complications associated with delayed treatment (5-9).

The association of CKD with other congenital anomalies is well-documented, with studies indicating that 60-88% of patients with CKD may present with additional musculoskeletal abnormalities, including congenital hip dislocation and clubfoot (3, 4). In our case, the absence of additional skeletal deformities is noteworthy, as it suggests a more isolated presentation of CKD. The literature highlights that the presence of concomitant deformities often necessitates a more comprehensive treatment approach, including the need for surgical intervention in more complex cases (5, 6, 10).

The etiology of CKD remains largely idiopathic, although it has been associated with factors such as muscle imbalance, ligamentous laxity, and anatomical abnormalities (2, 3). In our patient, the hyperextension of the knee and limited passive flexion were indicative of a structural deformity that required intervention. The treatment protocol employed, which involved above-knee cast immobilization in maximal flexion, is consistent with recommended practices for managing CKD. This approach has been shown to be effective in restoring knee function when initiated early (5, 6, 10).

At the conclusion of the six-week immobilization period, the patient exhibited significant improvement in the range of motion. This outcome is consistent with findings from other studies that report successful restoration of knee function through conservative management (4, 6, 11). However, it is important to note that not all cases of CKD respond favorably to non-operative treatment. The classification of CKD into types based on reducibility and stability can influence treatment strategies and outcomes (3, 4, 12). In cases where the dislocation is irreducible or associated with significant instability, surgical intervention may be warranted to achieve optimal results (2, 6).

CONCLUSION

In conclusion, this case underscores the importance of early recognition and appropriate management of congenital knee dislocation (CKD). The suc-

cessful outcome achieved through conservative treatment highlights the potential of non-operative strategies to restore knee function in neonates with CKD. Future research should focus on refining classification systems and treatment protocols to optimize outcomes for patients with CKD, particularly those with associated congenital anomalies.

Abbreviations

CKD - Congenital knee dislocation

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Author Contributions: All authors contributed substantially to all sections of the manuscript. All authors have read and approved the final version of the manuscript.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was not required, as this was a case report.

Informed Consent Statement: Written informed consent was obtained from the patient´s parents for the publication of this case report.

Data Availability Statement: All data generated or analyzed for this report are included in the published article.

NOTE: Artificial intelligence was not used as a tool in this study.

Sažetak

IZOLOVANA KONGENITALNA DISLOKACIJA KOLENA: PRIKAZ SLUČAJA

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Uvod: Kongenitalna dislokacija kolena je retko ortopedsko stanje koje karakteriše abnormalan položaj zgloba kolena pri rođenju, s procenjenom incidencom od 1 na 100 000 živorođene dece. Često se povezuje s drugim kongenitalnim anomalijama, što zahteva brzu dijagnozu i lečenje.

Prikaz slučaja: Muško novorođenče rođeno carskim rezom upućeno je na pregled ortopeda zbog deformiteta levog donjeg ekstremiteta. Početni pregled otkrio je hiperekstenziju levog kolena do približno -45 stepeni i ograničenu pasivnu fleksiju do 90 stepeni. Neurovaskularni status je bio normalan. Radiografski snimak potvrdio je hiperekstenziju kolena bez dodatnih deformiteta skeleta. Plan lečenja je uključivao natkolenu gipsanu imobilizaciju u maksimalnoj fleksiji, koja se menjala sedmično tokom šest sedmica. Na kraju perioda imobilizacije, pacijent je imao značajno poboljšanje lokalnog nalaza, puni opseg pasivne fleksije i ekstenzije kolena. Kontrolni pregled dve sedmice kasnije potvrdio je normalan pasivni i aktivni raspon pokreta, bez zaostalog deformiteta.

Zaključak: Rana intervencija kod kongenitalne dislokacije kolena ključna je za postizanje povoljnih funkcionalnih ishoda, naglašavajući efikasnost neoperativnog lečenja kod novorođenčadi.

Ključne reči: dislokacija kolena, kongenitalne abnormalnosti, konzervativno lečenje, neonatalna ortopedija.

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Case report

PEDICLED MUSCLE FLAPS FOR THE MANAGEMENT OF IMPLANT COMPLICATIONS IN THE LOWER LIMBS: A REPORT

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Abstract: **Introduction**: Metallic implants are widely used for the reconstruction of bony defects caused by fractures, excision of cancer, and degenerative bone disorders. These implants are associated with complications, including exposure and infection, particularly when vascularized tissue is needed for reconstruction. A key tool in plastic surgery to address these complications is the pedicled muscle flap.

Case Report: This article presents two cases in which pedicled medial gastrocnemius and peroneus brevis muscle flaps were successfully used to salvage the hardware and achieve effective wound coverage.

Conclusion: Pedicled medial gastrocnemius and peroneus brevis muscle flaps are valuable options for covering complicated skin defects over exposed implants.

Keywords: hardware salvage, peroneus brevis, medial gastrocnemius, pedicled muscle flap, external fixators, free flap, graft take, total knee arthroplasty.

INTRODUCTION

Implants are commonly used in the lower limbs to manage degenerative, neoplastic, and traumatic conditions. However, they carry a significant risk of exposure, infection, and failure, particularly in trauma cases. The literature reports a hardware infection rate of up to 27% in Gustilo type III open tibia fractures (1). When complications arise, a multifaceted approach is used to salvage the implant, which includes debridement, antibiotics, and muscle flap coverage (2,3). We present two cases in which pedicled muscle flaps were successfully used to salvage the implants in the lower extremities.

CASE PRESENTATION

Medial Gastrocnemius Muscle Flap

A 62-year-old female presented with a non-healing wound (Figure 1) two months after undergoing right total knee replacement for chronic osteoarthritis. Her medical history included controlled hypertension (on ramipril 5 mg/day), hypothyroidism (on thyroxine 100 micrograms/day), and an uneventful cholecystectomy for symptomatic cholelithiasis 9 years prior. On examination, she was morbidly obese (weight 103 kg; BMI 34 kg/m²). A dehiscence measuring 3.5 x 3 cm with necrosis was observed at the distal end of a 15 cm long postoperative scar over the right knee (Figure 1 A-B).

Wound debridement and exploration revealed a 7 cm deep sinus that accommodated the entire shaft of a size 00 Spratt Brun bone curette (Figure 1 C-D), placing the hardware of the replaced knee at significant risk of exposure. There were no signs indicative of chronic arterial insufficiency. Blood work revealed leucocytosis and elevated C-reactive protein (CRP) levels. Microbiological analysis of the wound swab identified gram-positive bacteria (Staphylococcus aureus/epidermidis). Antibiotics were initiated according to the sensitivity reports, and the VAC-Instil system with Granudacyn (Molynlyke) antiseptic solution was

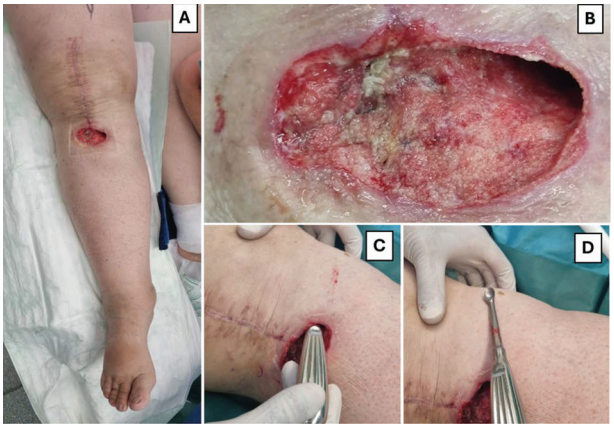

Figure 1*. **A-B)** Chronic wound post-total knee replacement. **C-D)** Wound leading to a 7 cm deep sinus. (Image credits: Saleh Alhotan - Author)*

applied to the wound, set at 125 mm Hg continuous pressure with added wash-suck cycles (15 minutes wash, 3 hours suck) twice daily.

Following nine days of diligent wound care, swabs showed no signs of bacterial growth. A pedicled, proximal-based medial gastrocnemius muscle flap with a meshed split-thickness skin graft was used to close the wound. The skin graft was harvested from the right medial thigh. Postoperatively, the VAC (vacuum-assisted closure) system was reapplied with continuous pressure of 75 mmHg, and the knee joint was immobilized in a macron cast to prevent flexion (figure 2 A-B). The VAC system was discontinued on the fifth postoperative day when 100% graft take was achieved, and the muscle flap showed no signs of infection and was viable (Figure 2 C-D). On the seventh postoperative day, the patient was discharged to home care. The graft donor site and flap harvest surgical incision healed without complications. At the 6-month telephonic follow-up, the patient reported no complaints and was highly satisfied with the outcome.

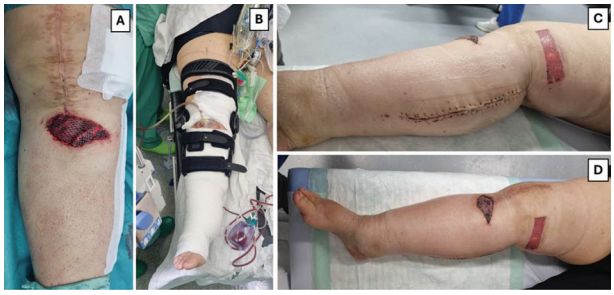

***Figure 2**. **A)** Gastrocnemius muscle flap with meshed split-thickness skin graft. **B)** Wound attached to the VAC system, and knee immobilized with a macron cast. **C-D)** Healed wound, surgical incision, and skin graft donor site, 2 weeks post-surgery. (Image credits: Saleh Alhotan - Author)*

Peroneus Brevis Muscle Flap

A 58-year-old female presented with an exposed plate and screws four weeks after open reduction and internal fixation (ORIF) of a fracture in the lower third of the fibula. She had controlled diabetes (managed with oral hypoglycemics) and hypertension (treated with ramipril). Her medical history included a laparoscopic appendectomy performed 15 years ago. On examination, she was of average build (weight: 82 kg; BMI: 27.7 kg/m²) and showed no clinical signs of chronic arterial insufficiency. The wound, measuring 5 cm x 2.5 cm, showed exposed plate and screws along the lower lateral surface of the left leg (Figure 3 A-B). The wound edges appeared healthy, with no significant discharge. Blood work was normal, and a CT scan of the left leg revealed incomplete healing of the fracture, but no signs of active osteomyelitis. Wound swabs did not grow any bacteria.

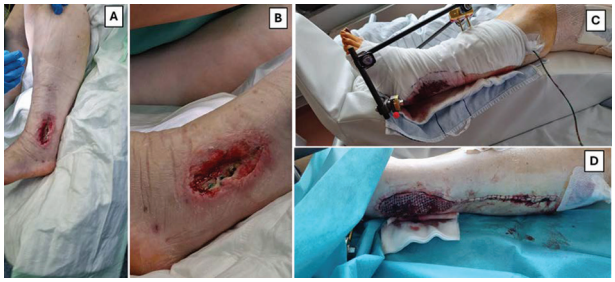

***Figure 3. A-B)** Exposed hardware over the lateral surface of the left leg. **C)** Blood soakage of dressing on the first postoperative day. **D)** Hematoma at the flap inset site. (Image credits: Saleh Alhotan - Author)*

The wound was debrided under general anesthesia, the hardware was removed, and external fixators were applied by the orthopedic team. A VAC system with 125 mm Hg pressure was applied for 5 days. Wound biopsy revealed no bacterial growth, and wound closure over the exposed bone was achieved under general anesthesia using a distally based pedicle peroneus brevis muscle flap with a meshed skin graft. Postoperatively, the VAC system (continuous pressure 75 mmHg) was reapplied.

However, on the first postoperative day, profuse soaking of the dressings was observed (Figure 3C), and upon removal, bleeding and hematoma formation (Figure 3D) were detected. This required limited re-exploration to evacuate clots and achieve hemostasis. After this, the course was uneventful, and by the fifth day, about 80% of the skin graft had taken (Figure 4A). The patient was discharged home on the seventh postoperative day and was advised to follow up with the orthopedic team, who later removed the external fixators after 8 weeks. The flap was fully viable, and complete skin coverage was gradually achieved as the patient was followed up for 10 weeks (Figures 4B-C).

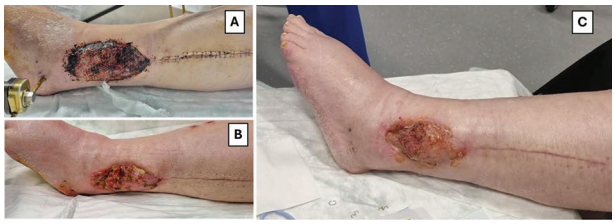

***Figure 4**. **A)** Viable flap with 80% graft take at 5 days. **B)** Viable flap with 90% skin coverage at 3 weeks. **C)** Viable flap with complete skin coverage at 10 weeks. (Image credits: Saleh Alhotan - Author)*

DISCUSSION

The pedicled gastrocnemius muscle flap is considered a reliable option for soft tissue reconstruction around the knee and upper leg, particularly when ex-

posure of bone, tendon, hardware, or joint capsule threatens the limb (4). Each head of the gastrocnemius muscle can be independently harvested due to its distinct vascularization, with a vascular pedicle supplying each head. This flap is particularly well-suited for restoring soft tissue and the extensor mechanism around the knee and popliteal fossa. The large muscle belly fills the dead space, and its transfer does not significantly impair the function of the donor limb, resulting in minimal donor-site morbidity (5).

In our case, the flap was harvested as muscle only, and skin coverage was achieved with a split-thickness skin graft. Alternatively, the gastrocnemius flap may be raised as a chimeric musculocutaneous flap, avoiding the need for a skin graft and the associated prolonged immobilization (6).

Tetreault et al. (7) analyzed the risk factors for medial gastrocnemius flap failure in total knee arthroplasty (TKA) patients and found that 52% of patients experienced persistent or recurrent infection. At four years, the survivorship of the TKA prosthesis was 48%. Importantly, no flap-related complications were reported. The authors concluded that the high failure rates were not related to the flaps themselves but to the complexity of the clinical issues at hand.

The peroneus brevis is a versatile and reliable flap that can be harvested with minimal donor-site morbidity (8). Its unique vascular supply runs down its deep aspect, connecting perforators from the anterior tibial artery and peroneal artery. This feature allows the flap to be raised on a single perforator, either proximally or distally, depending on the requirements. The peroneus brevis flap is easy to harvest and suitable for coverage of small- to moderately large distal leg, ankle, and foot defects. Donor-site closure is typically possible by primary intention, resulting in a linear and aesthetic scar (8, 9).

Well-vascularized pedicled flaps provide blood flow to the recipient area, facilitating the delivery of systemic antibiotics, immune cells, and antibodies. This enhances infection control and promotes wound healing. In advanced healthcare facilities with robust microvascular surgery capabilities, free flaps are often preferred over pedicled flaps for covering wounds with exposed hardware. However, Fallico et al. (3) reviewed the outcomes and complications of both free and pedicled flaps for exposed hardware in the lower extremities and concluded that pedicled flap reconstruction should be reconsidered as a valid alternative option when possible.

CONCLUSION

Pedicled muscle flaps, including the gastrocnemius and peroneus brevis, are viable options for managing soft tissue defects, particularly in complex clinical situations involving exposed metal implants. Mastery of these flaps by plastic and reconstructive surgeons is crucial for limb salvage, especially when resources for free flap procedures are limited.

Acknowledgments / Patient Consent: The patients have given consent for their case history and images to be used for research and publication, provided their identities are not disclosed. The author acknowledges the patients' participation and commitment to this research.

Contribution of Authors: The manuscript was drafted by a single author (SAH), who is also the operating surgeon for the reported cases.

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Conflicts of Interest:There are no conflicts of interest.

Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

VEZANI MIŠIĆNI REŽNJEVI ZA LEČENJE KOMPLIKACIJA IZAZVANIH IMPLANTATIMA U DONJIM EKSTREMITETIMA

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Uvod: Metalni implantati se široko koriste u rekonstrukciji koštanih defekata izazvanih prelomima, ekscizijom tumora i degenerativnim bolestima kostiju. Međutim, ovi implantati su povezani sa komplikacijama, uključujući izlaganje i infekciju, posebno u slučajevima kada je potrebna upotreba vaskularizovanog

tkiva za rekonstrukciju. Vezani mišićni režnjevi predstavljaju ključni alat u plastičnoj hirurgiji za rešavanje ovih komplikacija.

Prikaz slučaju: Ovaj članak prikazuje dva slučaja u kojima su vezani mišićni režnjevi medijalnog gastroknemijusa i peroneusa brevisa uspešno primenjeni za spašavanje implantata i postizanje efikasnog pokrivanja rana.

Zaključak: Vezani mišićni režnjevi medialnog gastroknemijusa i peroneusa brevisa predstavljaju vredne opcije za pokrivanje komplikovanih kožnih defekata na izloženim implantatima.

Ključne reči: spašavanje implantata, peroneus brevis, medialni gastroknemijus, vezani mišićni režnjevi, spoljašnji fiksatori, slobodan režanj, uzimanje grafta, totalna artroplastika kolena.

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Review article

INFLAMMATORY MECHANISMS IN COLORECTAL CANCER: THE ROLE OF CYTOKINES AND DIETARY INFLAMMATORY INDEX - A REVIEW

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Abstract: Colorectal cancer is one of the most common malignant tumors, with numerous studies highlighting the role of inflammation in its onset and progression. Cytokines such as IL-6 and TNF-α play a crucial role in sustaining inflammation, contributing to the malignant transformation of cells. The dietary inflammatory index, which reflects the intake of pro-inflammatory nutrients, is associated with an increased risk of developing colorectal cancer. Serum cytokine concentrations may serve as biomarkers for risk assessment, while dietary modifications aimed at reducing inflammation can significantly impact both prevention and therapy. This knowledge opens possibilities for a personalized approach to the treatment and prevention of colorectal cancer.

Keywords: Colorectal Neoplasms, Inflammation, Cytokines, Feeding Behavior.

INTRODUCTION

Colorectal cancer (CRC) is one of the leading causes of cancer-related mortality worldwide, with genetic, epigenetic, and environmental factors playing a significant role in its prevalence (1). Key genes involved in CRC pathogenesis include *Tumor Protein 53* (*TP53*), *Adenomatous Polyposis Coli* (*APC*), *Kirsten Rat Sarcoma Viral Oncogene Homolog* (*KRAS*), and those responsible for DNA mismatch repair, such as *Mismatch Repair* (*MMR*) genes (2). Mutations in *TP53* are frequently associated with tumor progression, whereas mutations in *APC* constitute one of the initial steps in CRC development, triggering a cascade of genetic changes that may lead to the malignant transformation of intestinal cells (2, 3). Similarly, mutations in *KRAS* occur in a substantial number of cases, with their detection holding prognostic significance (4, 5). The frequency of these mutations varies among patients, underscoring the importance of advanced diagnostic techniques for their identification and classification. These advancements pave the way for a more personalized approach to CRC treatment (6, 7).

Inflammation plays a critical role in carcinogenesis, including CRC. Inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease, are significant risk factors associated with an increased likelihood of CRC development (8). In these conditions, chronic inflammation drives continuous regeneration of damaged cells and tissues, potentially leading to mutations and changes that promote malignant transformation (9–13). Additionally, inflammation contributes to the creation of a microenvironment that stimulates epithelial cell proliferation in the colon, fosters angiogenesis, and recruits immune cells, which may further damage surrounding tissues and promote mutations (10).

Moreover, inflammation induces the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (*TNF-α*), interleukin-6 (*IL-6*), and interleukin-1 beta (*IL-1β*), which activate signaling pathways associated with tumor cell proliferation, survival, and migration (14–17). Systemic inflammation, triggered by factors such as obesity, smoking, and alcohol consumption, is also linked to CRC, as it amplifies the body's pro-inflammatory response (18, 19, 20). Conversely, factors such as regular physical activity and a diet rich in anti-inflammatory components

(e.g., fruits, vegetables, omega-3 fatty acids) help reduce inflammation, thereby exerting a protective effect against CRC (2, 14, 15, 21). While the roles of cytokines, inflammatory processes, and dietary patterns are well-documented, many aspects of their interplay and precise impact on carcinogenesis and disease prognosis remain unclear (14, 15, 17).

Although advanced diagnostic methods have improved the understanding of genetic mutations in *TP53*, *APC*, and *KRAS*, further research is required to enable personalized therapeutic approaches, particularly concerning the role of inflammation at various stages of the disease (22). Additionally, growing evidence highlights the importance of dietary factors and physical activity in regulating inflammation and reducing CRC risk. However, the lack of consensus regarding optimal dietary and physical activity regimens warrants further investigation (2, 14, 15, 21).

The aim of this study is to examine the significance and interconnection between cytokines, inflammatory responses, and specific dietary patterns in the context of CRC by analyzing existing evidence. This analysis seeks to elucidate the mechanisms underlying these complex interactions. Furthermore, the study aims to contribute to the understanding of how these relationships can inform the prevention, diagnosis, and therapy of CRC, thereby advancing the development of personalized treatment strategies.

CYTOKINES AND THEIR ROLE IN CRC

Cytokines are soluble proteins that act as mediators in numerous immune and inflammatory reactions. Although predominantly secreted by leukocytes, particularly macrophages and T lymphocytes, cytokines can also be produced by other cells in the body (23). Cytokines, especially interleukins as a subgroup, significantly influence various cell types, including leukocytes and other body cells, promoting malignant transformation and becoming key contributors to the development and progression of pathological conditions such as carcinoma (24). Tumor cells can activate oncogenic signaling pathways through cytokine secretion, thereby supporting tumor growth (25).

Chronic inflammation, which is commonly observed in the tumor microenvironment, plays a crucial role in cancer progression. In this context, pro-inflammatory cytokines, such as IL-6, Interleukin 17A, Interleukin 17ATumor Necrosis Factor Alpha (TNF-α), and Interferon Gamma (IFN-γ), produced during inflammation, can directly contribute to tumor growth and spread (26). The CRC microenvironment exhibits high concentrations of these cytokines, which enhance the inflammatory response and have the potential to stimulate various oncogenic signaling pathways. For instance, IL-6 is known not only to promote tumor growth but also to increase the tumor's ability to metastasize to other parts of the body (27). TNF-α, associated with advanced disease stages, also plays a significant role in modulating the tumor microenvironment, promoting metaplasia and invasiveness (28, 29).

Conversely, Interleukin-10 (IL-10), often considered an anti-inflammatory cytokine, has a complex role in the tumor microenvironment. While IL-10 reduces the inflammatory response, which can be beneficial in preventing tissue damage, excessive production of this cytokine may suppress an effective immune response to the tumor (30). This effect can contribute to tumor development by reducing the activity of cytotoxic T lymphocytes and macrophages, which are critical for eliminating tumor cells (31, 32). Some studies suggest that elevated levels of IL-10 may be associated with poor prognosis in patients with various cancers, including CRC. In such cases, IL-10 may contribute to immune suppression, allowing tumor cells to survive and spread (29).

However, cytokines such as Interleukin-12 (IL-12), a pro-inflammatory cytokine, have demonstrated anti-tumor activity in various studies (33). IL-12 exerts its effects by activating natural killer (NK) cells and T lymphocytes, enhancing the body's capacity to eliminate tumor cells. Although the effects of IL-12 in the tumor microenvironment are complex, evidence suggests its potential therapeutic application due to its ability to amplify the immune response against tumors. Unfortunately, the therapeutic use of IL-12 remains underdeveloped because of challenges related to its stability and potential side effects (33, 34).

The elevated concentration of pro-inflammatory cytokines in the tumor microenvironment is often used as a biomarker of poor prognosis, as it may indicate accelerated tumor growth and metastasis. Given the complex role of cytokines in tumor biological dynamics, understanding their specific functions could aid in the development of novel therapeutic strategies targeting cytokines and their signaling pathways (35). For instance, cytokine pathway inhibitors may enable selective modulation of the inflammatory response, potentially enhancing the immune response to the tumor and reducing its capacity to spread (36).

DIETARY INFLAMMATORY INDEX AND CRC RISK

The Dietary Inflammatory Index (DII) is an innovative tool designed to quantify the inflammatory potential of a diet and its impact on disease develop-

ment, such as colorectal cancer (CRC). Developed in 2009, the DII synthesizes the effects of dietary components on inflammation in the body, using data from numerous studies linking diet to inflammatory processes (37–40). The index categorizes diets as pro-inflammatory or anti-inflammatory, with a higher DII score indicating a diet that promotes inflammation, while a lower score reflects a diet with reduced inflammatory potential (39, 40, 41).

Consumption of pro-inflammatory foods, such as red and processed meats, has been associated with an increased risk of CRC (37, 42). Conversely, diets rich in fiber and anti-inflammatory components are linked to a reduced risk of CRC (38). Studies have demonstrated a significant correlation between high DII scores and an elevated risk of CRC, while lower DII values indicate a reduced risk (43). These findings suggest that dietary modifications aimed at reducing inflammatory potential could be a crucial strategy for CRC prevention and management (38, 43).

Previous research has analyzed inflammation markers such as C-reactive protein (CRP), IL-6, and TNF-α, showing a positive association between high DII scores and elevated levels of these biomarkers (24, 32, 39). For example, higher DII scores were associated with increased high-sensitivity CRP levels in several studies (41, 44–46). Additionally, elevated DII scores have been linked to a greater risk of other cancers and higher mortality rates from cardiovascular and cancer-specific causes (47–49).

However, there remains a lack of data on the precise relationship between DII scores and cytokine profiles, particularly pro-inflammatory and anti-inflammatory cytokines, in CRC patients. This presents a significant avenue for future research (50, 51, 52). Such investigations could enhance our understanding of the impact of diet on the inflammatory microenvironment in CRC (38, 40). Furthermore, these findings could pave the way for the development of new therapeutic strategies, including immunotherapy and dietary adjustments aimed at reducing inflammation (53).

ASSOCIATION BETWEEN SERUM CYTOKINE LEVELS AND THE DIETARY INFLAMMATORY INDEX

DII serves as a valuable tool for assessing the inflammatory potential of a diet and its impact on systemic inflammation. A higher DII score indicates a pro-inflammatory diet that may elevate levels of pro-inflammatory cytokines, whereas a lower DII score, reflecting an anti-inflammatory diet, is associated with reduced levels of cytokines such as IL-6 and TNF-α (39, 40, 41).

Interestingly, studies have demonstrated a positive correlation between higher DII scores and elevated levels of inflammatory markers such as CRP, IL-6, and TNF-α. This correlation suggests that an inflammatory diet can modulate the body's immune response, potentially contributing to the development or progression of CRC (41, 54, 55). Research indicates that patients with higher DII scores are at increased risk of CRC, with those in the highest DII score quartile showing up to a 40% greater risk compared to those with lower scores (43, 52, 56).

Although the link between inflammatory cytokines and DII is well established, limitations exist in current research. Many studies have focused on only one or a few cytokines without evaluating a broader spectrum. Including a wider range of both pro-inflammatory and anti-inflammatory cytokines could provide a more comprehensive understanding of the mechanisms by which diet influences inflammation and CRC progression (50, 51, 52).

Improved insight into this relationship could aid in developing more effective strategies for CRC prevention and treatment. These strategies might include dietary modifications and immunotherapy aimed at reducing inflammation and, consequently, lowering the risk of cancer development (38, 57).

CLINICAL SIGNIFICANCE AND PERSPECTIVES IN THERAPY AND PREVENTION

Understanding the relationship between serum cytokine concentrations, the DII, and CRC development holds significant potential for advancing diagnostics, personalized nutrition, and treatment strategies for patients with this disease (37). Biomarkers such as TNF-α, IL-6, and CRP provide valuable insights into systemic inflammation, a key factor in CRC development and progression (39, 41, 58).

Diagnostics leveraging these biomarkers could enable the identification of patients in the early stages of CRC, when treatment options are most effective and impactful. For instance, elevated levels of inflammatory cytokines, particularly IL-6, have been linked to more aggressive forms of CRC and could serve as indicators of disease progression (39, 41). Additionally, these biomarkers could identify high-risk individuals before the onset of clinical symptoms, facilitating the implementation of preventive measures and earlier interventions (59, 60).

Beyond diagnostics, these biomarkers support personalized approaches to nutrition and treatment. Tailored dietary plans based on specific cytokine levels and DII scores could aim to reduce inflammation and minimize CRC risk. Recommendations for an an-

ti-inflammatory diet rich in fiber, omega-3 fatty acids, and antioxidants may substantially reduce systemic inflammation and, consequently, the risk of CRC development or progression (39, 41). Furthermore, personalized dietary interventions might enhance treatment responses, such as chemotherapy efficacy, by mitigating inflammation, improving therapeutic outcomes, and reducing adverse effects (34).

In the context of therapy, the manipulation of inflammatory cytokines through biological drugs or specific immunotherapies also represents a promising direction. Research indicates that inhibiting specific cytokines, such as TNF-α or IL-6, has the potential to direct therapy towards specific molecular pathways, thereby increasing treatment efficacy and reducing side effects (40, 41). Additionally, research in inflammation-reducing therapies could introduce new approaches to treating patients with CRC, particularly those with high inflammatory scores or advanced stages of the disease (43, 44, 54, 55).

Finally, the significance of biomarkers such as IL-6, TNF-α, and CRP in CRC prevention should not be overlooked. Their integration into routine practice could help identify individuals at high risk and monitor the effectiveness of preventive interventions, such as dietary changes, exercise, and supplementation (24). A healthy lifestyle, which includes reducing inflammation, could be a key factor in lowering CRC incidence, with biomarkers serving as tools for assessing the success of these preventive strategies (39, 41, 57).

CONCLUSION

Our study explored the impact of serum cytokine concentrations and the DII index on the onset and progression of CRC, aiming to identify their significance in the pathogenesis of the disease.

An analysis of data from available medical literature highlighted the significant role of pro-inflammatory cytokines, such as IL-6, TNF-α, and Interleukin-17A, in increasing inflammation and contributing to the onset and progression of CRC. Additionally, the DII index, reflecting both nutritional and inflammatory parameters, proved to be a useful predictive marker in relation to cytokine levels and the prognosis of these patients. Elevated cytokine levels, combined with a higher DII index, contributed to the deterioration of clinical status and poorer prognosis. These findings suggest that targeting inflammatory pathways, along with optimizing nutrition, could have significant therapeutic value in the treatment of CRC. Further research is needed to thoroughly examine the role of diet in modifying inflammatory responses and their connection to serum cytokine levels, which could contribute to the development of personalized therapeutic approaches for CRC patients.

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Sažetak

INFLAMATORNI MEHANIZMI KOD KOLOREKTALNOG KARCINOMA: ULOGA CITOKINA I DIJETALNOG INFLAMATORNOG INDEKSA

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Karcinom debelog creva jedan je od najčešćih zloćudnih tumora, a brojna istraživanja ističu uticaj inflamacije na njegov nastanak i progresiju. Citokini kao što su IL-6 i TNF-α igraju ključnu ulogu u održavanju inflamacije, koja može pridoneti malignoj transformaciji ćelija. Inflamatorni indeks u prehrani, koji se odnosi na unos proinflamatornih nutrijenata, povezan je s povećanim rizikom od razvoja kolorektalnog karcinoma. Koncentracije citokina u serumu mogu poslužiti kao biomarkeri za procenu rizika, dok modifikovane prehrambene navike usmerene na smanjenje inflamacije mogu značajno uticati na prevenciju i terapiju. Ova saznanja otvaraju mogućnosti personalizovanog pristupa u lečenju i prevenciji raka debelog creva.

Ključne reči: kolorektalne neoplazme, inflamacija, citokini, obrasci ishrane.

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Review article

BRAIN-COMPUTER INTERFACES IN NEUROREHABILITATION FOR CENTRAL NERVOUS SYSTEM DISEASES: APPLICATIONS IN STROKE, MULTIPLE SCLEROSIS AND PARKINSON'S DISEASE

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Abstract: Brain-computer interfaces (BCIs) represent an innovative approach to neurorehabilitation for neurological conditions, particularly stroke, multiple sclerosis, and Parkinson's disease. This paper provides a comprehensive analysis of current BCI applications, technological developments, and clinical outcomes in these conditions. Recent advances in electroencephalography-based BCIs have demonstrated promising results, with classification accuracies exceeding 90% in stroke rehabilitation and comparable performance in multiple sclerosis and Parkinson's disease. Meta-analyses of stroke rehabilitation trials (n=235) indicate significant motor function improvements, with standardized mean differences of 0.79 in upper limb assessment scores compared to conventional therapy. Disease-specific challenges necessitate tailored approaches, while hybrid systems combining multiple signal types and integration with virtual reality or robotic assistance enhance therapeutic potential. The development of portable, home-based systems offers increased therapy intensity but raises concerns about remote monitoring and safety protocols. This review synthesizes current evidence supporting BCI applications in neurorehabilitation and highlights critical areas for future research, including cognitive rehabilitation optimization and the standardization of outcome measures for cross-condition comparison.

Keywords: brain-computer interface, neurorehabilitation, stroke, multiple sclerosis, Parkinson's disease, motor imagery, neuroplasticity.

INTRODUCTION

Diseases of the central nervous system, such as stroke, multiple sclerosis (MS), and Parkinson's disease (PD), represent significant global health challenges, with diverse pathologies affecting neural structure and function. Stroke remains one of the leading causes of adult disability, affecting approximately 16.3 million people worldwide annually, as estimated by the WHO. Half of all stroke survivors experience lasting disabilities that impact motor and cognitive functions (1). The challenges of stroke-related neuroplasticity necessitate effective rehabilitation methods that target damaged neural pathways to restore motor function and improve quality of life.

Multiple sclerosis, affecting roughly 1.8 million people globally (WHO), causes neurodegeneration and demyelination, disrupting motor and sensory processing and leading to physical and cognitive impairments (2). Current MS therapies often prove insufficient in addressing progressive motor decline and cognitive dysfunction (3). Parkinson's disease affects approximately 1% of individuals over 60, causing motor deficits due to the degeneration of dopamine-producing neurons, which results in tremors, rigidity, and bradykinesia (4). Traditional rehabilitation methods show limitations in providing targeted neurostimulation for PD's progressive symptoms (5).

These conditions present substantial challenges in neurorehabilitation, as existing approaches often fail to achieve long-term recovery due to the brain's limited capacity for self-repair. While conventional rehabilitation remains a cornerstone of treatment for these neurological disorders, its limitations in addressing disease progression highlight the need for complementary therapeutic approaches to enhance rehabilitation outcomes.

Brain-computer interfaces (BCIs) establish direct communication channels between the brain and external devices, enabling control of assistive technologies and therapeutic systems through neural signal interpretation. These systems fall into two main categories:

invasive and non-invasive interfaces. Electroencephalography (EEG) is a widely used non-invasive BCI method, valued for its cost-effectiveness, safety, and practical implementation (6). Motor imagery (MI)-based BCIs show promise in motor function restoration by leveraging the brain's ability to activate motor regions during imagined movement. These systems detect and translate neural activity into physical or virtual actions (7). EEG-based BCIs effectively capture motor-related signals, particularly sensorimotor rhythms associated with imagined movement, thereby engaging neuroplastic mechanisms that promote motor recovery (8, 9).

BCIs offer significant value in neurorehabilitation by harnessing neuroplasticity—the brain's ability to reorganize and strengthen neural connections through activity (10). In stroke rehabilitation, BCIs facilitate repetitive, targeted activation of specific neural pathways, reinforcing motor intention through movement simulation tasks. This process, combined with BCI feedback via visual or robotic-assisted systems, supports neural circuit reorganization and functional recovery (11, 12).

This paper examines recent developments in BCI-based neurorehabilitation for stroke, MS, and PD, analyzing clinical applications and emerging research directions. The analysis covers EEG-based BCI applications in motor, cognitive, and speech rehabilitation, including MI-based BCIs for upper limb motor recovery and EEG-based network analysis in chronic stroke patients. Additionally, it explores BCI integration with virtual reality (VR) and robotics—technologies that enhance user engagement and promote neuroplasticity through interactive therapeutic environments (13). Given the experimental nature of BCI-based treatments, this review also addresses technical challenges related to neurological signal accuracy and user-specific calibration, as well as ethical considerations in clinical rehabilitation (14, 15).

By evaluating current BCI methodologies, this paper provides a comprehensive analysis of optimal BCI integration in neurorehabilitation, offering insights for researchers and clinicians advancing this field.

BRAIN-COMPUTER INTERFACE TECHNOLOGY IN NEUROREHABILITATION

Brain-computer interfaces (BCIs) have emerged as innovative tools in neurorehabilitation by establishing direct communication pathways between the brain and external devices. These systems have shown significant development in recent years, offering various approaches to facilitate motor recovery and neural plasticity in patients with neurological conditions. A bibliometric analysis by Angulo Medina et al. (15) revealed a substantial increase in BCI research focused on rehabilitation applications, particularly in motor recovery and cognitive rehabilitation. The integration of advanced signal processing techniques and artificial intelligence has expanded these systems' capabilities, enabling more precise and adaptive rehabilitation protocols (16). Understanding the different types of BCIs, their underlying signal acquisition methods, and the current technical challenges is essential for advancing their clinical implementation.

Types of BCIs Used in Rehabilitation

Motor Imagery (MI)

Motor imagery-based BCIs demonstrate value in neurorehabilitation, especially for stroke recovery. Research has identified distinct patterns of neural activation during MI tasks in stroke patients, showing increased activity in the contralateral motor area, while healthy controls exhibit higher activity in the ipsilateral motor area (8). MI-BCIs show notable effectiveness in the beta band, where stroke patients demonstrate significantly higher clustering coefficients during MI tasks compared to active and passive movements. Studies reveal that node strength in the gamma band during MI paradigms shows marked improvement over both active and passive paradigms, suggesting enhanced neural engagement during imagery-based tasks (8). Miladinović et al. (17) conducted a systematic study of temporal parameters in MI-BCI systems, determining that time windows of 1-2 seconds provide an optimal balance between classification accuracy and system responsiveness. Their research compared multiple classification approaches, with linear discriminant analysis showing superior performance for MI task classification.

Passive BCIs

Passive BCIs monitor brain states without requiring active user commands, offering an alternative approach to rehabilitation. Simon et al. (14) emphasize these systems' particular value for patients with severe motor impairments who may find active BCI control challenging. Recent developments have integrated passive BCIs with virtual reality and robotic systems to create more engaging rehabilitation environments (13) for patients with limited abilities, including those with complete paralysis.

Closed-loop BCIs

Closed-loop BCI systems provide continuous adaptation based on patient performance and physiolog-

ical feedback. Saga et al. (18) developed an approach combining EEG and EMG in a closed-loop system, demonstrating feasibility for continuous motion control. Zhan et al. (9) provided evidence that BCI-FES (functional electrical stimulation) systems can improve motor function in chronic stroke patients, showing significant improvements in Fugl-Meyer assessment scores compared to FES-only controls.

Signal Acquisition and Processing Techniques

EEG remains the primary signal acquisition method in rehabilitation BCIs due to its practical advantages in clinical settings. A comprehensive bibliometric analysis by Tsiamalou et al. (6) identified EEG as the most significant input method for BCIs, citing its non-invasive nature, accessibility, and cost-effectiveness. Recent advances in signal processing have focused on improving classification accuracy through various methods. Guerrero-Mendez et al. (19) investigated the effects of temporal and frequency segmentation combined with common spatial pattern methods for movement identification, demonstrating the importance of dynamic temporal segmentation strategies. Additionally, Rosanne et al. (20) introduced novel features based on EEG amplitude modulation dynamics, showing significant improvements in classifier performance when combined with conventional power spectral features.

Challenges and Limitations

Signal Noise and Classification Accuracy

BCI systems continue to face significant technological challenges despite recent advances. Simon et al. (14) identified several critical barriers to widespread BCI adoption, including signal quality variability and maintaining consistent classification accuracy across sessions. Miladinović et al. (17) specifically addressed these issues in their work on optimizing real-time MI-BCI performance, highlighting the balance between classification accuracy and system responsiveness.

User Adoption

Gunduz et al (21) reviewed challenges in novel stroke neurorehabilitation approaches, emphasizing the heterogeneity of patient populations and the need for standardized methodologies. Their work highlights the importance of biomarker-driven individualized approaches and large-scale clinical trials with well-targeted patient populations.

Ethical and Practical Barriers

A recent bibliometric analysis by Angulo Medina et al. (15) identified system inefficiencies and accessibility issues as key challenges. The authors emphasize the need for expanding global participation in BCI research and development, particularly in underrepresented regions, while addressing ethical considerations, including data privacy and equitable access to BCI technologies. The scientific community continues to evaluate the long-term efficacy of BCIs and their impact on rehabilitation alongside existing treatment options (15, 22).

BRAIN-COMPUTER INTERFACE APPLICATIONS IN STROKE REHABILITATION

Motor Rehabilitation

Mechanisms of BCI in Post-Stroke Recovery

BCIs have demonstrated significant potential as therapeutic interventions for post-stroke motor recovery. These systems facilitate neuroplasticity through direct neural feedback loops, enabling patients to engage in rehabilitation exercises even without voluntary movement capacity (14). The therapeutic mechanism relies on coupling intended motor actions with sensory feedback, reinforcing neural pathways involved in motor control. Recent neurophysiological studies have revealed underlying mechanisms of BCI-mediated recovery. Su et al. (8) documented significant alterations in brain network connectivity during BCI interventions, particularly in the beta frequency band. Their findings showed enhanced clustering coefficients during motor imagery tasks compared to active and passive movements, suggesting distinct patterns of functional reorganization. These studies observed increased activity in contralesional motor areas, indicating potential compensatory mechanisms in the recovery process.

Clinical Applications and Intervention Protocols

Several therapeutic protocols have been developed for BCI-mediated stroke rehabilitation. MI-BCIs have shown promise in clinical settings. In a significant clinical study, Irimia et al. (12) evaluated MI-BCI control in stroke patients using the recoveri X system. Their research demonstrated high classification accuracies (mean 87.4%) across patient sessions, with peak accuracies exceeding 96%. Notably, stroke patients achieved higher control accuracies than previously reported in healthy subjects, potentially due to increased therapeutic motivation. Their intervention protocol combined motor imagery with simultaneous functional electrical stimulation (FES) and visual

feedback through simulated environments, creating a comprehensive sensorimotor feedback loop. Building on these findings, Kaviri and Vinjamuri (16) implemented advanced source localization techniques with a neural network architecture, achieving 91.03% classification accuracy with dipole fitting. Their methodology demonstrated superior performance compared to conventional approaches in differentiating motor imagery patterns. The integration of multiple physiological signals has enhanced therapeutic applications. Saga et al. (18) developed a hybrid system combining EEG and EMG, enabling continuous motion detection and feedback, facilitating more natural movement patterns during rehabilitation sessions.

Clinical Outcomes and Therapeutic Efficacy

Meta-analytic evidence supports the clinical efficacy of BCI interventions in post-stroke motor recovery. A systematic review of nine randomized controlled trials (n = 235) by Cervera et al. (10) demonstrated a standardized mean difference of 0.79 in upper limb Fugl-Meyer Assessment scores compared to control interventions, suggesting clinically meaningful improvements in motor function following BCI therapy. Further evidence comes from comparative effectiveness research. Ang et al. (11) showed that BCI-triggered robotic feedback achieved comparable motor gains to intensive robotic therapy while requiring significantly fewer movement repetitions (136 versus 1,040 repetitions per session), suggesting enhanced therapeutic efficiency through more precise timing of sensorimotor feedback.

Cognitive and Speech Rehabilitation

Cognitive Recovery Outcomes

BCI interventions have shown efficacy in addressing post-stroke cognitive deficits. Controlled trials of EEG-based neurofeedback training have demonstrated specific improvements in working memory and short-term memory function (23). These cognitive improvements appear to be protocol-specific, with effectiveness noted in interventions targeting upper alpha frequency modulation.

Speech and Language Recovery

Recent technological advances have expanded BCI applications to speech rehabilitation. Systematic investigation of BCI-based communication systems has demonstrated feasibility for patients with severe post-stroke speech impairments (24). These systems utilize neural signal processing to decode speech intentions, providing alternative communication pathways for severely affected patients.

Recent Clinical Advances and Future Directions

Protocol optimization continues to advance therapeutic applications. Miladinović et al. (17) identified optimal temporal parameters for real-time MI-BCI implementation, determining that 1-2 second processing windows maximize both classification accuracy and therapeutic responsiveness. BCI intervention accessibility has improved through technological developments. Craik et al. (25) validated a low-cost, mobile EEG-based system achieving clinical-grade signal quality (SNR = 121 dB, CMRR = 110 dB) while maintaining closed-loop functionality. These developments suggest potential for expanded therapeutic applications in outpatient and home-based settings. Despite these advances, significant challenges remain in protocol standardization and clinical implementation (14). Future research directions include the development of adaptive therapeutic protocols and integration of artificial intelligence for enhanced signal processing. Additionally, large-scale clinical trials are needed to establish optimal treatment parameters and identify patient populations most likely to benefit from BCI interventions.

BRAIN-COMPUTER INTERFACE APPLICATIONS IN MULTIPLE SCLEROSIS REHABILITATION

Motor Rehabilitation

BCIs for Motor Impairment in MS

Multiple sclerosis (MS) presents unique rehabilitation challenges due to its progressive nature and variable symptom presentation. Brain-computer interface technology has emerged as a promising intervention for addressing motor impairments in MS patients. Carrere et al. (26) investigated BCI combined with functional electrical stimulation (FES) for gait rehabilitation in MS patients, demonstrating statistically significant post-treatment improvements in gait speed and walking ability. Their findings showed earlier event-related desynchronization onset latency after treatment, suggesting changes in functional brain connections involved in sensorimotor rhythm modulation. Recent feasibility studies have shown promising results for BCI application in MS patients. Russo et al. (27) demonstrated that neural sources generating motor imagery originated from similar motor areas in MS patients compared to neurotypical participants, though with notable differences in alpha power during image-

ry tasks, indicating preserved motor imagery circuits for BCI control despite disease progression.

Neuroplasticity and MS

Evidence suggests specific neuroplastic mechanisms influenced by BCI interventions in MS patients. Pinter et al. (28) examined the effects of EEG-based neurofeedback training through fMRI studies in MS patients. Their research revealed increased fractional anisotropy and functional connectivity within the salience and sensorimotor networks following successful BCI training. These structural and functional changes correlated with cognitive improvements, suggesting beneficial neuroplastic adaptations from BCI interventions.

Cognitive Rehabilitation

Memory and Executive Function Training

Cognitive impairment affects a significant proportion of MS patients, particularly impacting attention, processing speed, and executive function. Kober et al. (23) demonstrated significant improvements in long-term memory and executive functions through EEG-based neurofeedback training in MS patients. These improvements occurred specifically in patients who successfully learned to self-regulate their brain activity through neurofeedback training. Riccio et al. (29) evaluated a hybrid BCI system combining P300-based BCI with conventional assistive technologies, showing comparable usability to conventional assistive technology inputs, suggesting potential applications for cognitive training and communication support.

Recent Clinical Advances and Future Directions

BCI implementation in MS rehabilitation faces several distinct challenges. Buyukturkoglu et al.(30) identified fatigue as a significant factor affecting BCI performance, documenting specific EEG-derived functional connectivity patterns associated with MS-related fatigue. Their findings suggest the need for fatigue monitoring and adaptation mechanisms in future BCI systems. Disease progression variability presents additional complications for long-term BCI implementation. Shiels et al. (31) demonstrated that while MS patients achieved BCI control comparable to healthy controls, performance variability was higher, potentially due to disease-related fluctuations, indicating the need for adaptive BCI systems. Martinez-Cagigal et al. (32) developed an asynchronous P300-based BCI web browser achieving an average accuracy of 84.14% in MS patients, demonstrating feasibility for practical, daily-use applications despite disease-related limitations. However, fatigue management and system adaptability remain critical considerations for long-term use. Recent technological developments show promise in addressing these challenges. Chen et al. (33) demonstrated successful implementation of steady-state visual evoked potential (SSVEP)-based BCIs for assistive device control in MS patients, suggesting multiple BCI paradigms might accommodate different disease progression stages and symptom presentations. Future directions for BCI applications in MS rehabilitation include the development of hybrid systems combining multiple input modalities (26), integration of artificial intelligence for adaptive control (27), and implementation of fatigue management strategies (30). Additionally, the development of home-based BCI training systems, as demonstrated by Pinter et al. (28), may improve accessibility and facilitate more consistent therapeutic applications.

BRAIN-COMPUTER INTERFACE APPLICATIONS IN PARKINSON'S DISEASE REHABILITATION

Motor Rehabilitation

Addressing Motor Symptoms

Parkinson's disease (PD) manifests through a complex array of motor symptoms, including resting tremor, bradykinesia, rigidity, and postural instability, which significantly impact daily activities and quality of life (4). BCI technology has emerged as an intervention option for addressing these motor manifestations, offering both rehabilitative and assistive approaches for symptom management (34). Recent advances have led to the development of non-invasive and invasive BCI systems categorized into two approaches: rehabilitative BCIs aimed at promoting neuroplasticity and recovery, and assistive BCIs designed to provide direct control over external devices or stimulation parameters (5, 35).

Closed-loop BCIs for Adaptive Treatment

Closed-loop BCI systems, particularly in conjunction with deep brain stimulation (DBS), represent a significant advancement in PD treatment. These systems provide real-time feedback and adjust stimulation parameters based on ongoing neural activity and motor performance (36). Studies have demonstrated superior clinical outcomes compared to conventional approaches, with evidence showing better preservation of functional daily beta fluctuations and improved motor control (37). Machine learning algorithms have

enhanced these systems' capability to identify patient-specific neural markers of motor performance. Castaño-Candamil et al. (38) demonstrated that supervised machine learning approaches can identify individual neural markers that are both sensitive to therapy and potentially useful as controllable variables in adaptive BCI systems.

Cognitive Rehabilitation

Executive Function and Memory Support

Beyond motor symptoms, cognitive decline represents a significant challenge in PD management. BCI-based cognitive training paradigms have shown promise in addressing executive function and memory deficits. Recent work combining BCI with virtual reality and artificial intelligence has demonstrated potential for enhancing adaptive responses and improving quality of life (13). Motor imagery-based BCI systems have shown particular promise in cognitive rehabilitation, improving both motor planning and execution through cognitive motor network engagement (39). This approach has demonstrated specific benefits for gait control, where motor imagery integration with BCI feedback can help patients overcome locomotor deficits.

Recent Clinical Advances and Future Directions

BCI implementation in PD rehabilitation continues to evolve with several significant developments. Rossi et al. (40) proposed integrating action observation treatment (AOT) with BCI-triggered muscle stimulation, suggesting potential enhancement of motor execution during rehabilitation sessions. Belkacem et al. (41) reviewed advanced closed-loop BCI systems incorporating various stimulation techniques (electric, magnetic, and optogenetic), demonstrating how feedback-based adaptation could improve therapeutic outcomes. Regarding signal acquisition and processing, Merk et al. (42) demonstrated electrocorticography (ECoG) superiority over subthalamic local field potentials for movement decoding in PD, with performance correlating to disease state. Their connectomic analysis approach showed potential for predicting individual channel performance across patients, supporting personalized BCI implementations. While Möller et al. (5) emphasize the need for additional research to establish feasibility, efficacy, and safety of technology-based neurorehabilitation in PD patients, key areas for future development include standardization of protocols across different disease stages, development of more user-friendly and accessible systems, integration of artificial intelligence for improved accuracy and adaptability, investigation of potential neuroprotective effects, and long-term studies to evaluate sustained benefits.

The field continues to advance, focusing on developing sophisticated closed-loop systems that adapt to individual patient needs and disease progression patterns. Recent advances in electrophysiological recording and analysis techniques, combined with machine learning approaches, suggest promising directions for BCI applications in PD rehabilitation (36).

Comparative Analysis of Brain-Computer Interface Applications in Stroke, MS, and PD

Efficacy Comparison

Brain-computer interface applications demonstrate varying levels of effectiveness across stroke, multiple sclerosis (MS), and Parkinson's disease (PD). In stroke rehabilitation, BCI systems present the most robust evidence base, with meta-analyses of nine randomized controlled trials (n = 235) showing a standardized mean difference of 0.79 in upper limb motor recovery compared to control interventions (10). MS studies demonstrate that patients can achieve BCI control comparable to healthy individuals (27, 31), though with higher performance variability due to disease-related fluctuations, with accuracy rates ranging from 84.14% to 93.18% depending on the paradigm used (29, 32). In PD, closed-loop BCI applications show particular promise, with adaptive systems demonstrating superior clinical outcomes compared to conventional approaches (37), including better preservation of functional daily beta fluctuations and improved motor control (36, 37).

Disease-Specific Challenges and Adaptations

Each condition presents unique challenges requiring specific BCI adaptations. Stroke rehabilitation requires BCIs to address lesion location heterogeneity and its impact on neural signal generation (9, 14). Studies show that both ipsilateral and contralateral motor areas may need targeted intervention depending on lesion location (8). MS systems must adapt to both disease progression and symptom fluctuation, with studies identifying specific EEG-derived functional connectivity patterns associated with fatigue(30). These systems require session-by-session calibration based on patient status (31). PD applications face challenges of dynamic symptom fluctuation and medication effects, necessitating sophisticated closed-loop systems that adjust stimulation parameters based on real-time neural activity (36, 37). These adaptive systems must account for both motor and non-motor symptoms, as demonstrated

by variations in beta-band activity and movement decoding performance across medication states (42).

Patient Suitability and Customization

Patient characteristics significantly influence BCI effectiveness across all three conditions. For stroke, technical factors such as optimal processing time windows (1-2 seconds) affect system responsiveness and accuracy (17), while individual brain network connectivity patterns can predict therapeutic response (9). In MS, successful BCI implementation requires consideration of both fatigue levels and disease stage, with studies showing that neurofeedback training effectiveness correlates with specific changes in brain microstructure and functional connectivity (28). MRI studies reveal that successful BCI users show increased fractional anisotropy and enhanced connectivity within the salience and sensorimotor networks (28). In PD, movement decoding performance correlates with disease severity, with electrocorticography showing superior results compared to subthalamic recordings (42). The effectiveness of closed-loop systems varies with individual patient characteristics and disease progression (37), highlighting the need for personalized calibration approaches.

Promising Cross-Condition Findings

Several BCI approaches show promise across all three conditions, though with varying implementation requirements. Motor imagery protocols demonstrate effectiveness across conditions, achieving classification accuracies of 91.03% in stroke (16), comparable accuracies to healthy controls in MS (27), and successful integration with gait control in PD (39). Studies show that motor imagery activates similar motor areas across conditions (7), though with disease-specific variations in signal characteristics. Hybrid systems combining multiple signal types improve reliability across conditions, particularly when integrating EEG with EMG for continuous motion detection (18) or combining BCI with conventional assistive technologies(29). Recent advances in artificial intelligence and adaptive algorithms have enhanced system performance across all three conditions (15,43), suggesting a promising direction for future development.

Future Directions and Emerging Trends

Advancements in BCI Technology

Artificial Intelligence and Machine Learning Integration

Artificial intelligence is advancing BCI applications across neurological conditions. Machine learning algorithms improve signal classification accuracy and enable real-time adaptation to patient states (43). Recent developments in neural networks and advanced signal processing have achieved superior performance in decoding motor intentions, with classification accuracies exceeding 91% (16).

Hybrid BCIs

Emerging hybrid systems combine multiple neuroimaging and physiological monitoring approaches. The integration of EEG with EMG has demonstrated improved outcomes, enabling continuous motion detection and more natural interaction in rehabilitation settings (18). These multimodal approaches show improved reliability and broader application potential compared to single-modality systems.

Home-Based BCI Rehabilitation

The development of portable, user-friendly BCI systems enables home-based rehabilitation. Craik et al. (25) demonstrated the feasibility of low-cost, mobile EEG-based BCIs with high signal quality (SNR = 121 dB, CMRR = 110 dB) and reliability. Such systems could increase therapy intensity and accessibility, though they require careful consideration of remote monitoring and safety protocols.

Ethical Considerations and Quality of Life

The implementation of BCI technology requires addressing several key concerns. Access equity remains a significant challenge, with current systems often limited to specialized centers (15). Privacy and data security considerations become increasingly important as systems move to home settings. Long-term impacts on quality of life require systematic monitoring, particularly in progressive conditions like MS and PD.

Suggested Areas for Further Research

Several critical areas require additional investigation:

- Optimization of BCI protocols for cognitive rehabilitation across conditions, building on promising findings from both MS and stroke studies.
- Development of adaptive algorithms for disease progression in MS and PD, considering the dynamic nature of these conditions.
- Integration of BCI systems with existing rehabilitation protocols, focusing on complementary rather than replacement approaches.

• Standardization of outcome measures for cross-condition comparison, enabling more robust evaluation of intervention effectiveness.

• Long-term effectiveness studies in home-based settings, particularly important given the chronic nature of these conditions.

BCI technology in neurorehabilitation continues to advance toward increasingly sophisticated, personalized, and accessible systems. As highlighted by recent reviews (15), success depends on addressing both technical advances and practical implementation challenges. The field's evolution from technical achievements to patient-centered, home-deployable solutions represents a crucial step toward broader clinical adoption. Standardization of protocols and outcome measures remains essential for establishing evidence-based guidelines across conditions while maintaining flexibility for condition-specific adaptations.

CONCLUSION

Brain-computer interfaces have emerged as transformative tools in neurorehabilitation, demonstrating significant potential across stroke, multiple sclerosis, and Parkinson's disease treatment. The evidence presented in this review highlights both the remarkable progress in BCI technology and the distinct challenges that remain. Meta-analytic findings support BCIs' clinical efficacy, particularly in stroke rehabilitation, while emerging applications in MS and PD show promising results through adaptive and closed-loop systems. The integration of artificial intelligence, advanced signal processing, and hybrid approaches has substantially improved BCI performance and reliability. Classification accuracies exceeding 90% in motor imagery tasks and successful implementation of home-based systems demonstrate the technology's growing maturity. However, the field must address several critical challenges for widespread clinical adoption, including protocol standardization, accessibility, and long-term effectiveness evaluation.

Disease-specific adaptations have proven crucial for successful BCI implementation. Stroke rehabilitation benefits from targeted neural pathway activation, MS applications require fatigue management and adaptation to disease progression, and PD systems show promise through real-time symptom monitoring and stimulation adjustment. The development of portable, user-friendly systems represents a significant step toward broader therapeutic applications, though careful consideration of remote monitoring and safety protocols remains essential.

Future directions should focus on optimizing cognitive rehabilitation protocols, developing sophisticated adaptive algorithms for disease progression, and establishing standardized outcome measures for cross-condition comparison. The potential for home-based rehabilitation could significantly impact therapy intensity and accessibility, particularly benefiting patients with chronic conditions. As BCI technology continues to evolve, its role in neurorehabilitation will likely expand, offering increasingly personalized and effective treatment options for patients with neurological conditions.

Abbreviations

BCI - brain-computer interface
MS - multiple sclerosis
PD - Parkinson's disease
EEG - electroencephalography
MI - motor imagery
WHO - World Health Organization
EMG - electromyography
FES - functional electrical stimulation
VR - virtual reality
DBS - deep brain stimulation
ECOG - electrocorticography
SNR - signal-to-noise ratio
CMRR - common-mode rejection ratio
(f)MRI - (functional) magnetic resonance imaging

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Sažetak

INTERFEJSI MOZAK-RAČUNAR U NEUROREHABILITACIJI BOLESTI CENTRALNOG NERVNOG SISTEMA: PRIMENA KOD MOŽDANOG UDARA, MULTIPLE SKLEROZE I PARKINSONOVE BOLESTI

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Interfejsi mozak-računar predstavljaju inovativni pristup u neurorehabilitaciji neuroloških stanja, posebno moždanog udara, multiple skleroze i Parkinsonove bolesti. Ovaj rad pruža sveobuhvatnu analizu trenutnih primena interfejsa mozak-računar, tehnološkog razvoja i kliničkih ishoda kod ovih stanja. Nedavni napredak u sistemima zasnovanim na elektroencefalografiji pokazuje obećavajuće rezultate sa tačnošću klasifikacije preko 90% u rehabilitaciji nakon moždanog udara i uporedivim performansama kod pacijenata sa multiplom sklerozom i Parkinsonovom bolešću. Meta-analize studija rehabilitacije moždanog udara (n = 235) ukazuju na značajna poboljšanja motorne funkcije, sa standardizovanim razlikama od 0,79 u ocenama gornjih ekstremiteta u poređenju sa konvencionalnom terapijom. Specifični izazovi bolesti zahtevaju prilagođene pristupe, dok hibridni sistemi koji kombinuju više tipova signala i integraciju sa virtuelnom realnošću ili robotskom asistencijom pokazuju povećan terapeutski potencijal. Razvoj prenosivih sistema za kućnu upotrebu pruža mogućnosti za povećanje intenziteta terapije, istovremeno postavljajući pitanja o daljinskom praćenju i protokolima bezbednosti. Ovaj pregled sintetiše trenutne dokaze koji podržavaju primenu interfejsa mozak-računar u neurorehabilitaciji, istovremeno naglašavajući ključne oblasti za buduća istraživanja, uključujući optimizaciju kognitivne rehabilitacije i standardizaciju mera ishoda za poređenje između različitih stanja.

***Ključne reči**:* interfejs mozak-računar, neurorehabilitacija, moždani udar, multipla skleroza, Parkinsonova bolest, motorna imaginacija, neuroplastičnost.

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Review article

ABDOMINAL PSEUDOCYST DUE TO VENTRICULOPERITONEAL SHUNT: AN UNCOMMON COMPLICATION OF A COMMON NEUROSURGICAL PROCEDURE

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Abstract: For over a century, the ventriculoperitoneal shunt has been a standard neurosurgical procedure for treating hydrocephalus. However, this procedure is associated with a variety of complications. One uncommon but notable complication is the abdominal cerebrospinal fluid (CSF) pseudocyst. This pseudocyst is histologically characterized by a fibrous wall devoid of an epithelial lining, and its exact etiopathogenesis remains unclear. Patients with abdominal CSF pseudocysts often present with nonspecific symptoms, and treatment is tailored to each individual's clinical situation. This article reviews the epidemiology, etiopathogenesis, clinical characteristics, histology, imaging features, and available treatment options for abdominal CSF pseudocysts.

Keywords: Ventriculoperitoneal shunt, pseudocyst, neurosurgery, hydrocephalus, cerebrospinal fluid, shunt revision.

INTRODUCTION

Ventriculoperitoneal (VP) shunt surgery is a commonly performed neurosurgical procedure used to treat hydrocephalus. It takes advantage of the peritoneal surface's ability to absorb cerebrospinal fluid (CSF) (1). VP shunt complications are frequent, with 60% of shunts failing within ten years of placement, and up to 30% failing within the first year (2). Abdominal complications are particularly common and include fluid collections, peritonitis, gut perforation, shunt catheter displacement, fracture, migration, knot formation, and abscess formation (3, 4). Fluid collections secondary to VP shunt placement are relatively rare and typically present in two forms (5, 6): the accumulation of CSF (known as CSF ascites) and encapsulated fluid collections, referred to as abdominal pseudocysts (APCs). APCs, also known as 'CSFomas,' were first described by Harsh in 1954 (7). Their incidence is low, ranging from 0.33% to 6.6%, with a recurrence rate of 19.8% (8).

This article reviews the epidemiology, etiopathogenesis, clinical characteristics, histology, imaging features, and available treatment options for APCs.

Methods and materials

A comprehensive search was conducted in PubMed, Google Scholar, and ResearchGate using the following keywords: *'peritoneal cerebrospinal fluid pseudocyst,' 'pseudocyst after ventriculoperitoneal shunt,' 'abdominal pseudocyst,'* and *'complications of ventriculoperitoneal shunt.'* No specific timeframe was set for the literature search; however, articles published within the last two decades were prioritized.

Epidemiology

Abdominal pseudocysts (APCs) occur more commonly in children than in adults. The formation of an APC can take anywhere from three weeks to five years following the placement or revision of a VP shunt (6, 9). In some instances, formation has been reported to occur more than a decade later. For example, Wang HC et al. (10) described a 68-year-old woman who experienced increasing stomach pain and distention for four months. She had been treated for idiopathic normal pressure hydrocephalus with a VP shunt 15 years prior, and a 15-cm APC was detected upon evaluation (10).

Pathogenesis

Several hypotheses have been proposed to explain the pathophysiology of cerebrospinal fluid (CSF) pseudocysts, including elevated protein levels in CSF, a foreign body reaction to silicone, and alterations in CSF absorption caused by persistent subclinical inflammation or infection (9, 11).

In various studies, 17–80% of cases have been found to have a subclinical infection, with pathogens such as *Streptococcus*, *Staphylococcus aureus*, and *Staphylococcus epidermidis* identified from CSF cultures (12). However, repeated CSF cultures may appear sterile, and the infection can remain latent. In a review of 18 case reports, Ohba et al. (9) found that only 3 (16.7%) of the patients had *Staphylococcus epidermidis* cultured, while 15 (83.3%) had sterile CSF. Adults are reported to have a higher rate of infection than children (9).

Mobley et al. (13) suggested several risk factors for the development of APCs, including a history of necrotizing enterocolitis, previous shunt revisions, and prior abdominal surgery (excluding shunt revision). In contrast, Gmeiner et al. (14) found that the etiology of hydrocephalus, age at the first surgical procedure, and the type of first surgical procedure did not contribute to APC formation.

APCs may adhere to the parietal peritoneum or the serosal surface of abdominal viscera, or move freely within the peritoneal cavity. This explains why some APCs cause intestinal obstruction, while others undergo torsion.

APCs may also develop in relation to the liver, leading to hepatobiliary symptoms. Hepatic APCs can be classified as intra-axial or extra-axial. In intra-axial hepatic APCs, the tip of the VP shunt lodges within the liver parenchyma, forming a pseudocyst. In extra-axial hepatic APCs, the tip penetrates only Glisson's capsule, resulting in a hepatic subcapsular pseudocyst (15, 16).

Histopathology

An APC is characterized by a fibrous wall and the absence of an epithelial layer (Figure 1). This lack of epithelium differentiates APCs from true cysts (17,18,19). Other pathological features that may be observed in APCs include granulomatous tissue, acute inflammatory changes, lymphocytic infiltration, and an outer layer of fatty tissue of mesenteric origin (9).

Clinical Presentation

Symptoms of APCs are generally nonspecific. Patients may present with abdominal pain, distention, and a palpable lump, or may exhibit low-grade fever, backache, poor appetite, and shortness of breath (20). The pressure from the APC increases the VP shunt's resistance to CSF flow, which can lead to shunt dysfunction and raised intracranial pressure. This often manifests in children as headache, nausea, and vomiting (21).

APCs can grow to large sizes and, due to their mass effect, may obstruct the inferior vena cava, ureters, and intestines (22-25). Leung (22) reported a 14-year-old girl who presented with bilateral ankle edema as the sole symptom of a large non-infected APC. Imaging revealed obstruction of the inferior vena cava (IVC) and bilateral hydronephrosis caused by the APC. MPharm et al. (23) described a 12-year-old girl with bilateral lower limb pitting edema and abdominal distension; imaging showed compression of the IVC from a massive (20 × 18 × 8 cm) septate APC. Buyukyavuz et al. (26) reported a 3-year-old boy with a pseudocyst who presented with a hyponatremic seizure. Wang B et al. (27) reported a 19-year-old female with a VP shunt who presented with abdominal distension resembling that of a full-term pregnancy; the pseudocyst contained 12.7L of fluid.

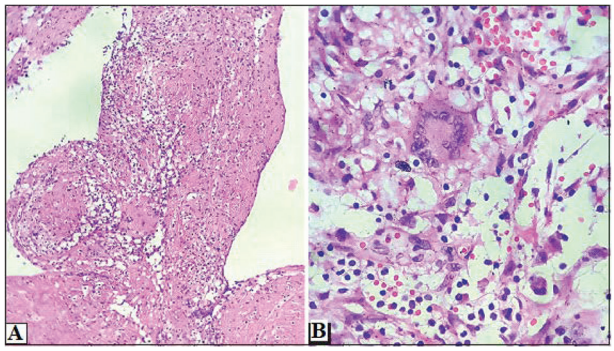

Figure 1. *Histopathology of CSF pseudocyst. (A) Photomicrograph showing a fibro collagenous cyst wall without definite lining epithelium (Hematoxylin and Eosin stain, 100×). (B) Photomicrograph showing cyst wall with many non-caseating epithelioid cell granulomas with Langhans giant cells (Hematoxylin and Eosin stain, 400×). Image credit: Shetty D, et al. Intriguing case of giant intra-abdominal pseudocyst: Diagnostic dilemma. Int J Health Sci (Qassim). 2020 Sep-Oct;14(5):58-60.Reused under the terms of the Creative Commons Attribution-Noncommercial-Share Alike 3.0 Unported*

Imaging studies

Ultrasound

Ultrasound is a rapid, non-invasive, and radiation-free imaging modality that can effectively diagnose APCs at a low cost (28, 29). On ultrasound, APCs appear as distinct hypoechoic or anechoic (black) fluid collections with well-defined hyperechoic (bright) margins. The tip of the VP shunt is often visualized within the pseudocyst as two hyperechoic (bright) lines (27, 28, 29), as shown in Figure 2. Chronic lesions may have multiple internal septations. Infected APCs typically exhibit debris and internal echoes (2). Larger lesions can exert pressure on adjacent organs (22-25).

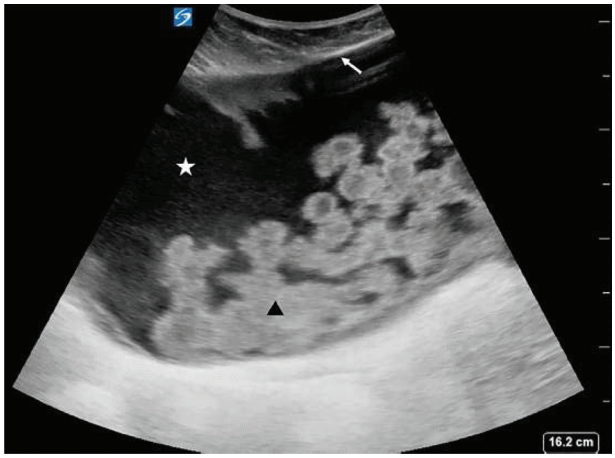

Figure 2. *Point-of-care ultrasound performed with a curvilinear probe in the right lower quadrant shows a large, anechoic (black) collection of cerebrospinal fluid (white star) encapsulated by a fibrous layer (white arrow) and containing echogenic debris and hyperechoic (white) septations (black arrowhead). Image credits: Guest et al. Abdominal Cerebrospinal fluid pseudocyst diagnosed with point-of-care Ultrasound. Clin Pract Cases Emerg Med. 2019 Jan 7;3(1):43-46. doi: 10.5811/cpcem.2018.11.40780. Reused under the terms of the Creative Commons Attribution-Noncommercial-Share Alike 3.0 Unported*

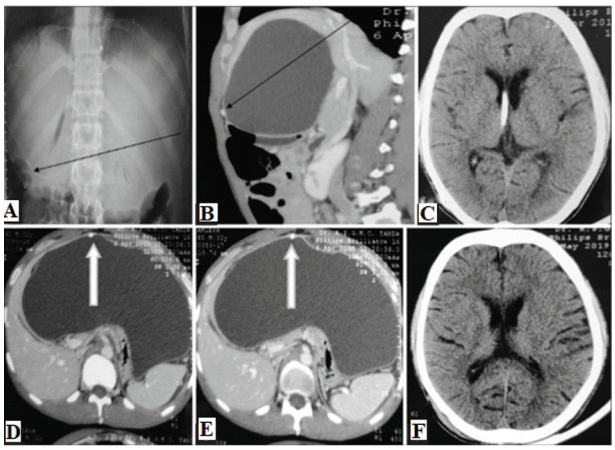

Figure 3. *(A)An X-ray showing the abdominal end of the shunt (black arrow) in the location of pseudocyst. (B, D, E) non-contrast computed tomography (NCCT) abdomen showing large pseudocyst abdomen with abdominal catheter lying along its anterior wall, as shown by black and bold white arrows. (C) NCCT head showing the ventricular end of the shunt. (E)NCCT head after removal of the shunt with no hydrocephalous. Image credits: Kumar M, et al. Central dilemma in CSF pseudocyst - A case series and review of literature. J Neurosci Rural Pract. 2022 Oct-Dec;13(4):753-758. doi: 10.25259/JNRP-2021-7-25. Reused under the terms of the Creative Commons Attribution-Non-Commercial-Share Alike 4.0 License*

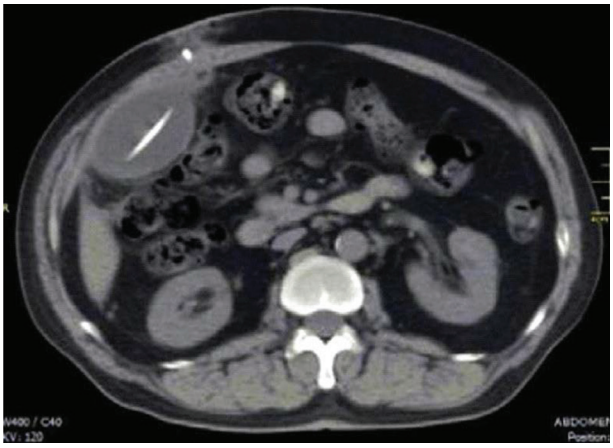

Figure 4. *Axial CT showing abdominal fluid collection adjacent to ventriculoperitoneal shunt catheter tip located on right abdomen. Image credits: Risfandi M, Celia C, Shen R. Abdominal wall pseudocyst as a complication of ventriculoperitoneal shunt insertion: a case report. Pan Afr Med J. 2022 Jan 10;41:23. doi: 10.11604/pamj.2022.41.23.29426. Reused under the terms of the Creative Commons Attribution International 4.0 License (*https://creativecommons.org/licenses/by/4.0/*)*

CT Scan

CT scans delineate a loculated cyst-like structure at the distal tip of the VP shunt, and the measurement of attenuation values helps characterize the water content (Figure 3 and 4). CT scans also assist in ruling out other etiologies, such as peritonitis, bowel obstruction, ascites, appendicitis, diverticulitis, abscess, and cystic abdominal lesions (20, 30).

Nuclear Medicine

A nuclear medicine shunt-o-gram can be used to identify APC. It reveals the normal passage of a radiotracer through the shunt tubing but without normal dispersion into the peritoneal cavity. Schmieder and Schraml (31) reported its successful use in a 73-year-old man who presented with forgetfulness, gait disturbance, and urinary incontinence. The shunt-o-gram showed normal antegrade flow through the patent tubing of the VP shunt, but with spillage into the peritoneal cavity without dispersion. CT further confirmed the diagnosis.

Plain X-ray Abdomen

A plain X-ray of the abdomen may reveal features of mass effect if the APC is large (Figure 3A). Similarly, it can identify signs of bowel obstruction or pneumoperitoneum, helping to rule out other differential diagnoses.

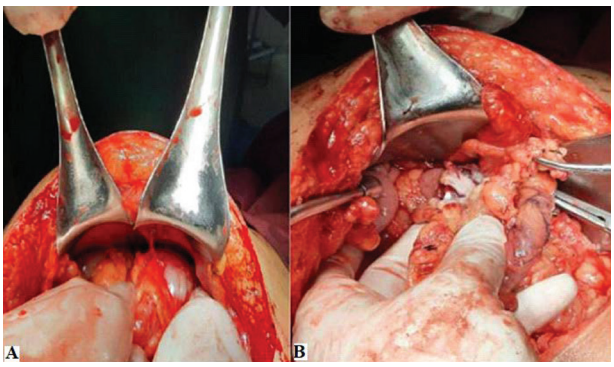

Figure 5. *Peritoneal cerebrospinal fluid pseudocyst as depicted on CT scan in Figure 3 : (A) pseudocyst before aspiration; (B) pseudocyst after aspiration of 750 ml of fluid, the distal shunt was identified. Image credits: Risfandi M, Celia C, Shen R. Abdominal wall pseudocyst as a complication of ventriculoperitoneal shunt insertion: a case report. Pan Afr Med J. 2022 Jan 10;41:23. doi: 10.11604/pamj.2022.41.23.29426. Reused under the terms of the Creative Commons Attribution International 4.0 License (*https://creativecommons.org/licenses/by/4.0/*)*

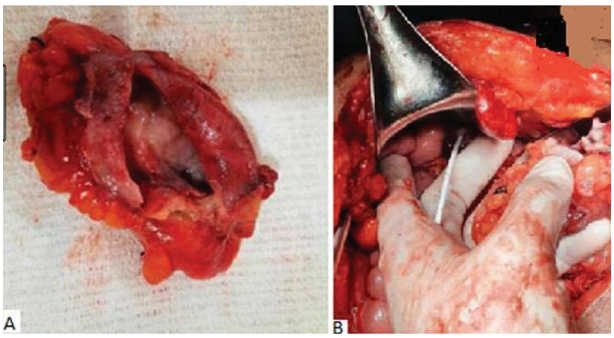

Figure 6. *Abdominal pseudocyst as depicted in Figures 3 &5. A) intraperitoneal cyst 10cm x 8cm x 7cm was excised; B) the distal side of the peritoneal shunt catheter was reinserted to the abdominal cavity. Image credits: Risfandi M, et al. Abdominal wall pseudocyst as a complication of ventriculoperitoneal shunt insertion: a case report. Pan Afr Med J. 2022 Jan 10; 41:23. doi: 10.11604/pamj.2022.41.23.29426. Reused under the terms of the Creative Commons Attribution International 4.0 License (*https://creativecommons.org/licenses/by/4.0/*)*

Differential Diagnosis

APC and CSF ascites are closely related differential diagnoses that can be difficult to distinguish. Clinically, shifting dullness is absent in pseudocysts and present in CSF ascites. Imaging technologies aid in making the final diagnosis. Cystic abdominal lesions such as pancreatic pseudocyst, cystic ovarian neoplasm, lymphocele, cystic teratoma, enteric duplication cyst, mesenteric cyst, and cystic mesothelioma are other differential diagnoses. A comprehensive evaluation employing cutting-edge imaging techniques and in-depth histopathology analysis is necessary for an accurate diagnosis.

Management

External drainage or surgical excision of APC (Figure 5 and 6) followed by shunt system reconstruction and repositioning of the abdominal catheter of the shunt are the major treatment options (1, 20, 21) mentioned in the literature. The approaches adopted for the surgical intervention are minimally invasive (laparoscopic) or laparotomy (Figure 6). There is no universally accepted therapeutic approach for CSF pseudocysts, and each patient's treatment should be tailored based on the specific clinical presentation. Following external drainage and cessation of CSF inflow, the absence of secretory epithelium results in collapse and gradual disappearance of APCs.

If the peritoneal cavity is unsuitable due to adhesions or infection in shunt-dependent patients, the

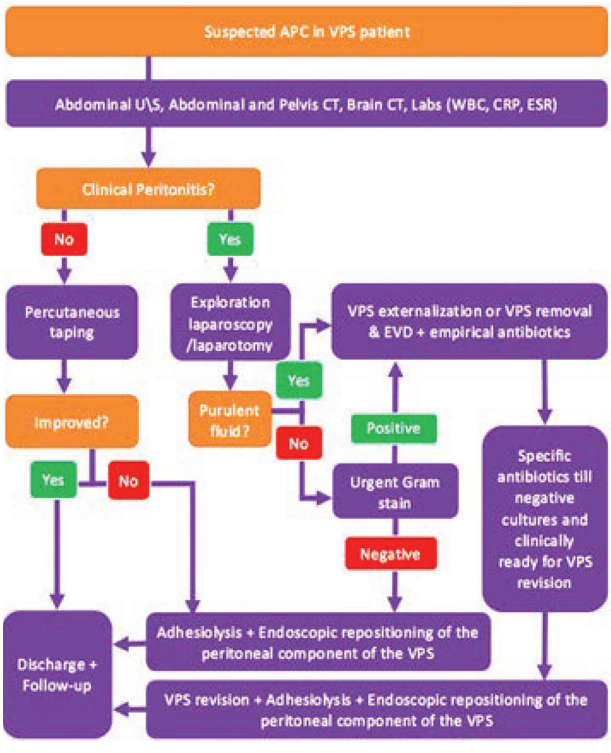

Figure 7. *An algorithm that summarizes the approach for patient with abdominal CSF pseudocyst. Image credits: Fatani GM, Bustangi NM, Kamal JS, Sabbagh AJ. Ventriculoperitoneal shunt-associated abdominal cerebrospinal fluid pseudocysts and the role of laparoscopy and a proposed management algorithm in its treatment. A report of 2 cases. Neurosciences (Riyadh). 2020 Aug;25(4):320-326. doi: 10.17712/nsj.2020.4.20200053. Reused under the terms of the Creative Commons Attribution-NonCommercial License (CC BY-NC)*

abdominal end of the VP shunt may be externalized and placed at an alternate site on the same or contralateral side of the abdomen after eradication of infection. Ventriculo-atrial (VA) shunt, ventriculo-pleural (VPL) shunt, or endoscopic third ventriculostomy are the other available options if the abdomen is not suitable. In patients with shunt independence, shunt removal may be undertaken safely.

Various algorithms have been proposed in the literature to suggest management strategies (20, 33). An easy-to-apply algorithm was proposed by Fatani et al. (32), as depicted in Figure 7.

CONCLUSION

Ventriculoperitoneal shunt placement poses a lifetime risk of complications, necessitating careful monitoring. Every healthcare provider should be aware of abdominal pseudocysts and consider them when making a differential diagnosis in patients with VP shunts who present with vague abdominal symptoms. Treatment is tailored according to clinical circumstances, and the management strategy continues to evolve.

Abbreviations

VPS: Ventriculoperitoneal shunt
CSF: Cerebrospinal fluid
APC: Abdominal pseudocyst
IVC: Inferior vena cava
CT: Computed tomography scan
NCCT: Non-contrast computed tomography scan
VA: Ventriculoarterial
VPL: Ventriculopleural
EVD: External ventricular drain

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Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

ABDOMINALNA PSEUDOCISTA KOD VENTRIKULOPERITONEALNOG ŠANTA: RETKA KOMPLIKACIJA ČESTE NEUROHIRURŠKE PROCEDURE

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Ventrikuloperitonealni šant je standardna neurohirurška procedura za lečenje hidrocefalusa već više od jednog veka. Iako je efikasna, procedura je povezana s različitim komplikacijama, među kojima je abdominalna pseudocista retka, ali klinički relevantna. Ova pseudocista histološki se karakteriše fibroznom kapsulom bez epitela, dok njena tačna etiopatogeneza ostaje nejasna. Klinička slika je nespecifična, što otežava dijagnozu, a terapijski pristup se prilagođava individualnim karakteristikama pacijenta. U ovom radu se razmatraju epidemiologija, etiopatogeneza, kliničke karakteristike, histološki nalazi, radiološke osobine i dostupne terapijske opcije za ove abdominalne pseudociste.

Ključne reči: ventrikuloperitonealni šant, pseudocista, neurohirurgija, hidrocefalus, cerebrospinalna tečnost, revizija šanta.

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Review article

IMMEDIATE AND DELAYED HYPERSENSITIVITY REACTIONS TO PROTON PUMP INHIBITORS: A REVIEW ARTICLE

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Abstract: Proton pump inhibitors (PPIs) are among the most widely prescribed medications in clinical practice, primarily used for managing acid-related gastrointestinal disorders. While generally regarded as safe, with adverse effects being rare and typically mild, PPIs have been associated with hypersensitivity reactions. These reactions, which may be immediate or delayed, vary in severity from mild to potentially life-threatening.

This review provides an in-depth analysis of key aspects of PPI use, with a particular emphasis on the pathophysiological and clinical characteristics of both immediate and delayed hypersensitivity reactions. It also explores cross-reactivity among PPIs and offers a practical framework to assist clinicians in diagnosing and managing these conditions effectively. Additionally, the review highlights the critical need for further research to develop standardized diagnostic and therapeutic protocols, enabling personalized and evidence-based care for patients experiencing PPI-related hypersensitivity.

Keywords: Proton pump inhibitors, hypersensitivity reactions, immediate hypersensitivity, delayed hypersensitivity, prick test, patch test, lymphocyte activation test, cross-reactivity.

INTRODUCTION

Proton pump inhibitors (PPIs) are widely prescribed for managing acid-related gastrointestinal conditions such as gastric and duodenal ulcers, dyspepsia, gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, *Helicobacter pylori* (*H. pylori*) eradication, and the prevention and management of ulcers associated with nonsteroidal anti-inflammatory drugs (NSAIDs) (1). These drugs suppress gastric acid production by irreversibly inhibiting the H^+/K^+-ATPase enzyme in gastric parietal cells (2). Although generally considered safe and effective, PPIs have been associated with a range of adverse effects (1). Among these, hypersensitivity reactions stand out as significant clinical concerns, encompassing a spectrum of manifestations from mild dermatological symptoms to severe systemic complications (3).

Immediate hypersensitivity reactions (HSRs) to PPIs are primarily IgE-mediated and occur rapidly after drug administration, presenting with symptoms such as urticaria, angioedema, and potentially life-threatening anaphylaxis. These reactions are driven by histamine release from mast cells and basophils and are further complicated by cross-reactivity among PPIs due to their structural similarities. This cross-re-

activity limits therapeutic options and necessitates careful diagnostic evaluation (4).

Delayed hypersensitivity reactions to PPIs are less common but often more severe, primarily mediated by type IV hypersensitivity mechanisms involving T-cell activation. These reactions present a broad spectrum of clinical manifestations, ranging from mild cutaneous symptoms to severe systemic involvement, including potentially fatal conditions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) (5).

This review integrates current evidence on the pathophysiology, clinical manifestations, diagnostic methods, and management strategies for both immediate and delayed PPI-induced HSRs, offering guidance to clinicians in addressing these uncommon but clinically significant challenges.

PPIs: Structure, Mechanism of Action, and Pharmacokinetics

The class of proton pump inhibitors (PPIs) includes six FDA-approved drugs: rabeprazole, lansoprazole, pantoprazole, esomeprazole, omeprazole, and dexlansoprazole (1). These weakly basic substituted benzimidazoles are specifically designed to accumulate in the highly acidic environment of parietal cell canaliculi, achieving high local concentrations and effectively inhibiting the H^+/K^+ATPase—the proton pump responsible for gastric acid secretion (6, 7). Administered as enteric-coated tablets or capsules to protect against gastric degradation, PPIs are absorbed in the proximal small intestine (6). Despite a short plasma half-life of approximately one to two hours, their duration of action is significantly extended due to their unique mechanism.

Once in the acidic canaliculus, PPIs are protonated and converted into their active sulfenamide form, which covalently binds to specific cysteine residues on the proton pump, causing irreversible inhibition of acid secretion. Recovery of acid production requires the synthesis of new proton pumps or the activation of resting ones (6). The activation kinetics and binding site preferences of individual PPIs, influenced by their chemical structures, determine their biological activity and duration of inhibition. Rapidly activated PPIs bind fewer cysteine residues, allowing for faster recovery of acid secretion, while delayed activation facilitates binding to additional sites, prolonging their effect (7).

PPIs are prodrugs requiring acid activation and are metabolized primarily by the cytochrome P450 system, with CYP2C19 and CYP3A4 playing key roles. Genetic polymorphisms, particularly in CYP2C19, significantly impact plasma levels and efficacy, underlining the importance of individual variability in therapeutic outcomes (8).

Clinical Applications of PPIs

Proton pump inhibitors are indispensable in the management of a range of acid-related disorders. They are the first-line therapy for gastroesophageal reflux disease (GERD), particularly in patients with erosive esophagitis, where they promote effective symptom relief, esophageal mucosal healing, and the prevention of complications such as stricture formation or Barrett's esophagus. In non-erosive GERD, PPIs are also highly effective in symptom control compared to H2 receptor antagonists (9).

In the context of peptic ulcer disease, PPIs play a pivotal role in both healing and prevention. For ulcers associated with *Helicobacter pylori* infection, PPIs are an integral part of eradication regimens, as they suppress gastric acid, enhancing the efficacy of antibiotics like amoxicillin and clarithromycin. For NSAID-induced ulcers, PPIs reduce the risk of ulcer formation and facilitate healing, especially in high-risk individuals such as older adults or those with a history of ulcers (9, 10).

High-dose PPIs are essential in managing Zollinger-Ellison syndrome, a rare condition characterized by gastrin-secreting tumors that lead to excessive gastric acid production. PPIs effectively control acid hypersecretion, alleviating symptoms and preventing complications like severe peptic ulceration (11).

In critically ill patients, PPIs are commonly employed for stress ulcer prophylaxis, particularly in those with risk factors such as mechanical ventilation, coagulopathy, stroke, or burns. PPIs are also used in managing eosinophilic esophagitis, where they can reduce esophageal inflammation and improve symptoms in a subset of patients (9).

Additionally, functional dyspepsia—a common condition characterized by upper abdominal discomfort or pain—may respond to PPI therapy, particularly in cases associated with acid-related symptoms (12). Other less common indications include their use in treating gastric hypersecretory states and assisting in the management of conditions like laryngopharyngeal reflux, where acid plays a contributing role (9, 13).

Adverse Effects of PPIs

PPIs are generally well-tolerated, though their use can result in both short-term and long-term adverse effects. In the short term, common side effects include gastrointestinal symptoms such as diarrhea, constipa-

tion, nausea, and abdominal discomfort. Headaches are also frequently reported among users (14).

Long-term use of PPIs, however, has been associated with more significant complications. Chronic suppression of gastric acid can impair the absorption of essential nutrients, including vitamin B12, magnesium, and calcium, leading to conditions such as anemia, hypomagnesemia, and osteoporosis. Prolonged acid suppression has also been linked to a higher risk of infections, such as *Clostridioides difficile*-associated diarrhea and small intestinal bacterial overgrowth (SIBO) (15, 16). Moreover, there is an increased susceptibility to respiratory infections, including pneumonia.

Emerging evidence suggests a potential relationship between long-term PPI use and chronic kidney disease or acute interstitial nephritis. Cardiovascular risks have also been postulated, with some studies reporting a possible link to myocardial infarction in certain populations, though the data remain inconclusive (15). Neurological concerns, such as cognitive decline and dementia, have been noted in association with extended PPI use; however, causality has not been firmly established (17).

Additionally, gastrointestinal effects such as gastric hyperplasia and the development of fundic gland polyps have been observed, particularly in long-term users (18). While these polyps are generally benign, they warrant monitoring to ensure patient safety.

PPIs as a Risk Factor for Allergic Disease Development

Emerging evidence suggests that gastric acid suppression, including the use of PPIs, contributes to the development of allergic diseases (3). Maternal PPI use during pregnancy has been associated with an increased risk of asthma in offspring, highlighting the need for cautious prescribing during pregnancy to mitigate potential respiratory risks in children (19). Similarly, the use of acid-suppressive drugs within the first six months of infancy has been linked to a heightened likelihood of developing allergic diseases later in life, indicating a critical window during which such medications may influence immune development (20).

A large Swedish cohort study of 80,870 matched pairs of children and adolescents further supports this association, demonstrating that PPI use significantly increases the risk of incident asthma. This risk was particularly pronounced in infants and toddlers, with hazard ratios (HRs) of 1.83 for children under six months and 1.91 for those aged six months to two years. Variability in asthma risk among individual PPIs was observed, with pantoprazole exhibiting the highest HR of 2.33. These findings underscore the necessity of prescribing PPIs to children only when clearly indicated, carefully balancing the therapeutic benefits against the potential risks (21).

Mechanistically, PPIs suppress gastric acid secretion, permitting intact food allergens and protein-bound oral drugs to persist in the digestive tract, thereby enhancing their capacity to sensitize and trigger allergic reactions. Additionally, PPIs may promote Th2-biased immune responses, particularly in the offspring of sensitized mothers. Impaired gastric acid production, whether due to PPI use or conditions like atrophic gastritis, has been strongly associated with an elevated risk of sensitization to oral allergens and drugs (22).

HSRs to PPI: Underlying Mechanisms and Clinical Features

While generally safe, hypersensitivity reactions (HSRs) to PPIs, although infrequent, are increasingly recognized as significant adverse events. These reactions encompass a broad spectrum of clinical manifestations, ranging from mild cutaneous symptoms to severe systemic involvement, and may present early or delayed (23). The growing awareness of these adverse effects necessitates a detailed understanding of their underlying mechanisms and clinical features.

Immediate HSRs

The majority of HSRs to PPIs are immediate in onset and predominantly IgE-mediated, as confirmed through diagnostic methods such as skin prick tests (SPT), intradermal tests (IDT), oral provocation tests (OPT), and basophil activation tests (BAT) (4). These reactions occur when antigens bind to IgE molecules attached to high-affinity FcεRI receptors on mast cells, leading to the release of inflammatory mediators, including histamine, leukotrienes, and prostaglandins, which cause the characteristic symptoms of hypersensitivity (24). Immediate HSRs are more common in females, with reported rates ranging from 61% to 81.5%, and are primarily observed in adults, with a mean age between 43 and 54 years across multiple studies (25, 26, 27). Only a few cases have been reported in pediatric patients (28).

Studies have identified differences in the prevalence of PPI-induced HSRs based on the specific PPI involved. Bose et al. reported omeprazole as the most frequently implicated PPI (45.76%), followed by lansoprazole (20.34%), pantoprazole (16.95%), esomeprazole (14.41%), and rabeprazole (2.54%) (25). Conversely, Bonadonna et al. identified esomeprazole as the most frequently involved (30%), followed by

lansoprazole (26.4%) and omeprazole (18.9%) (26). A 2013 study by Ozdemir et al. found lansoprazole to be the primary culprit in 80% of cases, with esomeprazole (16.9%), pantoprazole (13.8%), rabeprazole (3.1%), and omeprazole (1.5%) occurring less frequently (27). A subsequent analysis in 2020 by the same group, which included data from 12 studies involving 395 patients and 416 immediate HSRs, found lansoprazole to account for the highest proportion of cases (40.6%), followed by omeprazole (26.2%), pantoprazole (15.6%), esomeprazole (14.4%), and rabeprazole (3.1%) (5). The researchers suggested that regional prescribing practices may influence the distribution and prevalence of hypersensitivity reactions associated with specific PPIs. Notably, there are no reported cases of immediate HSRs to dexlansoprazole.

Across various studies, urticaria and/or angioedema were observed in 44.1% to 49.2% of patients, while anaphylaxis, the most frequently reported clinical presentation, occurred in 50.8% to 53.6% of cases (5, 27). Additional manifestations included generalized pruritus, hypotension, non-urticarial skin rashes, erythema, and dyspnea or shortness of breath (25), reflecting the diverse clinical spectrum of immediate hypersensitivity reactions to PPIs. Immediate hypersensitivity reactions most commonly occur within the first hour of medication intake (75.4%), but they can also present up to 24 hours later (24.6%) (27). A patient with a history of pantoprazole-induced anaphylaxis exhibited a 7-hour latency period, with a positive IDT supporting an immediate hypersensitivity mechanism (29). In another case, a 47-year-old Hispanic male was referred for recurrent idiopathic anaphylaxis, with the most recent episode occurring 3 hours after pantoprazole intake and previous episodes reported at 24, 10, and 4 hours post-intake. Positive IDT with pantoprazole confirmed an IgE-mediated hypersensitivity reaction (30). This delayed onset may be attributed to the enteric coating of PPIs, which can slow the release of the active compound. Additionally, polymorphisms in the CYP2C19 gene, associated with a poor metabolizer phenotype, have been hypothesized to influence the timing of reactions (29). Consequently, patients exhibiting symptoms consistent with immediate allergic reactions to PPIs, even when delayed up to 24 hours, may still involve an IgE-mediated mechanism. Such cases warrant further evaluation using immediate skin tests to confirm the underlying cause.

Delayed HSRs

Drug-induced delayed HSRs encompass a broad range of clinical manifestations, spanning from mild to severe presentations. Mild reactions, such as maculopapular exanthema (MPE) and fixed drug eruption (FDE), are typically self-limiting and resolve with appropriate management. In contrast, severe and potentially life-threatening cutaneous adverse reactions, including SJS, TEN, and DRESS, require urgent medical intervention due to their high morbidity and mortality risks. Although delayed HSRs are well-characterized for many drug classes, data specific to their association with PPIs remain limited (5).

Among hypersensitivity reactions to PPIs, non-IgE-mediated responses are relatively uncommon (14%) compared to IgE-mediated reactions (86%), of which 10% are type IV cell-mediated hypersensitivity responses (25). This finding suggests that type IV hypersensitivity, which includes reactions mediated by T cells and delayed in onset, is the most frequent mechanism underlying these reactions, as all hypersensitivity reactions beyond type II culminate in type IV responses.

A landmark 14-year case series has significantly advanced the understanding of PPI-related delayed cutaneous adverse reactions, reporting 69 cases—the largest dataset to date. The study identified a spectrum of clinical presentations, including 29 cases of MPE, 27 of SJS/TEN, 10 of DRESS, two of FDE, and one of acute generalized exanthematous pustulosis (AGEP). Esomeprazole emerged as the most commonly implicated PPI, particularly in severe cases such as SJS/TEN and DRESS (51%, 35/69), followed by omeprazole and lansoprazole. The latency period varied by reaction type, with an average of 18.6 days for MPE, 20.8 days for SJS/TEN, 7.0 days for AGEP, and 27.2 days for DRESS (31). These findings underscore the delayed nature of PPI-induced hypersensitivity and highlight the need for clinical vigilance in monitoring patients on PPI therapy.

Other cutaneous reactions associated with PPIs include symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), also referred to as drug-related baboon syndrome. A recent study reported three cases of SDRIFE linked to PPIs, with two cases caused by omeprazole and one by pantoprazole. The latency period for these reactions ranged from 3 to 7 days after drug administration (32). Additionally, cases of severe exfoliative dermatitis have been documented, including an 82-year-old male who developed symptoms two weeks after initiating esomeprazole therapy (33) and a 41-year-old male who experienced persistent dermatitis for 18 months after discontinuing omeprazole (34).

PPIs have also been identified as potential triggers for occupational exposure-related contact dermatitis, particularly in individuals frequently handling these medications (5, 35). In a study by Ghatan et al., ap-

proximately one-third of 96 individuals with suspected occupational exposure-related symptoms were diagnosed with omeprazole-specific allergy. The diagnosis was confirmed using patch testing or the lymphocyte transformation test (LTT), demonstrating the utility of these diagnostic tools in occupational settings (36). Additional reports have documented contact dermatitis linked to omeprazole in a horse breeder (37) and similar reactions associated with pantoprazole and lansoprazole (38, 39).

Another recognized immunological adverse reaction to PPIs is subacute cutaneous lupus erythematosus (SCLE), which typically manifests within the first year of treatment, though cases have been reported with latencies ranging from 1 week to 3–5 years. SCLE predominantly affects women (89%) and is associated with antibodies such as anti-Ro/SSA (73%) and antinuclear antibodies (61%). Lansoprazole and omeprazole are the most frequently implicated PPIs, with cross-reactivity documented among these medications. Individuals with a history of cutaneous lupus erythematosus appear to have an elevated risk of developing PPI-induced SCLE (40).

In addition to dermatological reactions, hematological adverse effects such as neutropenia, thrombocytopenia, and hemolytic anemia have been linked to PPI use (41,42,43). These conditions are thought to be mediated through type II hypersensitivity mechanisms, suggesting immune involvement in their pathogenesis (35).

This growing body of evidence highlights the diverse clinical spectrum of PPI-induced hypersensitivity reactions, emphasizing the importance of accurate diagnosis, awareness of underlying immune mechanisms, and tailored management strategies to mitigate associated risks.

Diagnostic Approaches

Immediate HSRs

The evaluation of HSRs to PPIs requires a multifaceted approach, incorporating clinical history, physical examination, and targeted diagnostic procedures. For IgE-mediated reactions, the preferred methods for confirming sensitization include SPT, IDT, and OPT. Advanced techniques, such as the BAT, can further aid diagnosis in ambiguous cases (4). Two pivotal multicenter studies, conducted by Bonadona et al. (26) and Ozdemir et al. (27), assessed the diagnostic utility of SPT and IDT compared to OPT in patients with PPI-induced HSRs.

In the Bonadona et al. study, 53 patients were analyzed, with 12 demonstrating positive skin test results, predominantly in cases of severe reactions. Skin tests exhibited high diagnostic accuracy, with 100% specificity, 100% positive predictive value, and 91.9% negative predictive value, though sensitivity was moderate at 50–61.3%. These findings highlight the value of skin testing in minimizing the need for OPT in patients with positive test results (26). Similarly, the Ozdemir et al. study evaluated 65 patients with suspected immediate HSRs to PPIs and 30 control subjects. SPT and IDT displayed high specificity (100%) and positive predictive value (100%), but sensitivity was moderate (58.8%). In 12 patients with negative diagnostic skin test results, OPTs with the suspected PPIs were conducted, yielding a positive result in eight cases (66.7%). This study concluded that skin tests are highly specific and valuable for diagnosing PPI-induced hypersensitivity, but OPT remains indispensable for confirming negative skin test findings (27).

SPTs were conducted using both undiluted commercial oral and injectable PPI formulations. Tablets and capsules were crushed and diluted in saline, and the tests were performed on the volar forearm. A wheal at least 3 mm larger than the negative control after 20 minutes was considered positive. For patients with negative SPT results, IDTs were conducted using serial dilutions of injectable PPI preparations. A small volume of the test solution was injected intradermally, and an increase in wheal size of at least 3 mm accompanied by erythema after 15 minutes was deemed positive. Patients with negative skin test results subsequently underwent single-blind, placebo-controlled OPTs with alternative PPIs. Doses were administered incrementally at 30-minute intervals until the full dose was reached or a reaction occurred. Vital parameters, including blood pressure, pulse, and FEV1, were closely monitored throughout. A positive OPT was defined by objective signs of hypersensitivity, such as urticaria, angioedema, bronchospasm, or a 20% reduction in FEV1 (27).

These studies collectively emphasize the critical role of skin tests in the diagnostic evaluation of immediate PPI-induced HSRs, while underscoring the complementary importance of OPT in confirming cases with negative skin test results. The dosages of PPIs utilized in these studies for skin testing and OPT are detailed in Table 1.

Currently, there are no studies on the detection of specific IgE antibodies for PPIs. The BAT has emerged as a promising diagnostic tool for immediate PPI allergic reactions, offering a sensitivity of 73.8% and specificity of 100% in studies involving omeprazole. Combining the BAT with skin tests increases diagnostic accuracy, enabling confident diagnoses of PPI HSRs in 85.7% of cases, though research on other PPIs remains limited (4).

Table 1. *Recommended nonirritant skin test concentrations and provocation doses for diagnosis of immediate HSRs to PPIs*

PPIs	SPT	IDT	OPT	References
Omeprazole	40 mg/ml	0.4, 4 mg/ml	5, 5, 10, 20 mg	**Bonadonna P, 2012** (26)
Pantoprazole	40 mg/ml	0.4, 4 mg/ml	5, 5, 10, 20 mg	
Esomeprazole	40 mg/ml	0.4, 4 mg/ml	5, 5, 10, 20 mg	
Rabeprazole	40 mg/ml	/	5, 5, 10, 20 mg	
Lansoprazole	30 mg/ml	/	5, 10, 15 mg	
Omeprazole	20 mg/ml 0.4, 4 mg/ml	0.004, 0.04, 0.4 mg/ml	5, 10, 20 mg	**Kepil Ozdemir S, 2013** (27)
Pantoprazole	40 mg/ml 0.4, 4 mg/ml	0.004, 0.04, 0.4 mg/ml	5, 10, 20 mg	
Esomeprazole	20 mg/ml 0.8, 8 mg/ml	0.008, 0.08, 0.8 mg/ml	5, 10, 20 mg	
Rabeprazole	20 mg/ml	/	5, 10, 20 mg	
Lansoprazole	30 mg/ml	/	7.5, 15, 30 mg	

*PPIs = Proton Pump Inhibitors; SPT = Skin Prick Test; IDT = Intradermal Test; OPT = Oral Provocation Test

Table 2. *Patch test preparations for the diagnosis of delayed HSRs to PPIs*

PPIs	Concentration	Solvent	Form	References
Omeprazole	30%	petrolatum	granules/tablets	**Bavbek S, 2024** (4)
Pantoprazole	30%	petrolatum	granules/tablets	
Esomeprazole	30%	petrolatum	granules/tablets	
Rabeprazole	30%	petrolatum	granules/tablets	
Dexlansoprazole	30%	petrolatum	granules/tablets	
Lansoprazole	30%	petrolatum	granules/tablets	
Pantoprazole	10%	petrolatum	powder	
Esomeprazole	10%	petrolatum	powder	

*PPIs = Proton Pump Inhibitors

Delayed HSRs

Diagnosing delayed HSRs to PPIs relies on a combination of detailed clinical history and patch testing, which is regarded as an effective and reliable approach. Patch testing offers a non-invasive method to confirm the involvement of PPIs in hypersensitivity reactions and is particularly useful when other diagnostic tools are limited (4). PPIs have been tested at concentrations ranging from 0.1% to 50%, using various vehicles such as petrolatum, saline, and occasionally alcohol (23). Patch tests are typically performed on the upper back or other suitable sites by applying small amounts of the prepared PPI mixture in specialized chambers. Reactions are assessed after a designated period, often 96 hours, to detect positive responses indicative of delayed hypersensitivity mechanisms (31). Lin et al. conducted patch testing 3–8 months after the resolution of delayed HSR episodes, using a panel of suspected drugs administered within one month of the onset. Powders were diluted to a 10% concentration in petrolatum, and 57% (4/7) of the patients exhibited a positive reaction, confirming the PPI's role in delayed HSR causation (31). Bavbek et al. recommend reducing PPI granules or tablets to a fine powder, diluting the material to a 30% concentration in petrolatum, and documenting the active ingredient concentration. For injectable formulations like esomeprazole and pantoprazole, they propose a 10% dilution in petrolatum (Table 2) (4).

The LTT is a widely used in vitro diagnostic tool for detecting delayed HSRs. This assay measures the

proliferation of drug-specific T cells upon stimulation with suspected offending drugs. In a study by Lin et al., LTT was performed on 27 patients with PPI-related delayed HSRs and 7 healthy controls. Peripheral blood mononuclear cells were cultured with the suspected PPIs and a solvent control for one week. The granulysin-based LTT demonstrated a sensitivity of 59.3% (16/27) and a specificity of 96.4% (27/28), with significantly higher granulysin release in the PPI-delayed HSRs group compared to controls. In contrast, the IFN-γ-based LTT showed a lower sensitivity of 29.2% (7/24) while maintaining a high specificity of 95.0% (19/20), with no significant differences in IFN-γ release between groups (31). Ghatan et al. examined occupational hypersensitivity reactions to omeprazole using LTT. Among 96 symptomatic individuals, 31 (32%) tested positive, compared to 2 of 21 control subjects (9.5%). Patch testing identified positive results in 33% (28/84) of symptomatic individuals, with a strong correlation between patch test and LTT results. Among those with positive patch tests, 82% (23/28) also had positive LTT results, demonstrating its high sensitivity and specificity. Combining patch testing with LTT identified an additional eight individuals with omeprazole allergy, underscoring the value of integrating these methods for improved diagnostic accuracy, particularly in cases of occupational hypersensitivity (36). These findings highlight the complementary roles of patch testing and LTT in diagnosing delayed hypersensitivity reactions to PPIs and their importance in managing drug-induced allergies.

The diagnostic utility of SPT and IDT with delayed readings for identifying delayed HSRs to PPIs remains poorly investigated. To date, the only available data comes from a study by Ghatan et al., which reported that all 18 individuals who underwent prick testing showed negative results (36). Similarly, the role of OPT in diagnosing T cell-mediated delayed reactions to PPIs is not well-defined. Although no studies have specifically evaluated the effectiveness of DPTs in PPI-induced delayed hypersensitivity, their use may be justified in cases with inconclusive clinical histories and negative skin test results. In nonsevere delayed reactions, DPTs could serve as a valuable tool to rule out PPI hypersensitivity (4). This approach ensures a more comprehensive assessment of delayed hypersensitivity to PPIs.

Cross-Reactivity Between PPIs

Cross-reactivity among PPIs is well-documented and primarily attributed to their structural similarities, particularly the modifications in the benzimidazole and pyridine rings (5). Four distinct patterns of cross-reactivity have been observed. In some cases, patients exhibit hypersensitivity to all available PPIs, a phenomenon known as whole group hypersensitivity. Others may experience allergic reactions specifically to omeprazole, esomeprazole, and pantoprazole, while tolerating lansoprazole and rabeprazole. Conversely, some patients show hypersensitivity exclusively to lansoprazole and rabeprazole but tolerate omeprazole, esomeprazole, and pantoprazole. Additionally, a pattern of selective hypersensitivity has been identified, where patients react to only one specific PPI while tolerating all others (1). Skin testing and oral provocation testing (OPT) are crucial for identifying safe alternatives for patients with hypersensitivity. Studies indicate that 61.6% of patients with immediate HSRs to one PPI may exhibit cross-reactivity to another (4). Comprehensive testing across all available PPIs is essential for accurately identifying safe options for affected patients.

Data on cross-reactivity in delayed HSRs to PPIs is more limited. A study by Lin et al. highlights the challenges of managing cross-hypersensitivity reactions due to the structural similarities among PPIs. In a cohort of 27 patients with PPI-related delayed HSRs, 13 patients were able to tolerate structurally different PPIs, while others exhibited cross-hypersensitivity, particularly within two structurally similar groups: the omeprazole-esomeprazole-pantoprazole group and the lansoprazole-dexlansoprazole-rabeprazole group. These findings underscore the importance of structural differences, such as side chain substitutions, in determining tolerability (31).

Management of HSRs to PPIs

Immediate HSRs

The first step in managing immediate hypersensitivity reactions (HSRs) to PPIs is to identify the suspected PPI as the causative agent and discontinue its use until the diagnostic process is complete. In cases of acute reactions, emergency interventions such as the administration of epinephrine, antihistamines, fluids, airway management, and corticosteroids are essential for stabilizing the patient (44). Skin testing should be performed on the suspected PPI, and if the results are positive, the implicated PPI should be avoided. If skin tests for the suspected PPI are negative and the reaction was mild, an oral provocation test (OPT) can be conducted. A negative OPT result excludes hypersensitivity, while a positive result confirms the need to avoid the specific PPI. In cases where skin tests are negative but there is a history of severe reactions to the suspected PPI, the drug should be avoided regardless.

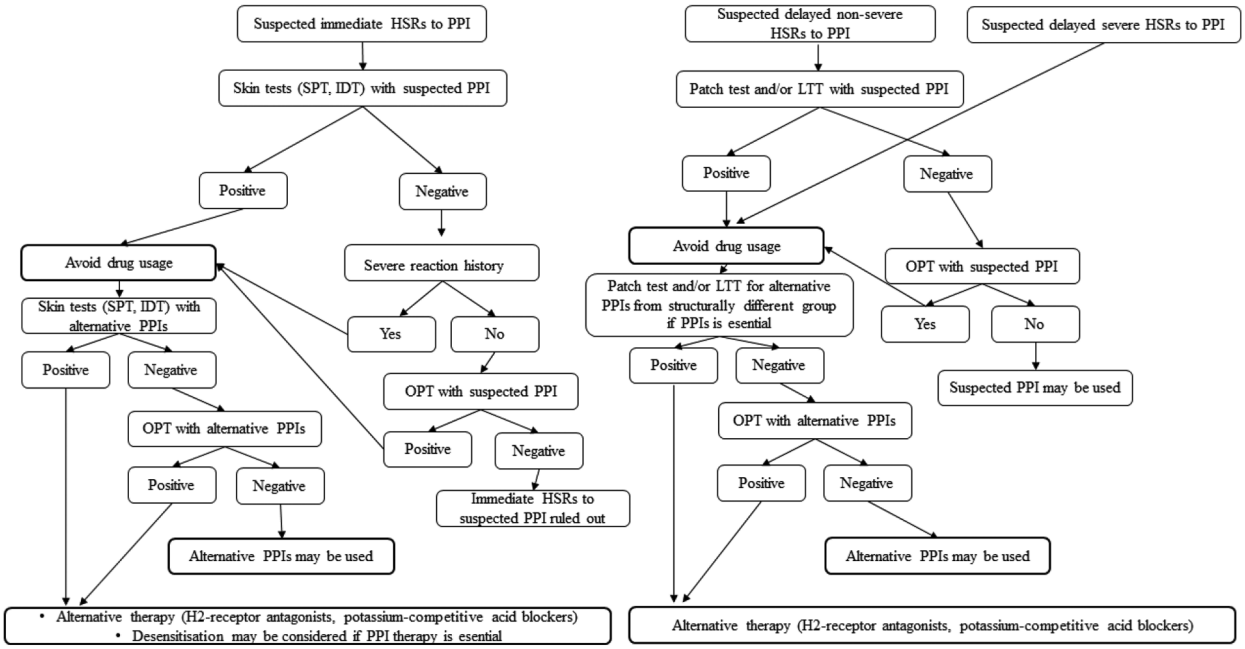
When PPI therapy is essential, skin testing and OPT should be performed on alternative PPIs within the same class to evaluate cross-reactivity. An alternative PPI with negative skin and OPT results may be safely used. If cross-reactivity is identified across all PPIs, alternative acid-suppressing medications such as histamine (H2)-receptor antagonists or potassium-competitive acid blockers (e.g., vonoprazan fumarate) should be considered (45). If PPI therapy is deemed essential, desensitization may be a viable therapeutic option (Figure 1); however, current data on desensitization protocols are limited, with only two documented case reports involving omeprazole and rabeprazole in immediate HSRs.

In one case, a 44-year-old man with immediate HSRs to omeprazole and Helicobacter pylori infection underwent oral desensitization using serial dilutions of omeprazole, starting at 0.001 mg and escalating over 5.6 hours to a final dose of 16 mg, successfully tolerating a 20 mg capsule thereafter. Post-desensitization skin tests showed significantly reduced reactivity, and the patient tolerated subsequent treatment with levofloxacin, tetracycline, and omeprazole (20 mg twice daily) for a 14-day therapy regimen without hypersensitivity, effectively managing his condition (46). In another case, a 26-year-old woman diagnosed with a duodenal ulcer experienced anaphylaxis after taking pantoprazole and esomeprazole. Skin testing confirmed hypersensitivity to all tested PPIs, leaving no alternative treatments. As a result, a desensitization protocol with rabeprazole was successfully implemented, enabling the patient to tolerate rabeprazole therapy without further hypersensitivity reactions (47).

These cases highlight the potential efficacy and safety of desensitization protocols for patients requiring PPIs despite a history of immediate HSRs. However, further research is needed to establish standardized desensitization approaches.

Delayed HSRs

The initial step in managing delayed HSRs to PPIs is to identify the suspected PPI as the causative agent and discontinue its use immediately. For non-severe delayed HSRs, patch testing, with or without an LTT, should be performed on the suspected PPI. A positive test result confirms hypersensitivity, and the implicated PPI should be avoided. If the patch test and/or LTT results are negative, an OPT can be conducted (4). A negative OPT excludes hypersensitivity, allowing for the continued use of the suspected PPI. However, if the OPT is positive, the specific PPI must be avoided, and alternative PPIs from a structurally different group should be evaluated using patch testing, LTT, and OPT. If all tests for the alternative PPI are negative, it may be safely used. If any of these tests are positive, alternative acid-lowering treatments should be used (45). In cases with a history of severe delayed HSRs, the suspected PPI should be avoided without testing. If PPI therapy is essential, the diagnostic steps for alternative PPIs mentioned above should be followed (Figure 1).



*HSRs = Hypersensitivity Reactions; PPIs = Proton Pump Inhibitors; SPT = Skin Prick Test; IDT = Intradermal Test; OPT = Oral Provocation Test; H2-Receptor Antagonists = Histamine Type 2 Receptor Antagonists; LTT = Lymphocyte Transformation Test

***Figure 1**. Schematic representation of the diagnostic and therapeutic approach for immediate and delayed HSRs to PPIs (authors archive)*

Management of severe delayed hypersensitivity reactions involves the immediate withdrawal of the causative drug, maintenance of proper hydration and electrolyte balance, regulation of body temperature, and meticulous care of damaged skin. Advanced strategies, such as autoclaved banana leaves, porcine xenografts, and stem cell therapies, have been explored to enhance wound healing. Pharmacological treatments, including corticosteroids, cyclosporine, intravenous immunoglobulins (IVIg), and newer agents like tacrolimus and biologics, have demonstrated varying levels of efficacy. Among these, cyclosporine has shown particularly promising results in reducing mortality rates. Emerging therapies, such as plasmapheresis and intravenous N-acetylcysteine, also show potential benefits, though their broader application is often limited by cost and accessibility (48).

Further research is required to refine these therapeutic strategies and establish standardized protocols for the diagnosis and management of delayed HSRs to PPIs, ensuring optimal patient outcomes.

Future Perspectives

The future of diagnosing and managing immediate and delayed hypersensitivity reactions (HSRs) lies in advancing diagnostic precision, leveraging personalized medicine, and developing innovative therapies. Emerging diagnostic tools, such as in vitro tests and biomarkers, are set to revolutionize accuracy, with the cytokine release enzyme-linked ImmunoSpot (ELISpot) assay gaining attention. This assay detects cytokine release, typically IFN-γ, when a patient's peripheral blood mononuclear cells are stimulated with suspected drugs, offering a reliable method to identify triggers. Pharmacogenomics, particularly the identification of genetic markers like human leukocyte antigens, is poised to play a pivotal role in personalizing treatment, enabling the identification of at-risk patients and optimizing drug selection (49).

On the therapeutic front, immunomodulatory treatments, including biologics that target specific inflammatory cytokines, show great promise for managing severe hypersensitivity reactions while minimizing side effects (50). Additionally, refined desensitization protocols will enhance the ability of patients to tolerate essential medications, even in cases of confirmed hypersensitivity. These advancements collectively aim to improve patient outcomes through safer, more precise, and individualized approaches to diagnosis and treatment.

Improved understanding of drug cross-reactivity will facilitate safer alternative therapy selection, particularly for structurally similar medications like PPIs. Alternative therapies, such as potassium-competitive acid blockers (45), will continue to evolve, offering safer options for affected patients. Challenges remain in establishing standardized diagnostic and treatment protocols and ensuring cost-effective, accessible solutions. Ongoing research into immune mechanisms and genetic factors is essential to advance the field. These advancements aim to deliver more accurate, efficient, and tailored care, improving outcomes and quality of life for patients with HSRs.

CONCLUSION

Hypersensitivity reactions to PPIs represent a significant clinical challenge due to their potential severity and the widespread use of these medications. A thorough understanding of the immunological mechanisms, clinical presentations, and appropriate diagnostic and therapeutic strategies is essential for optimal management. Future research should focus on improving diagnostic accuracy and exploring innovative approaches to minimize the risk of hypersensitivity while maintaining the therapeutic benefits of PPIs.

Abbreviations

PPIs - Proton Pump Inhibitors
GERD - Gastroesophageal Reflux Disease
H. pylori - Helicobacter pylori
NSAIDs - Nonsteroidal Anti-Inflammatory Drugs
HSRs - Hypersensitivity Reactions
SJS - Stevens-Johnson Syndrome
TEN - Toxic Epidermal Necrolysis
DRESS - Drug Reaction with Eosinophilia and Systemic Symptoms
SIBO - Small Intestinal Bacterial Overgrowth
SPT - Skin Prick Test
IDT - Intradermal Test
OPT - Oral Provocation Test
BAT - Basophil Activation Test
MPE - Maculopapular Exanthem
FDE - Fixed Drug Eruption
AGEP - Acute Generalized Exanthematous Pustulosis
SDRIFE - Symmetrical Drug-Related Intertriginous and Flexural Exanthema
LTT- Lymphocyte Transformation Test
SCLE - Subacute Cutaneous Lupus Erythematosus

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the study, performing the literature review, analyzing the data, and writing the manuscript. V.A., M.D.Z, K.Ć.,L.S. and S.V. assisted in the study design, data analysis, and manuscript writing. A.G., E.Ć.L., V.Z., H.P., M.M. and F.Dž. aided in data collection, interpretation, and manuscript preparation. L.S., E.Ć.L., and S.V. provided critical revisions and intellectual contributions to the manuscript. M.S. offered expert guidance and critical revisions.

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Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

RANE I ODLOŽENE HIPERSENZITIVNE REAKCIJE NA INHIBITORE PROTONSKE PUMPE: PREGLEDNI ČLANAK

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Inhibitori protonske pumpe su među najčešće propisivanim lekovima u kliničkoj praksi, prvenstveno se koriste za lečenje gastrointestinalnih poremećaja povezanih sa povećanim lučenjem hlorovodonične kiseline. Iako se generalno smatraju bezbednim, sa retkim i obično blagim neželjenim dejstvima, inhibitori protonske pumpe mogu biti povezani sa pojavom hipersenzitivnih reakcija. Ove reakcije, koje mogu biti rane ili odložene, variraju u težini od blagih do potencijalno životno ugrožavajućih. Ovaj pregled literature pruža detaljnu analizu ključnih aspekata primene inhibitora protonske pumpe, sa posebnim naglaskom na patofiziološke i kliničke karakteristike trenutnih i odloženih hipersenzitivnih reakcija. Takođe, rad istražuje ukrštenu reaktivnost među samim inhibitorima protonske pumpe i pruža praktičan vodič koji može pomoći lekarima u kliničkoj praksi u dijagnostikovanju i lečenju ovih stanja. Dodatno, rad ističe ključnu potrebu za daljim istraživanjima kako bi se razvili standardizovani dijagnostički i terapijski protokoli, omogućavajući personalizovanu i na dokazima zasnovanu negu za pacijente sa hipersenzitivnošću na inhibitore protonske pumpe.

Ključne reči: Inhibitori protonske pumpe, hipersenzitivne reakcije, trenutna hipersenzitivnost, odložena hipersenzitivnost, prick test, patch test, test aktivacije limfocita, ukrštena reaktivnost.

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Review article

NEUROPATHIC PAIN: CHALLENGES AND SOLUTIONS IN CLINICAL PRACTICE

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Abstract: Neuropathic pain is caused by abnormal processing of signals in the peripheral and central nervous systems. It is characterized by pain occurring without external stimulation or long after the injury has passed. Typically, it is chronic, with patients describing it as burning, stinging, stabbing, or tingling. Causes include diabetes, herpes zoster, surgery, stroke, multiple sclerosis, tumors, and injuries. Despite significant advances in neuropathic pain research in recent years, therapeutic options remain limited and often insufficiently effective. Symptomatic therapy for neuropathic pain is based on the use of drugs from four basic groups: antidepressants, anticonvulsants, local analgesics, and opioids. In addition to pharmacological methods, non-pharmacological interventions are also used in the treatment of neuropathic pain. A combination of these methods with pharmacological therapy often yields the best results.

Keywords: Neuropathic pain, Clinical presentation, Diagnosis, Therapy.

INTRODUCTION

According to the International Association for the Study of Pain (IASP), neuropathic pain (NeuP) is defined as pain resulting directly from damage or disease of the somatosensory system (1). The prevalence of NeuP is estimated at 7-10% of the global population, making it a significant public health issue (2). Treatment often involves the use of antidepressants and anticonvulsants, which are sometimes ineffective. As a result, new therapies, such as selective sodium channel antagonists and monoclonal antibodies, are being investigated (3). Rehabilitation and cognitive-behavioral therapy, supported by the environment and the active involvement of the patient, are key components of an integrated therapeutic approach to this complex chronic pain condition.

Definition of Neuropathic Pain

Neuropathic pain is caused by dysfunction or injury to the somatosensory system, which transmits sensations such as touch, temperature, and pain. Depending on whether the somatosensory component of the central or peripheral nervous system is affected, NeuP is categorized into two main types: central and peripheral NeuP (1). Peripheral NeuP results from damage to peripheral nerves, with common examples including diabetic neuropathy, postherpetic neuralgia, radiculopathy, and trigeminal neuralgia. In contrast, central NeuP is caused by lesions or diseases of the central somatosensory nervous system, with common causes being spinal cord injuries, stroke, brain injuries, and multiple sclerosis.

Nociplastic pain, a newer term defined by the IASP in 2017, refers to pain resulting from altered nociception without evidence of existing or potential tissue damage that would activate peripheral nociceptors or indicate disease or damage to the somatosensory system (4). Understanding the different types of pain, including neuropathic and nociplastic pain, is crucial for proper diagnosis and selection of appropriate therapy.

Classification of Neuropathic Pain

According to the 2008 grading system, NeuP is classified into three categories: possible, probable, and definite. Possible NeuP refers to the existence of pain with the incidence of a lesion or disease of the nervous system, with pain distribution in the corresponding anatomical region. Probable NeuP is characterized by

pain accompanied by sensory signs in the corresponding neuroanatomical region, confirmed by a neurological examination. Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system, confirmed by appropriate diagnostic tests. This classification systemfacilitates more accurate diagnosis and a more adequate selection of therapy for patients with NeuP (5).

Pathophysiology and Mechanisms of Neuropathic Pain

Neuropathic pain arises from lesions or dysfunctions in the peripheral or central nervous system, leading to aberrant processing of nociceptive signals (6). Key mechanisms involved include peripheral and central sensitization, ectopic activity of damaged nerve fibers, neuroinflammation, and reduced pain inhibition at the spinal cord level (7).

Peripheral sensitization occurs due to increased excitability of primary afferent neurons, with enhanced expression of sodium channels (e.g., Nav1.7, Nav1.8) and reduced activity of potassium channels (e.g., Kv1.1). This results in spontaneous firing of nerve fibers and increased sensitivity to stimuli (8).

Central sensitization, which develops in response to chronic afferent stimulation, involves enhanced activation of NMDA receptors, dysfunction of inhibitory interneurons, and increased release of pro-inflammatory cytokines, leading to abnormal pain perception.

Neuroinflammation, mediated by microglia and astrocytes, further contributes to heightened neuronal excitability and long-term changes in pain pathways (9).

These mechanisms collectively lead to phenomena such as **hyperalgesia** (increased sensitivity to pain) and **allodynia** (pain caused by non-painful stimuli), which are characteristic of neuropathic pain (10).

Clinical aspects of neuropathic pain

Neuropathic pain is a complex condition manifested by a wide range of clinical symptoms, including spontaneous pain, hyperalgesia, allodynia, and phantom pain (6). A detailed neurological examination is key to identifying the neuropathic component of pain, with an emphasis on recognizing "positive" and "negative" symptoms.

Spontaneous pain is the basic symptom of NeuP, where the painful sensation occurs without an obvious cause. This type of pain is often intense, long-lasting, and significantly impairs the patient's quality of life (11).

Hyperalgesia means an increased response to painful stimuli and is often the result of peripheral and central sensitization. It is common in the early stages of NeuP, especially after injuries to the nervous system or surgical interventions, and can last for weeks (12).

Allodynia is a painful response to painless stimuli, such as light touch or gentle pressure, and is associated with central sensitization which increases the sensitivity of the nervous system to stimuli that normally do not cause pain.

Phantom pain is a specific form of NeuP that occurs in patients after amputation. Its development is associated with neuroplasticity, whereby the reorganization of the central nervous system causes erroneous signals and painful sensations (13).

Recent research emphasizes the importance of an individualized approach in the treatment of NeuP, due to the diverse clinical manifestations and mechanisms that contribute to this condition (14). Frequently present comorbidities, such as anxiety and depression, further worsen the quality of life of patients, which indicates the need for a holistic and multidisciplinary approach to diagnosis and therapy (15).

Diagnosis of neuropathic pain

The diagnosis of neuropathic pain (NeuP) is based on a comprehensive approach that includes a detailed history, physical and neurological examination, laboratory analysis, electrophysiological testing, application of advanced imaging methods, and, in exceptional cases, skin or nerve biopsy. Given that pain is a subjective phenomenon, a key role in diagnosis is played by the patient's perception of pain, including its localization, distribution, intensity, quality, temporal dynamics, and factors affecting pain (1).

Validated unidimensional scales such as the Visual Analog Scale (VAS), Numerical Scale (NS), Verbal Scale (VS), and Facial Expression Scale are used to assess pain intensity. In addition, multidimensional tools such as the *Douleur Neuropathique 4 Questions* (DN4), *painDETECT Questionnaire*, and *Self-Administered Leeds Assessment of Neuropathic Symptoms and Signs* (S-LANSS) provide additional information about localization, the impact of pain on daily activities, mood, and the overall quality of life of patients (16).

Neurological examination often provides crucial information about the presence of "positive" or "negative" symptoms of NeuP, but alone is not sufficient to determine the etiology and extent of damage. Electrophysiological testing, including electromyoneurography (EMNG) and somatosensory evoked potentials (SSEP), helps localize and quantify damage to peripheral and central nerve pathways. However, these methods are not useful for the diagnosis of thin fiber

neuropathy, where quantitative sensory testing (QST) and laser-evoked potentials (LEP) are used. The LEP method enables a selective assessment of nociceptor function, with a high degree of sensitivity in detecting neuropathy of thin fibers (17, 18).

In cases of normal neurological and electrophysiological findings, a skin biopsy can confirm a decrease in the density of intraepidermal C-fibers, which is diagnostically significant, although the degree of decrease does not correlate with pain intensity (19). Additional methods, such as corneal confocal microscopy and the sudomotor axon-reflex test, are still used for research purposes and are not routinely available (20, 21).

Advanced functional neuroimaging techniques, such as PET and fMRI, provide insight into regional changes in blood flow and metabolic activity in the brain, including thalamic dysfunction and asymmetric activity of the somatosensory cortex in patients with NeuP (9). In rare cases, additional tests such as immunological blood tests and cerebrospinal fluid analysis (CSF) may be needed for a precise diagnosis of NeuP.

This multidisciplinary approach enables not only the confirmation of the diagnosis but also a better insight into the basic mechanisms of NeuP, which is essential for the individualization of therapy and the improvement of the patient's quality of life.

Treatment of neuropathic pain

The treatment of NeuP requires a comprehensive, multidisciplinary, and multimodal approach due to the complex mechanisms of origin and different localizations of damage to the nervous system. Therapy includes a combination of pharmacological and non-pharmacological methods to alleviate symptoms, improve functionality, and improve the quality of life of patients (Table 1).

Antidepressant drugs in the treatment of neuropathic pain

Antidepressants, especially tricyclic antidepressants (TCAs) and duloxetine have a significant role in

Table 1. *Treatment of neuropathic pain (revised by reference 12)*

Medicine	Starting dose	Maintenance dose	Maximum daily dose	Recommendations
Tricyclic antidepressants (TCAs)				
Amitriptyline	10-25 mg 1/d, in the evening	25-100 mg/d, evening	150 mg	First line
Nortriptyline	10-25 mg 1/d, in the evening	25-100 mg/d, evening	150 mg	First line
Imipramine	10-25 mg 1/d, in the evening	25-100 mg/d, evening	150 mg	First line
Selective noradrenaline/serotonin uptake inhibitors (SNRI/SSRI)				
Duloxetine	1x30 mg, in the morning	1x60 mg/d, in the morning	120 mg	First line
Venlafaxine	1x37.5 mg, in the morning	150-225 mg/d, in the morning	375 mg	First line
Anticonvulsants				
Pregabalin	1x25-50 mg, evening	150-300 mg/d	2x300 mg	First line
Gabapentin	3x100 mg/d, starting dose in the evening	1200-2400 mg/d	3x1200 mg	First line
Carbamazepin	200-400 mg/d	600-800 mg/d	1200 mg/d	First line (N. trigeminus)
Opioids				
Morphin	2x10-30 mg/d	Individual	240 mg/d	Third line
Oxycodone	2x5-10 mg/d	Individual	120 mg/d	Second line
Tramadol retard	2x50-100 mg/d	Individual	2x200 mg/d	Second line
Topical medications				
Lidocaine 5% patch	1-3 patch/d	1-3 patch/d	3 patch	Second line
Capsaicin 8% patch	1-4 patch/3 months	1-4 patch /3 months	1-4 patch /3 months	Second line

the treatment of NeuP due to their unique analgesic mechanism involving modulation of descending inhibitory pain pathways (22). Their efficacy has been confirmed in several clinical conditions, including painful diabetic neuropathy (23), postherpetic neuralgia (24), and central pain after stroke (25). These drugs not only relieve pain but do so independently of their antidepressant effect, which makes them suitable for patients with and without comorbid depression (15). Personalizing the therapeutic approach is essential to achieving the best results, taking into account the individual characteristics of patients, their comorbidities, and drug tolerance. Initial lower doses and a gradual increase to the maximally tolerated and effective dose enable the safe use of these drugs, while continuous monitoring of the therapeutic response and potential side effects contributes to the success of the treatment. For example, duloxetine is often used in the treatment of NeuP in patients with painful diabetic neuropathy because of its more favorable side effect profile compared to TCAs, although doses above 60 mg daily do not provide additional benefits in pain relief (26, 27). Venlafaxine, despite its potential utility in specific conditions such as chemotherapy-induced polyneuropathy and painful diabetic polyneuropathy, currently has limited use in NeuP therapy and requires further research to determine its precise role (28, 29).

Anticonvulsants in the treatment of neuropathic pain

The use of anticonvulsants in NeuP therapy represents a key segment of a multidisciplinary approach to this complex clinical condition. Their effectiveness is based on specific mechanisms of action that enable the reduction of the transmission of pain signals and the modulation of neuronal excitability. Gabapentin and pregabalin, voltage-gated calcium channel inhibitors, have been shown to reduce the release of excitatory neurotransmitters such as glutamate, thus successfully treating conditions such as postherpetic neuralgia, painful diabetic neuropathy, and central NeuP. Gabapentin is effective up to 3600 mg per day, while pregabalin offers added benefits in patients with insomnia and anxiety at doses up to 600 mg daily. (30,31,32). Carbamazepine and oxcarbazepine, anticonvulsants that act by blocking voltage-gated sodium channels, are particularly useful in the treatment of trigeminal neuralgia and painful diabetic neuropathy. Their action is based on the stabilization of neuronal membranes and the inhibition of the generation of ectopic impulses, with proven results at doses up to 1200 mg per day for carbamazepine (33). Lamotrigine, although primarily intended for epilepsy, has a significant role in the treatment ofhuman immunodeficiency virus (HIV)-related neuropathy and central NeuP after stroke. Other anticonvulsants, such as topiramate, lacosamide, and valproic acid, have also shown potential efficacy, especially in painful diabetic neuropathy, but their use requires further research and more clearly defined protocols (31, 32). Although anticonvulsants bring significant relief to patients with NeuP, their use requires careful dose titration and regular monitoring of side effects, especially in elderly patients and people with comorbidities. Common side effects include sedation, dizziness, edema, and weight gain, necessitating individualization of therapy to achieve an optimal balance between efficacy and safety (30, 31). Further research is necessary to improve the understanding of the molecular mechanisms of action of anticonvulsants and to define new strategies for their use.

Topical drugs in the treatment of neuropathic pain

Topical drugs represent a significant therapeutic option for localized NeuP, allowing direct application to the painful site and minimizing the risk of systemic side effects and interactions with other drugs. Lidocaine, in the form of a 5% patch, acts by blocking voltage-dependent sodium channels in afferent Aδ and C fibers, thereby effectively reducing pain (34). Capsaicin, available as a 0.075% cream or high-concentration patch (8%), acts by activating transient receptor potential(TRPV1) receptors, causing temporary depolarization and desensitization of sensory neurons (35).

Botulinum toxin

Botulinum toxin (BoNT-A) has been investigated in painful diabetic neuropathy (36), postherpetic neuralgia (37), trigeminal neuralgia (38), and central NeuP (39). The analgesic effect is achieved by muscle paralysis, reduction of spasms, improvement of blood flow, and release of nerve fibers from compression caused by muscle contraction. Clinical studies conducted on a smaller number of patients showed very positive results, but it is necessary to further investigate the effectiveness of BoNT-A in the treatment of peripheral and central NeuP in a larger sample of patients.

Opioid analgesics in the treatment of neuropathic pain

Opioid analgesics, including drugs such as tramadol, oxycodone, and morphine, are a key therapeutic option in the treatment of cancer pain, and they are also used in the treatment of persistent chronic non-cancer pain of moderate to severe intensity. In clinical

practice, opioids are classified into weak (tramadol, codeine, dihydrocodeine) and strong (morphine, oxycodone, fentanyl, pethidine) analgesics, and the choice of drug depends on the degree of pain and the patient's response to therapy. Tramadol is a synthetic analgesic that acts as a weak agonist at mu (μ), kappa (κ), and delta (δ) opioid receptors. As a second-line analgesic, tramadol is useful in the treatment of acute and chronic pain conditions, and due to its dual mechanism of action, it stands out as the analgesic of choice in the treatment of pain with a neuropathic component (40). The recommended starting dose is 50-100 mg twice a day, and the dose is gradually increased to a maximum of 400 mg per day. Oxycodone is a strong analgesic, about twice as strong as morphine, and is used to treat moderate to severe pain. Oxycodone can be administered orally (often in combination with paracetamol), rectally, parenterally, and epidurally. The initial dose is 5-10 mg twice a day, and the drug is gradually titrated according to the patient's needs. Oxycodone is particularly useful in elderly patients, as it shows better tolerability and fewer side effects compared to morphine (41). Morphine is an opioid that represents the "gold standard" in pain therapy with an intensity greater than 6 on the numerical scale. It can be administered orally, rectally, subcutaneously, transdermally, intramuscularly, intravenously, epidurally, and intrathecally. The initial dose for oral administration is 10-30 mg twice daily, especially in elderly patients, and the dose is later titrated according to tolerability (42). Morphine is extremely effective in controlling pain but requires careful titration due to potential side effects.

Cannabinoids

Cannabinoids are used as an adjunct in a multicomponent pharmacotherapeutic concept in carefully selected patients with resistant pain (43). Cannabinoids are particularly useful in managing painful spasticity in multiple sclerosis, cachexia in HIV, and potential applications in the therapy of Parkinson's disease, Alzheimer's disease, cerebral ischemia, and other inflammatory diseases (44). However, the lack of randomized studies limits their widespread application.

Non-pharmacological treatment of neuropathic pain

Non-pharmacological treatment of NeuP is an important part of the overall therapeutic approach, which often serves as a complement to pharmacological treatments. Different methods of physical therapy are used in daily clinical practice, such as transcutaneous electrical nerve stimulation (TENS), electromagnetic therapy, low-intensity laser, massage, and kinesitherapy. These methods help reduce pain and improve patients' functionality. TENS is one of the most commonly used techniques, although clinical evidence for its effectiveness varies, it is often used due to the relatively low risk of side effects (45). Electromagnetic therapy and low-intensity lasers have the potential to improve circulation and reduce pain, but their use requires additional research to confirm long-term effectiveness. Physiotherapy, which includes specific exercises to improve muscle strength and flexibility, is also used to relieve symptoms of NeuP, especially when pain is associated with limited mobility. Psychological approaches, such as cognitive and behavioral therapy, are integrated into treatment plans because of their effectiveness in managing chronic pain. These methods help patients better understand and manage their pain, reducing emotional distress and improving quality of life (46). Although non-pharmacological treatment is often complementary to pharmacological interventions, it plays an important role in a holistic approach to NeuP therapy (47). All these methods should be adapted to the individual needs of patients, taking into account their specific symptoms, comorbidities, and preferences.

CONCLUSION

Neuropathic pain represents a serious therapeutic challenge, due to its complex pathophysiology and often refractory nature. Modern NeuP treatment combines pharmacological and non-pharmacological methods, with antidepressants, anticonvulsants, and opioids being key in pain control, while topical treatments and physiotherapy help to improve patients' functionality. Although pharmacological therapy is the mainstay, non-pharmacological techniques, including psychological approaches such as cognitive and behavioral therapy, play an important role in a comprehensive treatment approach. Educating patients and healthcare professionals about the nature of NeuP and available therapeutic options can significantly contribute to better control of this complex condition.

Abbreviation

IASP - International Association for the Study of Pain

NeuP - Neuropathic pain

VAS - Visual analog scale

NS - Numerical scale

VS - Verbal scale

DN4 - Douleur Neuropathique 4 Questions

S-LANSS - Self-Administered Leeds Assessment of Neuropathic Symptoms and Signs

EMNG - Electromyoneurography

QST - Quantitative sensory testing
LEP - Laser-evoked potentials
CSF - Cerebrospinal fluid analysis
TCAs - Tricyclic antidepressants
HIV - Human Immunodeficiency Virus
TRPV1 - Transient receptor potentialreceptors
BoNT-A - Botulinum toxin
TENS - Transcutaneous electrical nerve stimulation

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Sažetak

NEUROPATSKI BOL: IZAZOVI I REŠENJA U KLINIČKOJ PRAKSI

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Neuropatski bol nastaje zbog abnormalne obrade signala u perifernom i centralnom nervnom sistemu. Karakteriše ga prisustvo bola bez spoljašnjeg nadražaja ili dugo nakon što je povreda prošla. Obično je hroničan, a pacijenti ga opisuju kao žarenje, peckanje, probadanje ili mravinjanje. Uzroci uključuju dijabetes, herpes zoster, hirurške intervencije, šlog, multiplu sklerozu, tumore i povrede. Uprkos značajnom napretku u istraživanju neuropatskog bola tokom poslednjih godina, terapijske mogućnosti ostaju ograničene i često nedovoljno efikasne. Simptomatska terapija neuropatskog bola se bazira na primeni lekova iz četiri osnovne grupe, a to su antidepresivi, antikonvulzivi, lokalni analgetici i opioidi. Pored farmakoloških metoda, u lečenju neuropatskog bola primenjuju se i nefarmakološke intervencije. Kombinacija ovih metoda sa farmakološkom terapijom često daje najbolje rezultate.

Ključne reči: Neuropatski bol, klinička slika, dijagnoza, terapija.

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Review article

MULTIOMICS INTEGRATION IN ANTI-TUBERCULOSIS DRUG DISCOVERY

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Abstract: Despite intensive global efforts, tuberculosis remains one of the leading global health burdens, with antimicrobial resistance being a significant challenge to managing the disease. In addition, the current drugs used to treat tuberculosis suffer from limitations, such as prolonged therapeutic duration and toxicity. Therefore, the development of new anti-tuberculosis drugs is a priority. However, this process faces several challenges. The introduction of a multiomics approach could serve as an ideal platform to accelerate drug development by addressing these challenges. This article reviews the potential role of multiomics in anti-tuberculosis drug development and briefly discusses the associated challenges in utilizing multiomics for drug discovery.

Keywords: tuberculosis, drugs, proteomics, multiomics, *Mycobacterium tuberculosis*, transcriptomics, metabolomics, genomics.

INTRODUCTION

Tuberculosis remains one of the leading global public health issues, with a significant disease burden. In 2024, approximately 10.8 million new cases were reported, 10% of which occurred in children, while 12% were linked to co-infection with human immunodeficiency virus (HIV) (1). Although the World Health Organization (WHO) has approved effective therapeutic regimens with an estimated 85% cure rate, around 1.6 million deaths were reported (2). Among the newly diagnosed cases, drug resistance was identified in 6.4 million, and 662,000 cases involved co-infection with HIV.

Multidrug resistance remains a major obstacle to global tuberculosis control efforts. Treating drug-resistant tuberculosis requires between 6 and 9 months, presenting significant challenges. The increasing prevalence of drug resistance adversely affects treatment strategies, prolonging therapy and complicating regimens compared to drug-susceptible tuberculosis. This highlights the urgent need for novel antimicrobial compounds effective against *Mycobacterium tuberculosis* (M. tb). Despite international efforts, only three new tuberculosis drugs—pretomanid, delamanid, and bedaquiline—have been introduced in recent years (3, 4).

Several logistical and physiological factors have hindered the development of new drugs using existing technologies, including the ability of drugs to penetrate the lungs, the lipid-rich nature of the bacterial cell wall, and intrinsic mechanisms of drug resistance. The introduction of multiomics technology offers a promising solution to these challenges (4). Multiomics aims to integrate and analyze combined molecular entities based on their biological classification, elucidating the roles of individual components. This approach can play a crucial role in identifying novel drug targets. When applied to tuberculosis research, multiomics can be utilized throughout the entire drug discovery process—from initial phases to preclinical and clinical stages—helping to define mechanisms of action (MoA), derivatives, and formulations for M. tb.

This review will evaluate the role of multiomics technology in the development of anti-tuberculosis drugs by analyzing key components of multiomics approaches, including genomics, metabolomics, proteomics, and transcriptomics (Table 1). It will also explore their potential in identifying and validating novel anti-tuberculosis drug targets and biomarkers for both efficacy and toxicity.

***Table 1**. Multi-omics strategies and the processes in reading (Sources: Ref No 4)*

Multi-omics approach	Molecular read-outs	Technology
Genomics	Genes (DNA)	Sequencing, exome
Epigenomics	Alteration of DNA	Modification-sensitive PCR and qOCR-next-generation sequencing, mass spectrometry
Transcriptomics	RNA and/or cDNA	RT-PCR and RT-qPCR, gene arrays, RNA-sequencing
Proteomics	Proteins	Mass spectrometry, western blotting, and ELISA
Metabolomics	Metabolites	Mass spectrometry, nuclear magnetic resonance (NMR) spectroscopy and HPLC
Lipidomics	Lipids	Mass spectrometry, Bioinformatics data mining, and Ionization techniques
Microbiomics	Microbes	16S profiling
Omic imaging	Tissues and biofluids	Functional and structural magnetic resonance imaging (fMRI and sMRI)

Multiomics Approach

Omics is a systems biology field that integrates different sets of biomolecules, such as RNA or metabolites, to enhance our understanding of molecular complexity in both health and disease states. Advances in omics technology have enabled the integration of multiple omic data types, collectively referred to as **multiomics**. This integrated approach provides a holistic understanding of biological processes by combining genomics, proteomics, microbiomics, metabolomics, transcriptomics, and other multiomics techniques (Table 1).

Multiomics approaches have been instrumental in healthcare and beyond. For example, omics technology enhances our understanding of disease pathogenesis. Additionally, multiomics aids in the identification of novel biomarkers. In terms of disease prevention, multiomics can help uncover genetic and molecular mechanisms that inform preventive strategies, improving both patient classification and clinical outcomes. Furthermore, omics technology plays a crucial role in identifying molecular targets for developing new therapeutic agents. In diseases such as infectious diseases and cancer, targeting specific proteins or mutations is a highly effective strategy for drug development and diagnostics.

The advent of artificial intelligence (AI) has further advanced multiomics by facilitating computational techniques such as bioinformatics, which can significantly enhance drug development and predict drug responses—essential for designing personalized treatment plans. Multiomics is also valuable in clinical trials, where multiomic data can be used to stratify trial participants and evaluate therapeutic interventions. Moreover, statistical analyses in multiomics research can help identify the risk of developing certain diseases, further expanding its role in predictive medicine.

These applications highlight the vast potential of multiomics technology in advancing healthcare and beyond (5).

***Table 2.** Different types of multiomics techniques (Source: Ref No 4)*

• Genomics: Use to study of genome sequences and DNA sequences variants (e.g. single nucleotide variations, insertion-deletions, copy number changes, structural changes
• Transcriptomics: Evaluate or measure complete set of RNA transcripts and their quantity in a cell or population of cell
• Proteomics: Use to quantify all protein identity and abundance in a sample such as serum, plasma, post-mortem samples. Also useful in analysing altered level of immune system-regulating proteins such as apolipoprotein
• Epigenomics: Use to identify chemical changes to DNA and proteins in cell that control gene expression. An epigenome is made of chemical compounds that change or highlight the genome is such as wat that it instruct it what to do, where to do it, and when to it. Cells have different epigenetic markers
• Metabolomics: Study of small molecules in the body. Four type of metabolomics: target metabolomics- identifying and quantifying small subsets of metabolites. It is ideal for identification of novel biomarkers; untargeted metabolomics- used to characterized all possible number of metabolites; fluxomics- monitors the movement of isotopic labels through metabolic intermediates and used to measure the reaction rates of metabolites; metabolites imaging- involves the detection and visualization of metabolites in tissues

Currently, different types of omics approaches are being used. Multi-omics sequencing allows the simultaneous evaluation of multiple molecular layers from a single sample, leading to a detailed elucidation of the biological system. It plays a significant role in combining complex data, which is essential for understanding biological matrices and pathways.

In single-cell multi-omics, a series of omic data are evaluated at the single-cell level to study complex diseases. Single-cell multi-omics can help develop an understanding of how different cell types in pathogens or tumors respond to therapies.

Spatial multi-omics utilizes multi-omics data by combining it with spatial information about the surrounding tissues or cells.

The Role of Innovative Technologies in Drug Development

The development of drugs is a complex process that begins with identifying novel targets and ends with introducing a drug into clinical settings. This process is typically long and expensive, with most drugs tested failing in clinical trials. The ultimate aim of drug development is to identify novel molecules that have an effect in the human body and establish an effective and safe profile that benefits patients.

The US Food & Drug Administration (FDA) estimates that it takes more than 12 years for an experimental drug to advance from the bench to the market (6). More than $20 billion is expended on a single drug discovery, with approximately 20% used in screening assays and toxicity testing (7). Furthermore, long administrative processes play a significant role in the high failure rates associated with new drug development.

While the cost of new drug development continues to rise, there is still a need for new drugs, especially for infectious diseases such as tuberculosis, malaria, and HIV/AIDS, where antimicrobial resistance (AMR) has become a global public health burden. The utilization of novel technologies can facilitate the development of new drugs. The use of genomics, metabolomics, proteomics, and other omics will be essential in facilitating drug development and contributing to more effective treatment regimens.

In tuberculosis medicine, new drugs are urgently needed to address both AMR and the duration of treatment. Different approaches to multi-omics data integration can be used for anti-tuberculosis drug discovery (8, 9). Among these is conceptual integration, in which databases and existing information are connected to various omics data according to measurable concepts or entities, such as genes or proteins. This method is useful for formulating theories and finding connections between various omics datasets. Two platforms for comparing omics data are STATegra and OmicsON (10, 11).

Combining statistical techniques to compare various omics datasets using quantitative metrics such as regression and correlation is known as statistical integration. This method is crucial for identifying trends and differences in omics data. It can also be used to determine whether drug response and gene expression are related. However, causal relationships between the omics data cannot be established using this technique (12).

Using mathematical or computational models to forecast a biological system's behavior based on various omics data is known as model-based integration. Drug absorption, distribution, metabolism, and excretion in various biological models can be assessed using pharmacokinetic/pharmacodynamic models (13, 14). This technique helps in understanding the biological system's dynamics and regulation (5). However, a limitation of this approach is that it requires prior knowledge and assumptions about the parameters and structure of the system.

Network and pathway data integration involves using networks or pathways that depict the composition and operation of a biological system, derived from various omics data. Pathways refer to biological processes that occur under specific conditions, while networks are graphically represented as nodes and interactions within the system (13). Omics data can vary in complexity and format, and this method allows for their integration. For example, it can be used to assess protein-protein interactions. However, this approach is not useful for understanding the system's geometric or temporal details.

Role of Multi-omics in Tuberculosis Drug Development

Multi-omics is a promising technology in the development of anti-tuberculosis agents (Figure 1), as it provides a platform to untangle the pathogenic mechanisms of TB infection, drug resistance, and the host's response to infection (15). Data generated from multi-omics can be utilized to address key research questions. One of the primary applications of multi-omics is the identification and validation of drug targets for therapeutic interventions. These drug targets are molecules that can be modified during the disease state. Targets may include genes, proteins, metabolites, or transcript markers associated with the pathogenic mechanisms of specific diseases, such as tuberculosis, COVID-19, and Dengue fever (5).

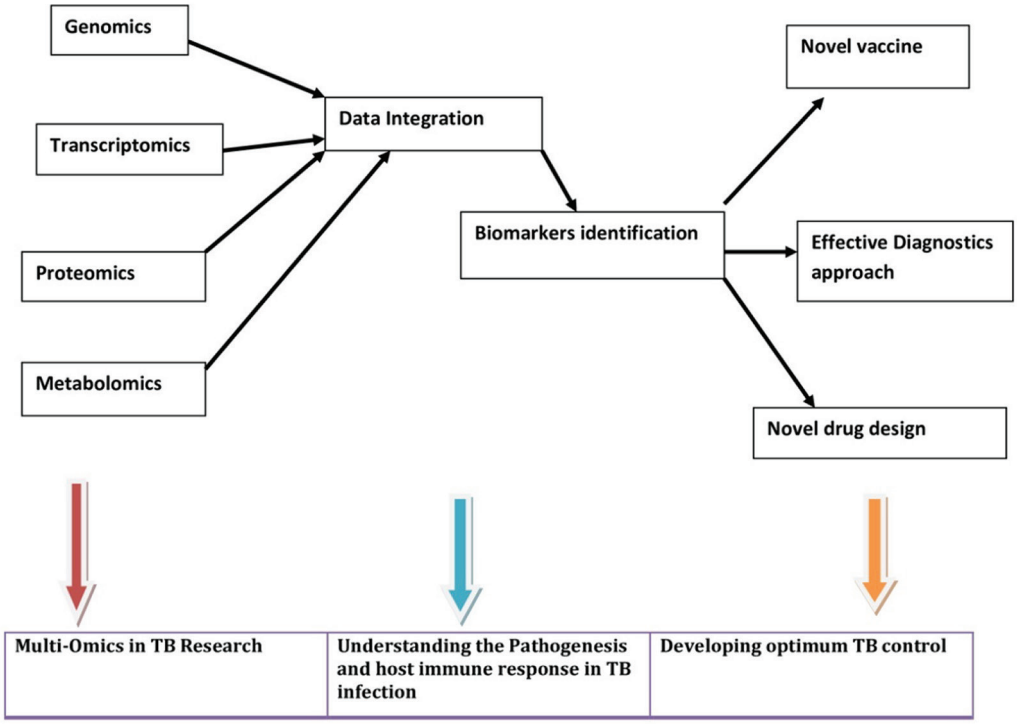

Figure 1. *Multi-omics flow in TB research (Source: Based on protocol of the AHRO small drug molecules development portfolio)*

In TB drug discovery, like in other disease states, multi-omics can be utilized for discovering and validating drug targets. It helps elucidate the disease profile or molecular signature, as well as the potential drug response, by integrating omics data from various levels of biological molecules. Multi-omics data can identify genes, proteins, metabolites, and transcript markers that are differentially expressed or regulated in diseased samples compared to healthy ones, or in individuals who respond to a drug versus those who do not (16). This approach enables the characterization of potential drug targets based on their role in the disease's pathogenic process and their response to drugs, ranking them based on differential expression, disease correlation, and other relevant criteria (5). Drug targets can then be validated using experimental models that assess the effects of modulating these targets in disease versus non-disease states. Multi-omics can also guide studies on gene knockdown, mutation, inhibition, and activation of drug targets (17).

Building molecular networks that integrate omics data—such as the correlations among genes, proteins, metabolites, and transcript markers—can help identify connections to the disease's pathogenic mechanisms and the drug's mechanisms of action (5).

Beyond discovery and validation, multi-omics is valuable for predicting and improving drug responses in various disease states. It can be used to identify markers of drug efficacy, safety, resistance, and other relevant indicators. In TB drug development, multi-omics can help identify genetic variants, such as single nucleotide polymorphisms (SNPs), protein and gene expression levels, and metabolites and transcript markers that influence individual responses to anti-TB drugs. Additionally, it can be used to predict optimal drug dosages during the discovery and formulation phases. Multi-omics can also categorize individuals based on their drug response, which can aid in predicting the efficacy, toxicity, safety, and duration of drug response, as well as other important markers (18, 19, 20).

Although no research specifically evaluates the role of multi-omics in TB drug research, several studies have explored its role in mycobacterial research. Wei et al. used multi-omics to investigate resistance mechanisms in folylpolyglutamylsynthetase-dihydrofolate synthetase gene (folC)-mutated and unmutated *M. tb* strains resistant to p-Aminosalicylic acid (PAS). They found that S-adenosyl-methionine (SAM)-dependent methyltransferases were upregulated, while PAS uptake was downregulated through the inhibition of certain drug transport pathways. These findings suggest that these pathways could serve as novel drug targets for PAS-resistant *M. tb* strains (21).

Krishnan et al. employed multi-omics to identify serum markers of tuberculosis in individuals with advanced HIV infection (22). In a case-control study using a multi-country, open-label randomized controlled trial, they compared a four-drug standard TB treatment with isoniazid preventive therapy among people living with HIV (PLWHIV) initiating antiretroviral therapy. The

study identified several indicators (microRNAs, metabolites, and cytokines/chemokines) associated with newly diagnosed TB among PLWHIV. They found that TNFα and CXCL10 levels were higher in cases than controls, while macrophage-derived chemokine (MDC, also known as CCL22) was higher in controls. This study highlighted the potential of multi-omics in identifying TB among severely immunocompromised PLWHIV.

Cui et al. used a multi-omics approach to evaluate the role and mechanism of DosR (dormancy survival regulator) in *Mycobacterium bovis* Bacillus Calmette-Guerin (BCG). Their study showed that DosR significantly impacted the transcription of 104 genes and 179 proteins, suggesting its involvement in amino acid synthesis and metabolism. These findings suggest that DosR may serve as a novel drug target against M. tb (23).

One of the problems of global health is AMR. Zhao et al. evaluated resistance to capreomycin (CAP), a cyclic peptide that is considered the best second-line treatment for tuberculosis, using multi-omics analysis (24). They evaluated CAP resistance (CAPr) using tlyA-Mtb strains (CAPr1) and tlyA point mutation CAPr M. tb strains (CAPr2), utilizing genomics, proteomics, and metabolomic techniques. They found that compared to CAPr2 strains, CAPr1 bacteria exhibited greater resistance to CAP. Additionally, CAPr1 strains showed greater drug tolerance than CAPr2 strains, which was associated with deficient S-adenosyl-L-methionine-dependent methyltransferase and abnormal membrane metabolism. Their research identified a novel drug resistance mechanism in M. tb in CAP therapy, which may help in understanding other resistance mechanisms in M. tb. Moreover, multi-omics was used to elucidate the correlation between drug similarities and drug efficacy in type 2 diabetes (19). Si et al. identified new targets for chronic kidney disease (CKD) using multi-omics. They discovered thirty-two new therapeutic targets in a thorough analysis of CKD patients' plasma using proteomics and transcriptomics. These included centrosomal protein of 170 kDa, liver-expressed antimicrobial peptide, fibroblast growth factor 5, oromoduline, and others. As a result, the researchers concluded that these new potential therapeutic targets might be used to develop new immunotherapy drugs, targeted medications, and CKD combination treatments (20). Bai et al. used data-based Mendelian randomization (MR) techniques to find a novel therapeutic target for Sjögren's syndrome (SS). Three proteins were shown to be associated with the risk of SS. TNFAIP3, PLAU, and BNT3A1 were among them. They therefore suggested novel drug targets for SS (25). All these studies show that multi-omics has potential in TB drug development, as outlined briefly below.

Novel pharmacological targets can be identified through genomics. Different microenvironments that provide beneficial routes for M. tb can be identified by inactivating genes through experimental mutation using genomics. These may be effective methods for discovering new targets. Genomics can also be crucial in clarifying the MOA of new medications. Whole genome sequencing (WGS) can be used to identify possible mutations that could impact a drug's mode of action. The MOA of bedaquiline was described by Kundi et al. in a study, which demonstrated that the medication works by targeting the bacterial F-ATP synthase's epsilon subunit (26). To enable the innovative use of licensed medications in TB treatment, WGS can also be used to determine the MOA of repurposed medications in TB. In an intracellular model of infection, Rybniker et al. found that lansoprazole protected against lung fibroblasts. This medication was found in the Prestwick Library pool, which included 1280 FDA-approved medications (7, 27).

Understanding M. tb transcriptomics is also crucial in identifying novel pharmacological targets for TB infection, as it links crucial genomic data to protein expression targets, revealing new target pathways and M. tb's response to exposure to that novel drug. Transcriptomics is an essential tool for understanding the biology of M. tb, the pathogenic mechanism of the bacteria, gene function, and the identification of new therapeutic targets (4). The drug mechanisms, including the metabolism of fatty acids, cholesterol, and the glyoxylate shunt of M. tb replicating within macrophages, were clarified by Schnappinger et al. and Rienksma et al. using transcriptomics (28, 29). Additionally, purimidine-imidazole detection during whole-cell screening of M. tb was reported by Pethe et al. (30). This lends more credence to the claim that WGS in transcriptomics is the ideal platform for discovering new, potentially effective therapeutic targets. As a result, using transcriptomics in conjunction with gene mining datasets may be an essential multi-omics tool for TB drug development. The MOA of a novel medicinal molecule can also be better understood with the aid of transcriptomics. According to a study by Wilson et al. using DNA microarray to clarify gene expression caused by isoniazid, exposure to the drug led to upregulation of five genes encoded by synthesis-type II fatty acid enzymes and other genes linked to isoniazid MOA (31). In addition, Boshoff et al. quantified the effect of various inhibitors that affect M. tb transcriptional responses (32) by characterizing TB metabolism utilizing various therapeutic agents, growth environments, and drug combinations. They were able to classify different medications according to their MOA. As a result, they used whole-cell data to predict novel MOA for the medications under study.

Drug discovery for tuberculosis may also benefit from a proteomics approach (33). Changes in protein levels indicate that proteomics may offer a valuable platform for characterizing the physiological response of M. tb and expression of novel targets. Although it has not yet attained the same potential as transcriptomics and genomics, both in vitro and in vivo data from certain research have suggested new pharmacological targets. Understanding the mechanism of virulence can facilitate the development of a cure for tuberculosis. By distinguishing the proteome profiles of virulent strains of intracellular and extracellular M. tb and BCG from infected macrophages, Liu et al. elucidated the virulence mechanism of M. tb. They discovered 1557 proteins linked to the pathogenicity of M. tb (34). These proteins were associated with particular pathways, including metabolic pathways, which can be targeted for therapeutic intervention. A database called ProteomicsDB has been created with several molecular resources to support proteomics research. For example, analysis of the database showed that GSK986310C is a candidate that is effective as a spleen tyrosine kinase (SYK) inhibitor (35). These resources will therefore be helpful in TB drug discovery research and may lead to the identification of inhibitors for TB infection. In a review study, Bisht et al. suggested that proteomics can be a useful platform for the discovery of biomarkers for TB and other diseases (36). It can also be useful in vaccine development and in providing a platform for developing a rapid test for diagnosing tuberculosis.

Finally, just as discussed with other "omics," metabolomics is another powerful approach that can facilitate drug discovery and development. As highlighted earlier (Table 2), it evaluates the metabolite profile in a biological system, providing insight into therapeutic targets in M. tb drug discovery by identifying metabolic pathways essential for the survival of the bacteria. In a review discussion, Yu et al. highlighted the role metabolomics can play in the identification of TB biomarkers (37). These biomarkers can be important in elucidating the MOA of drugs and also play a significant role in evaluating drug resistance and responses. The proteomics approach will be essential in TB drug development as it can help elucidate MOA and induced drug resistance during drug development. It can also play a role in predicting drug toxicity and treatment outcomes (38). With the advent of more omics approaches, multi-omics techniques can be critically used in identifying novel drugs for many disease conditions.

Challenges in Multiomics

Although multiomics holds great potential for use in human medicine, the technology faces several challenges. One major difficulty is the integration of data generated during the multiomics workflow. This is not an easy task due to the diversity of omics data produced. Each omics workflow generates different types of data, which complicates the analytical process. The vast volume of data produced by these high-throughput techniques further complicates matters. Transforming and combining the different sets of data is a challenge that must be addressed. Another issue is related to space. Spatial multiomics assays aim to image hundreds or thousands of genes and proteins together. This often results in many fluorophores occupying the same area in the cell, making it difficult to resolve individual genes or proteins (8). Establishing standardized protocols is another challenge. These protocols should outline how data are collected, evaluated, and interpreted. Finally, while multiomics has immense potential in research, research partnerships and collaborations are crucial for its advancement.

Future Prospects and Conclusion

The multi-omics approach is an exciting development in tuberculosis and infectious disease research, offering the potential to transform the discovery of anti-tuberculosis agents that could significantly improve the efficacy, safety, and specificity of novel drugs. Multi-omics can be incorporated into every phase of the drug discovery process, including genomics, proteomics, transcriptomics, and metabolomics. Despite the immense potential of omic technology, several challenges remain. Ethical considerations pose a significant challenge, as multi-omics data could reveal personal health information. This information might be used to stigmatize, discriminate against, or exploit individuals. Therefore, multi-omics data must be assembled with the privacy and confidentiality of the subjects in mind. Stringent protocols are needed to address these challenges, but these should not stifle scientific progress.

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Sažetak

MULTIOMIKS PRISTUPI U OTKRIVANJU LEKOVA PROTIV TUBERKULOZE

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Uprkos intenzivnim globalnim naporima, tuberkuloza i dalje predstavlja jedan od najvećih globalnih zdravstvenih problema, s antimikrobnom rezistencijom koja predstavlja značajan izazov u lečenju bolesti. Takođe, trenutni lekovi za lečenje tuberkuloze imaju ograničenja, kao što su produženo trajanje terapije i toksičnost. Zbog toga je razvoj novih lekova protiv tuberkuloze prioritet. Međutim, ovaj proces se suočava sa brojnim izazovima. Uvođenje multiomiks pristupa može poslužiti kao idealna platforma za ubrzanje razvoja lekova, rešavajući ove izazove. Ovaj članak istražuje potencijalnu ulogu multiomiks pristupa u razvoju lekova protiv tuberkuloze i ukratko razmatra izazove u korišćenju ovog pristupa za otkriće lekova.

Ključne reči: tuberkuloza, lekovi, proteomiks, multiomiks, Mycobacterium tuberculosis, transkriptomiks, metabolomiks, genomiks.

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Review article

STOCKHOLM SYNDROME: A DIMENSION OF TRAUMA

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Abstract: Stockholm syndrome is a complex psychological phenomenon in which some trauma survivors develop strong emotional bonds with their abusers. Despite the absence of clear diagnostic criteria and its exclusion from official psychiatric classification systems, the term has gained widespread recognition in both the media and scientific literature. This phenomenon typically occurs in situations involving significant power imbalances—such as child sexual abuse, intimate partner violence, human trafficking, and hostage situations—where the victim may develop positive feelings toward the abuser in response to extreme stress. Initially observed during a 1973 bank robbery in Stockholm, the syndrome has since been identified in various contexts.

Given its similarities to other psychiatric entities, such as post-traumatic stress disorder (PTSD) and identification with the aggressor, Stockholm syndrome remains a crucial area of research in understanding the psychological impact of extreme stress.

This paper explores Stockholm syndrome from psychological, psychiatric, and neurobiological perspectives, highlighting its implications for mental health, criminology, and forensic science. Further investigation into this phenomenon is essential for improving trauma treatment approaches, legal frameworks, and therapeutic strategies, ultimately enhancing our understanding of victim-perpetrator dynamics in high-stress situations.

Keywords: trauma, Stockholm syndrome, stress.

INTRODUCTION

Stockholm syndrome refers to a hypothetical phenomenon in which trauma survivors develop strong emotional attachments to their abusers (1, 2). Due to the absence of clear diagnostic criteria and similarities with other psychiatric conditions, it is not included in any official psychiatric classification systems. Nonetheless, the term has been widely popularized in the media and has been the subject of numerous scientific studies.

The essence of this concept lies in the fact that, in certain situations where the victim is expected to exhibit a “fight or flight” response, positive feelings toward the abuser may instead develop. This attachment can significantly influence the victim’s behavior.

Current research suggests that this phenomenon can emerge in any situation involving clear power imbalances, such as in cases of child sexual abuse, intimate partner violence, human trafficking, and hostage situations (1).

The syndrome was first described in 1973, following a bank robbery in Stockholm, where hostages developed positive feelings toward their captors. Since then, mental health professionals have observed that similar situations may lead to the development of this syndrome (1). Within current psychiatric classifications, there are notable similarities between Stockholm syndrome and established entities such as post-traumatic stress disorder (PTSD), identification with the aggressor, and others.

This paper aims to explain this phenomenon through well-established psychological, psychiatric, and neurobiological perspectives. Further research is crucial for understanding the complex psychological responses to extreme stress experienced in situations perceived as highly threatening and abusive.

This phenomenon also has significant implications for mental health, criminology, and forensic science. Understanding it can contribute to improved approaches to traumatized individuals, enhanced therapeutic frameworks, and more informed legal considerations—ultimately offering a better understanding of the dynamics between victim and abuser.

The goal of this paper is to provide a deeper understanding of this phenomenon and highlight its implications in the fields of trauma psychology and forensic psychiatry.

DEFINITION AND DIAGNOSTIC STATUS

Stockholm syndrome (SS) is a psychological phenomenon observed in some trauma survivors. It involves the development of a powerful emotional connection toward the abuser or controller (1, 2). Still considered a controversial topic, there is considerable ethical ambiguity surrounding this term. Numerous scientific papers explain that the phenomenon typically occurs in individuals who have survived traumatic situations marked by an extreme power imbalance (2, 3).

Although explored by many authors, one of the most significant reviews on this topic remains the one conducted by Graham, Rawlings, and Rimini. They highlighted that the central symptom of SS is the development of positive feelings in the victim toward the aggressor or abuser, which intensifies as the relationship progresses. Graham identified four important factors in the development of such emotional connections: perceived threat to survival, perceived kindness, perceived isolation, and perceived inability to escape (1).

This bond often manifests as positive feelings toward the perpetrator, despite the victim's suffering. Over time, victims may also exhibit negative emotions toward those attempting to help or free them—such as family, friends, or authorities—sometimes even perceiving these efforts as harmful. Additionally, the victim may begin to rationalize or justify the abuser's actions, supporting the reasoning behind the abuse. This dynamic is often reinforced when the abuser shows affection or positive regard toward the victim, further strengthening the connection. In some cases, the victim may engage in behaviors that support or protect the abuser, even at the expense of their own well-being. This complex psychological response is often seen as a coping mechanism to manage extreme stress and fear during periods of captivity or manipulation (3).

Despite its recognition in media and popular culture, Stockholm syndrome is not included as a diagnosis in any official classification of mental disorders (DSM or ICD). Standardized diagnostic criteria have not yet been described, and there is significant ambiguity in the use of the term. Furthermore, behaviors associated with it may be better understood as coping mechanisms in response to extreme stress rather than as a distinct syndrome. All of these factors contribute to Stockholm syndrome's exclusion from psychiatric classification systems.

PSYCHOLOGICAL AND NEUROBIOLOGICAL MECHANISMS

In order to understand the complexity of this condition, it is essential to be familiar with the concepts of trauma and dissociation, and the roles they play in shaping the victim's perception of reality and the world. Research indicates that trauma can lead to dissociative responses, which may contribute to the development of Stockholm syndrome.

During traumatic situations, victims often experience a flood of negative emotions such as fear, helplessness, and intense dread for their own lives. As a response to such extreme stress, victims can paradoxically develop an attachment to the abuser as a coping mechanism. Dissociation is a well-known defense mechanism used, in this case, to "detach from reality" and escape the pain, fear, or humiliation the victim is experiencing. Through dissociation, the victim might downplay or rationalize the abuser's actions, leading to feelings of sympathy or attachment that would seem counterintuitive in a less traumatic context (3).

Another important defense mechanism relevant to this topic was first described in 1937: identification with the aggressor. This occurs when the victim adopts the abuser's values, beliefs, or behaviors—often as a coping strategy to manage trauma or regain a sense of control. This psychological process can lead the victim to internalize the abuser's perspective, sometimes justifying or excusing their actions (4).

By aligning with the abuser, the victim reduces emotional and psychological conflict, diminishes the perceived threat, and reconciles the abuse with survival needs. This defense mechanism allows the victim to navigate the trauma while minimizing further harm.

OXYTOCIN AND CORTISOL

Research has emphasized the critical roles of the hypothalamic–pituitary–adrenal (HPA) axis, oxytocin, and cortisol in managing the body's response to stress. Dysregulation of these systems can lead to changes in the production and release of both cortisol and oxytocin, which in turn may alter the body's reaction to stress and increase vulnerability to the harmful effects of stressors.

Evidence suggests that the release of oxytocin in the brain helps regulate cortisol levels, supporting a rapid return of the body to its pre-stress state and moderating the HPA axis response to psychological stress. However, chronic stress may disrupt the function of these systems, reducing the synthesis and release of oxytocin. This disruption can impair the HPA axis's negative feedback mechanism, potentially leading to elevated cortisol levels (hypercortisolemia) (5, 6).

Oxytocin plays a crucial role in adult human bonding by promoting social behaviors such as pair bonding, recognition, and social interaction. It also supports physical attachment processes, such as wound healing,

as well as psychological and social bonding, which may enhance resilience to future traumatic events.

While oxytocin is essential for fostering attachment, cortisol—another key hormone—is released in response to stress. Cortisol prepares the body for immediate action by heightening alertness and influencing decision-making, but if elevated for prolonged periods, it can lead to both mental and physical exhaustion (7, 8).

Given the complex interaction between these hormones, it becomes clear how a paradoxical situation can arise in which a victim becomes emotionally attached to their abuser despite ongoing harm. This dynamic illustrates how the interplay between oxytocin and cortisol may shape emotional responses and attachment behaviors, even in the context of trauma.

PARALLELS WITH SIMILAR PSYCHIATRIC ENTITIES

TRAUMA BONDING

According to the American Psychological Association (APA), trauma refers to any distressing experience that evokes intense emotions such as fear, helplessness, dissociation, or confusion—strong enough to cause long-term negative impacts on an individual's attitudes, behaviors, and overall functioning. Traumatic events may result from human actions (e.g., assault, warfare, industrial accidents) or natural occurrences (e.g., earthquakes), and they frequently challenge an individual's perception of the world as fair, secure, and predictable. According to the same source, the term *bonding* describes the connection between two or more people, characterized by trust and mutual support (9).

Trauma bonding, as the term itself suggests, refers to a deep emotional connection between an abused individual and their abuser, often developed due to an ongoing cycle of abuse (10). This concept was first introduced by Dutton and Painter in 1993, who described it as the formation of "powerful emotional attachments" within abusive relationships (11). According to their theory, trauma bonding is developed, maintained, and reinforced by two key factors: power imbalances and intermittent cycles of good and bad treatment.

Dutton and Painter emphasized the critical role of the power imbalance, which underscores the victim's dependency and sense of powerlessness in contrast to the perpetrator's control and dominance. This dynamic is intensified by a vicious cycle in which periods of kindness or normalcy alternate with episodes of abuse, further distorting the victim's reasoning and diminishing their ability to leave the relationship. The resulting attachment to the abuser becomes a powerful psychological force (11).

Many authors have noted that the predisposition for trauma bonding may be rooted in early childhood, particularly in adverse childhood experiences. Such early experiences can distort one's understanding of love and attachment, normalizing emotional or physical abuse in later relationships (11, 12).

The strength of traumatic bonding depends on several factors, including the duration of the abusive relationship, the intensity of emotional attachment to the perpetrator, lack of social support, financial or housing insecurity, concerns over child custody, low self-esteem, fear of harm, and a sense of helplessness (11). Trauma bonding can occur across various contexts—such as human trafficking, domestic violence, and hostage situations—and affects individuals of all demographics, including all ages, genders, sexual orientations, socioeconomic statuses, races, and religions.

While trauma bonding and Stockholm syndrome share the core feature of developing emotional attachments to abusers, they differ in context and manifestation. Stockholm syndrome typically occurs in hostage or kidnapping scenarios, where victims develop emotional attachments to captors due to fear and dependency. In contrast, trauma bonding is more commonly associated with prolonged cycles of abuse in relationships, where intermittent kindness strengthens the emotional tie.

Despite these contextual differences, both trauma bonding and Stockholm syndrome involve psychological mechanisms that can trap victims in abusive environments and influence their ability or willingness to escape. It is important to note, however, that trauma bonding—like Stockholm syndrome—is not officially recognized in diagnostic classifications such as the DSM-5. Its conceptualization remains primarily used in clinical and research contexts to describe the psychological dynamics of abusive relationships.

According to the APA Dictionary of Psychology (American Psychological Association, 2015) trauma is defined as a disturbing experience from an event caused by a serious physical injury, human behavior, or nature that generates intense, long-term feelings of fear, helplessness, dissociation, and confusion; maladaptively effectuating a person's affective and cognitive behaviors.

IDENTIFICATION WITH THE AGGRESSOR

The concept, initially introduced by Ferenczi in 1936 and later redefined by Anna Freud, describes a process in which victims of abuse merge with and internalize the experiences of their perpetrators. Ferenczi's theory of identification with the aggressor

posits that the phenomenon is not simply the result of the aggressor's influence entering the victim's psyche and triggering reenactments of aggression. Rather, it involves a psychic split within the victim, whereby a part of the self becomes automatically imitative of the aggressor's behavior (13). This process is understood as an automatic, dissociative response intended to ensure survival in situations of persistent, inescapable harm—particularly when the victim is emotionally attached to and dependent on the abuser. Victims may not only comply with the perpetrator's demands but also become psychologically subordinated to the perpetrator's needs and desires. In an effort to minimize harm, they often develop heightened sensitivity to the perpetrator's emotions and behaviors, internalizing their perspective on the abuse. This can result in the victim rationalizing or denying the abuse, adopting the abuser's viewpoint, and potentially redirecting aggression either toward themselves or others (14). While identification with the aggressor and Stockholm syndrome share certain similarities, they also differ in significant ways. Identification with the aggressor involves adopting the perpetrator's traits or behaviors as a means of self-protection, whereas Stockholm syndrome is characterized by the development of positive feelings—such as empathy, affection, or even love—toward the abuser. The key difference lies in the nature of the attachment: in Stockholm syndrome, the victim minimizes or rationalizes the abuser's actions, believing they are not entirely harmful, whereas in identification with the aggressor, the victim mimics the abuser's behavior in an attempt to gain a sense of safety or control. Both responses serve as coping mechanisms, aiming to manage the traumatic experience and reduce psychological distress.

POST-TRAUMATIC STRESS DISORDER (PTSD)

Post-traumatic stress disorder is a persistent mental condition that significantly decreases the quality of life and deeply affects the survivor's perception and relationships. It develops after exposure to a traumatic event, which serves as the catalyst for its onset. Traumatic stress (real or perceived threats of harm, death, or sexual violence) is essential for the development of PTSD.

Key symptoms of PTSD include intrusive thoughts, emotional numbness, avoidance, hyperarousal, heightened sensitivity to stress, and significant cognitive and emotional disturbances (15). While both PTSD and Stockholm syndrome occur after a traumatic experience, they manifest with different symptoms. Some PTSD symptoms, such as flashbacks and hypervigilance, are also seen in individuals with Stockholm syndrome, but all other symptoms are missing.

PTSD develops after exposure to a traumatic event, which may or may not involve a power imbalance. Additionally, individuals with PTSD generally do not develop attachments to the aggressor. The main focus of PTSD is on distress and re-experiencing trauma, leading to avoidant behaviors, while Stockholm syndrome generally involves the development of positive feelings as a coping mechanism to feel safer.

DEPENDENT PERSONALITY DISORDER (DPD)

A shared component of these two conditions is a high degree of dependence on others. In Stockholm syndrome, the victim becomes dependent on the captor for emotional support or survival. Similarly, individuals with DPD may exhibit extreme dependency on others for decision-making, emotional support, and a fear of abandonment.

DPD, however, is not based on traumatic events; it is a long-term personality disorder. It is not characterized by forming emotional bonds with individuals perceived as abusers. Additionally, DPD represents a consistent pattern of behavior across various relationships (16, 17).

LEARNED HELPLESSNESS

This phenomenon was first introduced in 1967 by Seligman and Meyer and remains relevant in psychiatry and psychology today. It is described as a dysregulation of goal-directed behavior due to repeated failure to achieve a goal. Individuals in this state stop trying because their goals lose value, or they no longer believe that further effort will lead to success. They cease initiating actions or efforts, often believing that nothing will change the outcome (18).

While Stockholm syndrome involves a psychological attachment to the aggressor, with the resulting behavior aimed at reaching a specific goal, often to avoid further harm or secure a better outcome, learned helplessness focuses on a more general sense of powerlessness and resignation to an uncontrollable situation.

ETHICAL ASPECTS AND FORENSIC PSYCHIATRY

Understanding the psychological response to Stockholm syndrome is crucial for evaluating the harm experienced by victims and determining effective interventions. This phenomenon can be exploited by perpetrators to manipulate or control victims, particularly to avoid legal consequences. Forensic psychiatrists must consider the victim-perpetrator dynam-

ic, as it influences both the victim's behavior and the perpetrator's psychological state. Victims may appear uncooperative or even defend their abusers, complicating investigations and legal outcomes (19, 20). By integrating Stockholm syndrome into forensic assessments, professionals can better understand the complexities of abusive relationships and improve both legal and therapeutic interventions.

Ethical concerns arise around the victim's autonomy, as trauma bonding can impair decision-making and diminish the capacity for free choice. This raises questions about whether victims' actions are truly voluntary or influenced by psychological manipulation. Therapeutic approaches should empower victims to regain control and recognize the effects of trauma without re-traumatizing them. Mental health professionals have an ethical duty to ensure that victims receive treatment addressing these effects and helping them break free from the cycle of control (21).

The term "Stockholm syndrome" also carries ethical implications. It can sometimes minimize the severity of the abuser's actions by shifting focus to the victim's psychological response rather than the abusive dynamics. This may distort public perception, hindering recognition of the abuse's true impact and preventing victims from receiving necessary support and protection. The term must be used carefully in clinical, legal, and public contexts, ensuring it reflects the victim's experience without overshadowing the abuser's behavior or undermining the victim's dignity and rights to justice and care.

CONCLUSION

Trauma is a widely studied phenomenon in both psychiatry and psychology. While definitions of trauma may vary across disciplines, the underlying mechanisms and coping strategies remain consistent. Individuals exhibit varying predispositions and responses to high-stress situations, and the coping mechanisms they employ are influenced by numerous factors. Currently, there is no established method for predicting how an individual will respond to trauma. One potential psychological response is Stockholm syndrome. Although not formally recognized as a psychiatric diagnosis, Stockholm syndrome is a crucial consideration for professionals working with victims of abusive relationships, hostage situations, human trafficking, and similar circumstances. Its recognition can aid in understanding the multifaceted nature of trauma and illuminate the pathological dynamics between the victim and the perpetrator, thereby improving interventions and support strategies.

Abbreviations

SS – Stockholm Syndrome
PTSD – Post-traumatic stress disorder
DSM – Diagnostic and Statistical Manual of Mental Disorders
ICD – International Classification of Diseases
HPA axis – Hypothalamic–pituitary–adrenal axis
APA – American Psychological Association
DPD – Dependent Personality Disorder

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Sažetak

STOKHOLMSKI SINDROM: DIMENZIJA TRAUME

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Stokholmski sindrom je kompleksan psihološki fenomen koji podrazumeva da se kod pojedinih individua izloženih traumatičnim događajima razvijaju pozitivna osećanja prema zlostavljaču. Iako još uvek nema jasnih dijagnostičkih kriterijuma i nije deo zvaničnih klasifikacionih sistema, termin Stokholmski sindrom je široko rasprostranjen kako u medijima tako i u naučnoj literaturi. Do razvoja ovog fenomena obično dolazi u situacijama gde postoji jasno narušena dinamika moći kao što su zlostavljanje dece, partnersko nasilje, trgovina ljudima i talačke situacije, gde žrtva može razviti pozitivna osećanja prema zlostavljaču kao odgovor na ekstremni stres. Prvi put je opisan nakon pljačke banke u Stokholmu 1973. godine, a od tada je identifikovan u različitim kontekstima. S obzirom na sličnosti sa drugim psihijatrijskim poremećajima, Stokholmski sindrom predstavlja jednu od ključnih tema za razumevanje psihičkih posledica ekstremnog stresa.

Ovaj rad prikazuje Stokholmski sindrom kroz psihološke, psihijatrijske i neurobiološke perspektive, is-

tičući njegove implikacije za mentalno zdravlje, kriminalistiku i forenzičku nauku. Dalja istraživanja ovog fenomena su od suštinskog značaja za poboljšanje pristupa lečenju trauma, pravnih okvira i terapijskih strategija, što će konačno doprineti boljem razumevanju dinamike žrtve i zlostavljača u u izrazito stresnim situacijama.

***Ključne reči**:* trauma, Stokholmski sindrom, stres.

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UPUTSTVO AUTORIMA

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Radovi se uvek dostavljaju sa sažetkom na engleskom i srpskom jeziku. Strani autori podnose radove samo na engleskom jeziku. Za nazive lekova isključivo se koriste generički nazivi. Uređaji (aparati, instrumenti) se nazivaju trgovačkim nazivima, a njihov naziv i mesto proizvodnje treba navesti u zagradama. Ako se koristi kombinacija slovo-broj, broj treba precizno označiti superskriptom ili indeksom (tj. 99Tc, IL-6, O2, B12, CD8). Ako se nešto obično piše kurzivom, kao što su geni (npr. BRCA1), to bi trebalo na ovaj način pisati i u radu.

Ako je rad deo magistarske ili doktorske teze, ili istraživačkog projekta, to treba navesti u posebnoj napomeni na kraju teksta. Takođe, ako je članak prethodno predstavljen na nekom naučnom skupu, potrebno je navesti naziv, mesto i vreme održavanja skupa, kao i način na koji je rad objavljen (npr. promenjen naslov ili sažetak).

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Svaki deo rukopisa (naslovna strana, itd.) mora početi na posebnoj strani. Sve strane moraju biti numerisane po redosledu, počev od naslovne strane. Podaci o korišćenoj literaturi u tekstu označavaju se arapskim brojevima u zagradama, i to onim redosledom kojim se pojavljuju u tekstu.

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Ako je potrebno, može se dodati i podnaslov.

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Ako je bilo materijalne ili neke druge pomoći u izradi rada, onda se može sažeto izreći zahvalnost osobama ili institucijama koje su tu pomoć pružile.

Treba otkucati listu svih skraćenica upotrebljenih u tekstu. Lista mora biti uređena po abecednom redu pri čemu svaku skraćenicu sledi objašnjenje. Uopšte, skraćenice treba izbegavati, ako nisu neophodne.

U donjem desnom uglu naslovne strane treba otkucati ime i prezime, telefonski broj, broj faksa i tačnu adresu autora sa kojim ce se obavljati korespodencija.

Stranica sa sažetkom. Sažetak mora imati do 400 reči. Treba koncizno da iskaže cilj, rezultate i zaključak rada koji je opisan u rukopisu. Sažetak ne može sadržati skraćenice, fusnote i reference.

Ključne reči. Ispod sažetka treba navesti 3 do 8 ključnih reči koje su potrebne za indeksiranje rada. U izboru ključnih reči koristiti Medical Subject Headings — MeSH.

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Originalni rad treba da ima sledeće podnaslove: uvod, cilj rada, metod rada, rezultati, diskusija, zaključak, literatura.

Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura.

Pregled iz literature čine: uvod, odgovarajući podnaslovi, zaključak, literatura.

Bolesnici i metode/materijal i metode. Treba opisati izbor bolesnika ili eksperimentalnih životinja, uključujući kontrolu. Imena bolesnika i brojeve istorija ne treba koristiti.

Metode rada treba opisati sa dovoljno detalja kako bi drugi istraživači mogli proceniti i ponoviti rad.

Kada se piše o eksperimentima na ljudima, treba priložiti pismenu izjavu u kojoj se tvrdi da su eksperimenti obavljeni u skladu sa moralnim standardima Komiteta za eksperimente na ljudima institucije u kojoj su autori radili, kao i prema uslovima Helsinške deklaracije. Rizične procedure ili hemikalije koje su upotrebljene se moraju opisati do detalja, uključujući sve mere predostrožnosti. Takođe, ako je rađeno na životinjama, treba priložiti izjavu da se sa njima postupalo u skladu sa prihvaćenim standardima.

Treba navesti statističke metode koje su korišćene u obradi rezultata.

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Izbegavati korišćenje apstrakta kao reference, a apstrakte starije od dve godine ne citirati.

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Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Knjiga:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Poglavlje ili članak u knjizi:**

Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

Tabele. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom tabele iznad.

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1. **Article:** (all authors are listed if there are six or fewer, otherwise only the first six are listed followed by *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Book:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Chapter or article in a book:**

Trier JJ. Celiac sprue. In: Sleisenger MH, Fordtran J5, eds. Gastro-intestinal disease. 4 th ed. Philadelphia: WB Saunders Co, 1989: 1134–52.

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