TIMOČKI MEDICINSKI GLASNIK

TIMOK MEDICAL GAZETTE

Glasilo zaječarske podružnice Srpskog lekarskog društva
The Bulletin of the Zajecar branch of the Serbian Medical Association

Izlazi od 1976.
has been published since 1976.

Godina 2026 *Vol. 51 Broj 1*

Year 2026 *Vol. 51 No. 1*

YU ISSN 0350-2899

www.tmg.org.rs tmglasnik@gmail.com

TIMOČKI MEDICINSKI GLASNIK

TIMOK MEDICAL GAZETTE

Glasilo zaječarske podružnice Srpskog lekarskog društva **Izlazi od 1976.**
The Bulletin of the Zajecar branch of the Serbian Medical Association **has been published since 1976.**

VLASNIK I IZDAVAČ/OWNER AND PUBLISHER

Srpsko lekarsko društvo, podružnica Zaječar/
Serbian Medical Society, Branch of Zaječar
web adresa/web address: www.sldzajecar.org.rs

ADRESA REDAKCIJE/EDITORIAL OFFICE
Timočki medicinski glasnik
Zdravstveni centar Zaječar
Pedijatrijska služba
Rasadnička bb, 19000 Zaječar

ADRESA ELEKTRONSKE POŠTE/E-MAIL
tmglasnik@gmail.com
dusanbastac@gmail.com

WEB ADRESA/WEB ADDRESS
www.tmg.org.rs

Časopis izlazi četiri puta godišnje./The Journal is published four times per year.

TEKUĆI RAČUN/ CURRENT ACCOUNT
Srpsko lekarsko društvo, podružnica Zaječar 205-167929-22

ŠTAMPA/PRINTED BY
Spasa, Knjaževac

TIRAŽ/CIRCULATION 500 primeraka/500 copies

CIP - Каталогизација у публикацији
Народна библиотека Србије, Београд

61
TIMOČKI medicinski glasnik /
glavni i odgovorni urednik Prim Dr Sc med Dušan Bastać; - God. 1, br. 1 (1976)-
- Zaječar : Srpsko lekarsko društvo, podružnica Zaječar, 1976- (Knjaževac : Spasa). - 30 cm

Dostupno i na: http://www.tmg.org.rs. - Tromesečno
ISSN 0350-2899 = Timočki medicinski glasnik
COBISS.SR-ID 5508610

RECENZENTI TIMOČKOG MEDICINSKOG GLASNIKA 2006-2026

Bastać Dušan
Beleslin Branko
Biočanin Vladimir
Bjelaković Goran
Bogavac Mirjana
Bošnjak Petrović Vesna
Bulat Petar
Čovičković Šternić Nadežda
Ćuk Vladimir
Cvejić Vesna
Cvetković Zorica
Čvorović Vojkan
Čvorović Ljiljana
Dikić Đorđević Ana
Dimitrijević Milovan
Đorđević Nataša
Đorđević Vidojko
Golubović Zoran
Ignjatović Mile
Ilić Vekoslav
Jakovljević Vladimir
Jelenković Bratimirka
Joksimović Zoran
Jozić Tanja
Kocić Gordana
Krstić Zoran
Manojlović Snežana
Martinović Žarko
Micić Dragan
Milenković Branislava
Mitrović Predrag
Mitrović Slobodan
Mladenović Zorica
Nikolić Maja
Nikolić Slobodan
Panajotović Ljubomir
Pejčić Tatjana
Radojčić Ljiljana
Ranković Žarko
Romić Predrag
Runić Slobodan
Saravolac Siniša
Šijački Ana
Spalević Ljiljana
Srzentić Snežana
Stančić Ivica
Suvajdžić Vuković Nada
Tirmenštajn-Janković Biserka
Todorović Jelisaveta
Trbojević Božo
Vasiljević Mladenko
Veljković Radovan
Vučetić Dušan
Žigić Dane
Živić Saša
Živković Zorica
Živojinović Vesna

C O N T E N T S

INFLUENCE AND ASSESSMENT OF NUTRITIONAL STATUS IN PATIENTS UNDERGOING TREATMENT FOR COLORECTAL CANCER

Ivan Pantić (1,4), Srđan Petković (2,4), Milan Sibinović (1), Saša Dragović (1), Mihailo Bezmarević (1,3,4), Milan Jovanović (1,3), Boško Milev (1,3)

1) CLINIC FOR GENERAL SURGERY, MILITARY MEDICAL ACADEMY, BELGRADE, SERBIA; 2) DEPARTMENT OF GENERAL SURGERY, MILITARY HOSPITAL NOVI SAD, NOVI SAD, SERBIA; 3) FACULTY OF MEDICINE OF THE MILITARY MEDICAL ACADEMY, UNIVERSITY OF DEFENCE, BELGRADE, SERBIA; 4) NATIONAL SOCIETY FOR CLINICAL NUTRITION OF SERBIA (NUPENS), BELGRADE, SERBIA

Abstract: Introduction: Colorectal cancer (CRC) is one of the most common gastrointestinal malignancies, and patients' nutritional status plays a crucial role in postoperative recovery. Aim: This study aimed to assess the impact of nutritional status on postoperative outcomes in patients undergoing colorectal cancer surgery. Materials and Methods: This observational study included 50 patients who underwent colorectal cancer surgery. Data on anthropometric, laboratory, and clinical parameters were collected, including body weight, BMI, NRS-2002, SGA, and mGPS. Surgical variables such as type and duration of the procedure, as well as postoperative complications classified according to the Clavien–Dindo classification, were also evaluated. Statistical analysis was performed using t-test, χ^2 test, ANOVA, and logistic regression to assess the impact of nutritional status on postoperative outcomes. Results: Anthropometric, laboratory, and clinical parameters were analyzed using validated nutritional screening tools (NRS-2002, SGA). The results showed that patients with higher nutritional risk had prolonged hospital stays and an increased risk of postoperative complications. Inflammatory status, measured by the mGPS score, was significantly correlated with recovery time. Nutritional interventions, including preoperative supplementation, demonstrated potential in improving treatment outcomes. Conclusion: This study confirms the importance of early nutritional screening and individualized nutritional support in reducing postoperative complications and improving the quality of life of patients with colorectal cancer..

Key words: colorectal cancer, nutritional status, nutritional risk, postoperative course, nutritional support

INTRODUCTION

Colorectal cancer (CRC) is one of the most common gastrointestinal malignancies, with significant morbidity and mortality worldwide. Epidemiological data indicate that the incidence of CRC is increasing, which can be attributed to factors such as population aging, changes in dietary habits, and the rising prevalence of obesity. Surgical treatment remains the primary therapeutic option for most patients; however, nutritional status plays a crucial role in treatment outcomes, postoperative recovery, and patients' quality of life.

To understand the importance of nutritional support in surgical patients, it is necessary to know what happens to metabolism during and after surgery. Surgical intervention, as well as trauma, leads to the release of mediators of the systemic inflammatory response, resulting in the catabolism of glycogen, proteins, and fats, with subsequent release of glucose, free fatty acids, and amino acids into the circulation. The result is a loss of muscle mass, which impairs functional recovery after surgery. Preservation of muscle stores, reduction of lipolysis, and glucose oxidation are desirable factors in the postoperative period. Perioperative nutritional support alone has limited impact in the immediate postoperative period, within the first few hours after surgery, when the body is in a catabolic state. Nutritional support and physical activity are essential for the restoration of peripheral muscle mass and functional recovery after major surgery. Optimization of nutrition in moderately malnourished patients should be considered over a period of 7–10 days. In severely malnourished patients, the focus of intervention should be on correcting hypoglycemia, dehydration, electrolyte imbalance, infections, and micronutrient deficiencies. [1].

Definitive surgical treatment (extensive dissections, high-risk anastomoses) is recommended at a later stage, once the infectious focus has been resolved. Malnutrition is common in patients with colorectal cancer, as a result of chronic inflammation due to malignant disease, impaired food intake, renal dysfunction, and liver failure, and it may increase the risk of postoperative complications and prolong hospitalization. The causes of malnutrition in these patients are multifactorial and include reduced food intake due to gastrointestinal symptoms (nausea, vomiting, diarrhea, constipation), metabolic changes associated with malignancy, as well as the consequences of surgical and oncological treatments. Nutritional therapy (support) may also be indicated in patients without obvious, clinically apparent malnutrition as a consequence of the underlying oncological disease, in cases where prolonged interruption or reduction of oral intake is expected [2].

The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends systematic assessment of nutritional status and implementation of targeted nutritional interventions to improve treatment outcomes. Enteral and parenteral nutrition, oral nutritional supplements (ONS), and individualized nutritional approaches can significantly improve nutritional status and reduce postoperative complications. [3].

Preoperative nutritional support may reduce postoperative infections and improve wound healing, while an adequate perioperative nutritional strategy can contribute to faster recovery and a reduction in hospital treatment costs. [2].

ESPEN has redefined the criteria for the assessment of malnutrition based on two criteria:
BMI < 18.5 kg/m^2.
Total body weight loss > 10% or > 5% within the last three months, together with a reduced BMI. [2].

Disease-related malnutrition (DRM) is a subcategory according to the WHO, characterized by malnutrition with a BMI < 18.5 kg/m^2. The assessment of metabolic risk in DRM can be easily identified using NRS-2002. Recent studies have shown that preoperative albumin levels and body weight loss have a significant impact on postoperative outcomes and complication rates. [4].

Assessment of nutritional status in patients undergoing colorectal cancer surgery requires a multidisciplinary approach, including anthropometric, laboratory, and clinical parameters. The use of validated screening tools, such as the Nutritional Risk Screening (NRS-2002) and the Subjective Global Assessment (SGA), enables early identification of patients at increased nutritional risk and timely intervention. In addition, biochemical markers such as albumin, prealbumin, and C-reactive protein (CRP) play an important role in assessing nutritional status and predicting postoperative outcomes. [5].

The modified Glasgow Prognostic Score (mGPS), as an indicator of inflammation and nutrition, has previously been recognized as an important predictor of overall survival. mGPS, as an indicator of systemic inflammatory response, is significantly associated with metastatic disease. Some studies show a significantly lower five-year survival rate of 35.2% for mGPS 2 compared to 91.5% for mGPS 0. A higher mGPS is also associated with malnutrition. mGPS is an independent predictor of the incidence of surgical site infections (SSI). This complication may be associated with anastomotic dehiscence, which not only prolongs postoperative hospital stay but also increases the risk of disease recurrence. [7].

Aim

The aim of this study is to evaluate the impact of nutritional status on the postoperative course in patients with colorectal cancer, as well as to assess the effectiveness of different nutritional strategies in improving treatment outcomes.

Materials and Methods

This is a prospective observational study conducted at the Department of Surgery of the Military Medical Academy from January 2024 to March 2025 in patients operated on for colorectal cancer. The sample included patients who underwent a 7-day preoperative nutritional preparation, and data were analyzed in the postoperative recovery period during the same hospitalization. The inclusion criteria for the study were: Patients with histopathologically confirmed colorectal cancer. Patients undergoing surgical treatment. Availability of data on preoperative nutritional status.

Demographic, clinical, and laboratory parameters were analyzed, including anthropometric measures such as body weight and body mass index (BMI); nutritional status assessed by NRS-2002 and SGA; inflammatory status evaluated using mGPS; surgical data including type of operation, duration of the procedure, and blood loss; the Clavien–Dindo classification of postoperative complications; and postoperative outcomes such as length of hospital stay and complication rates.

The obtained data were analyzed using descriptive and inferential statistics. The monitored parameters in patients with preoperative nutritional preparation were compared, and the significance of differences was assessed using Student's t-test, χ^2 test, logistic regression, and correlation analysis..

This methodological framework enables the assessment of the impact of nutritional status on the postoperative course and the potential benefits of preoperative nutritional preparation..

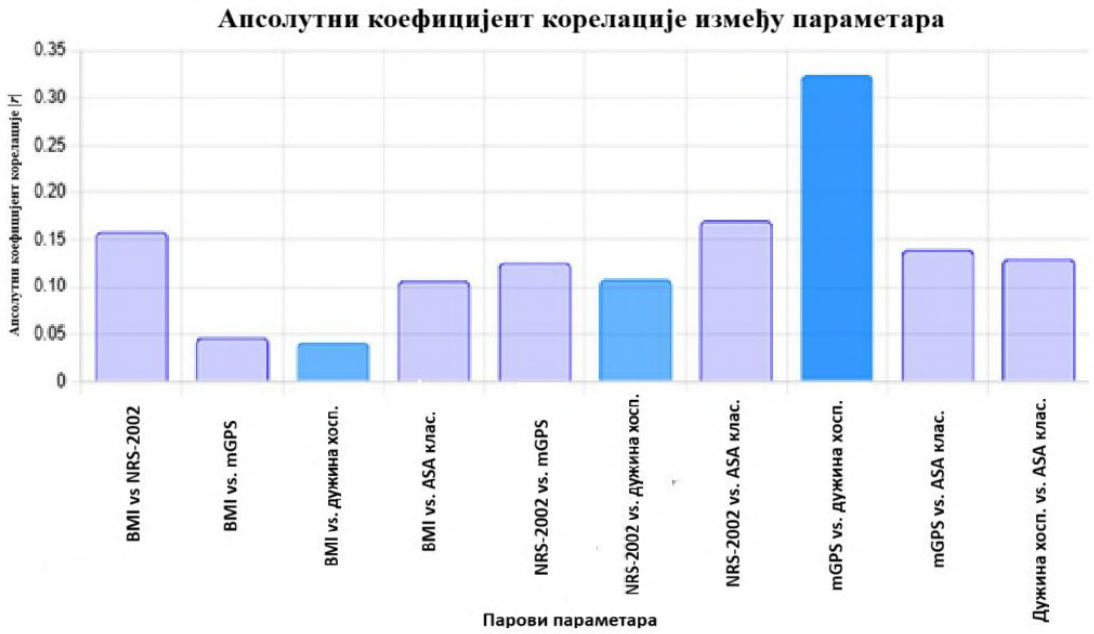
The study was approved by the Ethics Committee of the Military Medical Academy under number 132/2025 on September 25, 2025.

Results

Table 1. – Parameters Monitored in the Study and Their Mean, Minimum, and Maximum Values

Parameter	Mean value	Minimum value	Maximum value
Number of participants	50	/	/
Sex (M/F)	30/20	/	/
BMI	23.8	18.5	29.7
NRS-2002	2.1	0	4
*ASA*classification	1.9	1	3
mGPS	0.8	0	2
Clavien-Dindo	1.2	1	3
Length of hospital stay (days)	9.1	6	14

Table 2 – The height of the bars indicates the strength of the correlation (higher |r| = stronger relationship). Darker color indicates statistically significant associations.



These results indicate the following relationships:

• There is a weak positive correlation between BMI and NRS-2002, which may suggest that patients with higher BMI have a higher nutritional risk.

• The strongest positive correlation is between mGPS and length of hospital stay (0.3239), suggesting that inflammatory status may play a role in the duration of hospitalization.

t-test for BMI and length of hospital stay

• t-statistic: 157.85

• p-value: 9.20×10^{-120}

• p-value: < 0.05

• This result indicates a statistically significant association between BMI and length of hospital stay ($p < 0.05$), although the correlation coefficient suggests a weak negative relationship.

ANOVA test for NRS-2002 and length of hospital stay

• F-statistic: 2509.59

• p-value: 1.22×10^{-71}

• p-value: < 0.05

• There is a highly significant association between assessed nutritional risk (NRS-2002) and postoperative length of hospital stay, with strong statistical significance.

DISCUSSION

Colorectal cancer (CRC) is the third most common cancer and the fourth leading cause of cancer-related death [8]. Nutritional status is a very important indicator for predicting postoperative survival outcomes in CRC, and monitoring nutritional status is a common criterion used in treatment follow-up [9]. In this study, we demonstrated that nutritional status significantly affects the postoperative course in patients with CRC. Data analysis indicated a trend showing that patients with higher nutritional risk (NRS-2002 ≥ 3) have a longer postoperative hospital stay. Additionally, a negative correlation was observed between BMI and length of hospital stay, suggesting that patients with lower BMI values experience slower postoperative recovery [10]. The results indicate that lower BMI values, within the range of malnutrition, prolong the duration of postoperative recovery..

Some studies suggest that a high mGPS has a negative impact on survival in patients with colorectal cancer. In a meta-analysis, Tsung-Hsien Wu reviewed the existing evidence on the practicality of mGPS and confirmed its accuracy in predicting cancer prognosis. [11].

The systemic inflammatory response in patients, measured using the mGPS scale, showed a significant impact on the length of hospital stay, highlighting the importance of systemic inflammation in the postoperative period. In addition, the ASA classification was also correlated with the length of hospitalization, with patients in higher ASA classes experiencing longer recovery [12]. Furthermore, results from similar studies have shown that patients with a pronounced inflammatory response (elevated CRP, hypoalbuminemia) have an increased risk of postoperative complications and a longer recovery period [13]. This is consistent with our findings, where patients with higher mGPS scores had prolonged postoperative recovery.

Nutritional interventions, such as preoperative oral nutritional supplementation, have shown potential in reducing postoperative hospital stay and decreasing complication rates, which is consistent with previous research and ESPEN guideline recommendations. [2].

Comparing the results of our study with the available literature, it is evident that our findings are consistent with studies emphasizing the importance of nutritional screening and interventions. A study conducted in the United Kingdom showed that patients with malnutrition have a 30% longer hospital stay and a higher rate of postoperative complications compared to patients with adequate nutritional status [14]. Similarly, a study from Germany indicated that the implementation of an individualized nutritional protocol can reduce postoperative infections by 25% [15]. These findings support the importance of early nutritional intervention, which is also confirmed by our data..

CONCLUSION

It is stated here that the nutritional status of patients with colorectal cancer plays a key role in the postoperative course and treatment outcomes. Early screening of nutritional status and the implementation of individualized nutritional strategies may contribute to reducing postoperative complications and promoting faster patient recovery..

Further research aimed at determining the optimal duration of preoperative nutritional therapy and the implementation of personalized nutritional interventions is necessary in order to further improve treatment outcomes and the quality of life of patients with colorectal canc.

LITERATURE:

1. David GA Williams, Jeroen Molinger, Paul E Wischmeyer, The Malnourished Surgery Patient: A Silent Epidemic in Perioperative Outcomes?, Curr Opin Anaesthesiol. 2019 Jun;32(3):405–411.
2. Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S. et al. ESPEN practical guideline: Clinical nutrition in surgery. Clin Nutr. 2021 Jul;40(7):4745-4761.
3. T. Cederholm et al, ESPEN guidelines on definitions and terminology of clinical nutrition, Clinical Nutrition, Volume 36, Issue 1, February 2017, p49-64,
4. Deftereos I, Kiss N, Isenring E, Carter VM, Yeung JM. A systematic review of the effect of preoperative nutrition support onnutritional status and treatment outcomes in upper gastrointestinal cancer resection. Eur J Surg Oncol 2020;46(8):1423-34.
5. Gupta A, Gupta E, Hilsden R, Hawel JD, Elnahas AI, Schlachta CM, Alkhamesi NA. Preoperative malnutrition in patients with colorectal cancer. Can J Surg. 2021 Nov 25;64(6):E621-E629.
6. Rossi S, Basso M, Strippoli A, Schinzari G, D'Argento E, Larocca M, et al, Are markers of systemic inflammation good prognostic indicators in colorectal cancer?, Clinical Colorectal Cancer (2017), 4-5.
7. Masano Sagawa et al. Worse Preoperative Status Based on Inflammation and Host Immunity Is a Risk Factor for Surgical Site Infections in Colorectal Cancer Surgery, Journal of Nippon Medical School Vol.84 No.5
8. Inés Mármol, Cristina Sánchez-de-Diego, Alberto Pradilla Dieste, Elena Cerrada, María Jesús Rodriguez Yoldi,Colorectal Carcinoma: A General Overview and Future Perspectives in Colorectal Cancer, Int. J. Mol. Sci. 2017, 18(1), 197;
9. Zhi Wang et al, Study on the correlation between controlling nutritional status score and clinical biochemical indicators in patients with colorectal cancer, Helyon, Volume 10, Issue 5e27202, March 2024
10. Schwegler I, von Holzen A, Gutzwiller JP, Schlumpf R, Mühlebach S, Stanga Z. Nutritional risk is a clinical predictor of postoperative mortality and morbidity in surgery for colorectal cancer. Br J Surg. 2010 Jan;97(1):92-7.
11. Tsung-Hsien Wu, Yao-Te Tsai, Kuan-Yin Chen, Wing-Keen Yap, Chih-Wei Luan, Utility of High-Sensitivity Modified Glasgow Prognostic Score in Cancer Prognosis: A Systemic Review and Meta-Analysis, Int. J. Mol. Sci. 2023, 24(2), 1318;
12. Fukatsu K. Role of nutrition in gastroenterological surgery. Ann Gastroenterol Surg. 2019 Feb 25;3(2):160-168.
13. Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, et al Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin Nutr. 2014 Dec;33(6):929-36.
14. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z; Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003 Jun;22(3):321-36.
15. Braga M, Gianotti L, Vignali A, Di Carlo V. Immunonutrition in gastric cancer surgical patients. Nutrition. 1998 Nov-Dec;14(11-12):831-5.

The authors declare that they have no conflicts of interest..

IMPACT AND ASSESSMENT OF NUTRITIONAL STATUS IN PATIENTS UNDERGOING TREATMENT FOR COLORECTAL CANCER

Teodora Filipović (1,4), Dalibor Perić (2,4), Natalija Jovanović (3,4)

(1) DOM OF HEALTH KUČEVO; (2) GNJILANA HEALTH CENTER; (3) DOM OF HEALTH IN NIŠ; (4) FACULTY OF MEDICINE OF THE UNIVERSITY OF NIS

Summary: Introduction: Hypertension is one of the most significant risk factors for cardiovascular diseases and a leading cause of morbidity and mortality worldwide. During the COVID-19 pandemic, an increase in the number of individuals with newly diagnosed hypertension was observed, suggesting a possible association between SARS-CoV-2 infection, immune response, and vascular changes. Aim: To examine a possible association between COVID-19 infection, SARS-CoV-2 vaccination, and the occurrence of hypertension in the adult population. Materials and Methods: The study was conducted using an anonymous questionnaire that included 203 respondents of both sexes and three age categories. Lifestyle factors, previous COVID-19 infection, vaccination status, and the occurrence of hypertension were descriptively analyzed. Results: Of the total 203 respondents, 72.9% were female and 27.1% male. A total of 144 respondents (70.9%) had a history of COVID-19 infection, and 43 individuals (21.2%) had diagnosed hypertension. Among them, 17 individuals (40.5%) initiated antihypertensive therapy within the last 5 years, following COVID-19 infection. A total of 59.1% of respondents were vaccinated, and the majority did not report adverse effects. Conclusion: The results indicate a statistically significant association between COVID-19 infection and increased incidence of hypertension in the post-pandemic period (χ^2 = 21.3; p < 0.001), while vaccination against COVID-19 was not statistically significantly associated with newly developed hypertension..

Keywords: COVID-19, hypertension, vaccination, SARS-CoV-2, cardiovascular risk.

INTRODUCTION

Hypertension (HTN) is the most common chronic disease of modern society and a leading risk factor for the development of coronary artery disease, cerebrovascular events, and chronic kidney disease [1]. The global COVID-19 pandemic, caused by the SARS-CoV-2 virus, has prompted numerous studies on the impact of infection on the cardiovascular system. Proposed mechanisms include inflammatory processes, endothelial dysfunction, and dysregulation of the renin–angiotensin–aldosterone system (RAAS). [2,3].

During the pandemic, it was observed that individuals who had recovered from COVID-19, even in mild forms, often developed elevated blood pressure several months later [4]. The role of vaccination in the onset or worsening of hypertension has also been the subject of numerous discussions, although most data indicate that the benefits of vaccination significantly outweigh potential risks. [5].

Current research suggests that infection with SARS-CoV-2 may increase the risk of developing new-onset hypertension or worsening pre-existing hypertension, particularly in hospitalized patients and individuals with comorbidities. Studies investigating the effects of COVID-19 vaccination report rare and mostly transient episodes of elevated blood pressure, with no evidence of a causal relationship with persistent hypertension. Overall, there is a substantial body of evidence supporting an association between COVID-19 infection and hypertension, whereas the impact of vaccination remains insufficiently studied and requires further long-term research.

In a large retrospective cohort (~64,000 patients) from the Stony Brook Health System, new-onset hypertension was significantly more frequent in hospitalized COVID-19 patients compared with COVID-negative controls (HR ≈ 1.57; CI 1.35 – 1.81) and in non-hospitalized infected individuals (HR ≈ 1.42; CI 1.24 – 1.63) [6]. This finding suggests that infection may act as a trigger for new-onset hypertension, particularly in more severely ill patients. In the study by Trimarco et al. (2024), a 7-year cohort of over 200,000 adults demonstrated that the incidence of new hypertension increased during the pandemic period (2020–2022) from

approximately 2.11% to 5.20% annually (RR = 2.46) compared with the pre-pandemic period (2017–2019) [7]. This implies that the pandemic itself—including infection as well as indirect factors such as stress and reduced physical activity—may contribute to the rise in hypertension incidence. In the publication by Ebinger et al. (2022), it was shown that even individuals vaccinated with ⩾3 doses of mRNA vaccines had an increased risk of hospitalization if they had hypertension as a comorbidity. Although this does not directly address the onset of hypertension, the study confirms that hypertension remains an important risk factor for adverse COVID-19 outcomes [8]. Potential mechanisms include endothelial dysfunction following SARS-CoV-2 infection, systemic inflammation, activation of the renin–angiotensin–aldosterone system (RAAS), and increased arterial stiffness. A study by Marozzi et al. (2025) demonstrated increased arterial stiffness in individuals after SARS-CoV-2 infection [9]. A review of the relevant literature indicates that there is moderate to substantial evidence supporting an association between SARS-CoV-2 infection and an increased risk of new-onset hypertension or worsening of existing hypertension.

Regarding the impact of COVID-19 vaccination on the incidence or worsening of hypertension, there is a meta-analysis including approximately 357,387 participants which showed that about 3.20% (95% CI: 1.62–6.21) of subjects experienced some form of elevated blood pressure following COVID-19 vaccination. The proportion of cases that reached stage III hypertension or hypertensive urgency/emergency was about 0.6% (95% CI: 0.1–5.1%) [10]. In the study by Syrigos et al. (2022), 797 healthcare workers (mean age 48 years) who received the BNT162b2 (Pfizer) vaccine were monitored for blood pressure changes after vaccination. The results showed that seven individuals experienced a significant increase in blood pressure (grade 2 or 3 hypertension), which was transient and lasted 3–4 days [11]. The study by Ecina and Okura (2024) examines new-onset hypertension in vaccinated individuals compared to unvaccinated controls. The authors emphasize that it cannot be attributed to the vaccine alone with certainty, as participants with hypertension were older, had higher BMI, and more comorbidities [12]. Although there are reports of increased blood pressure following vaccination, the phenomenon is rare, most often transient, and currently insufficiently studied to claim that vaccination significantly contributes to the occurrence of hypertension in the population. Comparative consideration of existing research findings in the available literature shows that studies on infection are more numerous in terms of sample size and follow-up duration than studies on vaccination in the context of hypertension. In the case of infection, there is clear evidence of an increased risk of new-onset hypertension and worsening of pre-existing hypertension. In the case of vaccination, extremely rare episodes of elevated blood pressure may occur, but there is no strong evidence that vaccines cause persistent hypertension.

Based on this, future research should focus on distinguishing the contribution of the infection itself from indirect pandemic-related factors (reduced physical activity, increased stress, dietary changes) in the rise of hypertension. Additionally, it is necessary to determine whether there is a specific subpopulation in which vaccination (e.g., individuals with pre-existing hypertension) has a more pronounced effect on blood pressure regulation. Furthermore, longitudinal studies are needed that track blood pressure before vaccination, immediately after, and over longer follow-up periods (months/years), in order to clarify the role of immunoinflammation, endothelial dysfunction, RAAS activation, and changes in vascular function following infection and/or vaccination.

AIM

The aim of this study was to analyze the potential association between COVID-19 infection, SARS-CoV-2 vaccination, and the occurrence of hypertension in adults, while also assessing additional risk factors (sex, age, smoking, physical activity, and diet).

MATERIAL AND METHODS

The study was conducted during 2025 on a sample of 203 participants. The questionnaire consisted of 25 questions covering sociodemographic characteristics, dietary habits, physical activity, smoking, alcohol consumption, as well as data related to COVID-19 infection and vaccination. The analysis was performed descriptively using percentage distributions and hypothesis testing. Special emphasis was placed on participants with

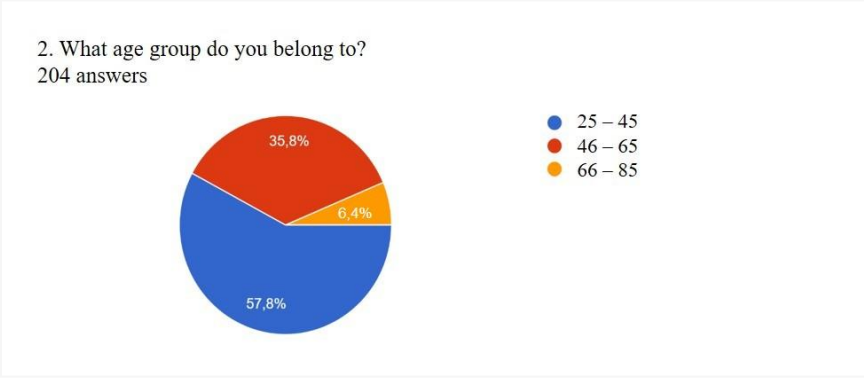
hypertension, the date of initiation of therapy, and a possible association with previous COVID-19 infection. The data were processed descriptively and analytically using SPSS v.26 software. Statistical significance testing was performed using the chi-square (χ^2) test for categorical variables. Statistical significance was accepted at $p < 0.05$..

COVID-19 vaccination and hypertension – age and hypertension. Although mean age values were not available for each group, preliminary analysis suggests that hypertension is more common in the middle-aged category (>45 years).

RESULTS

Age structure of participants (Figure 1): Out of 203 respondents, the most represented group was the younger population aged 25–45 years (57.6%), followed by the middle-aged group of 46–65 years (35.8%), while the older population aged 66–85 years was the least represented (6.4%).

Graph 1. Distribution of the age structure of respondents



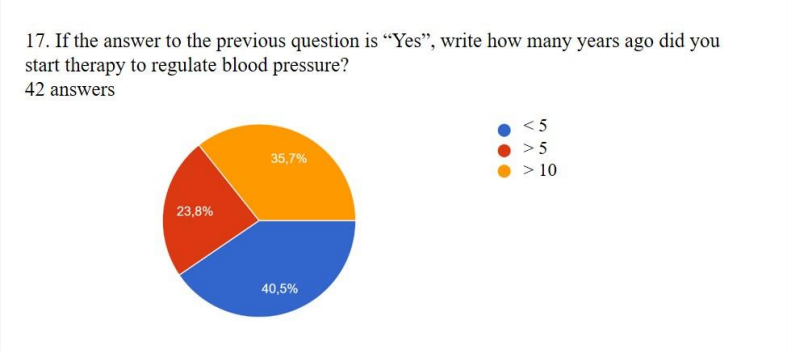
Gender structure and hypertension:
The study showed a predominance of female participants, with 148 (72.9%) women, while there were almost three times fewer men—55 (27.1%). No statistically significant difference was found in the prevalence of hypertension between men and women ($p > 0.05$).
Lifestyle habits (Table 1):
Smoking was present in a smaller proportion of participants—30.5%, while alcohol consumption was reported by slightly less than half of the respondents (47.3%). Most participants reported moderate physical activity (3–4 times per week or daily; 73.4%), which is a reassuring finding in terms of cardiovascular prevention.

Table 1. Habits and risk factors

Habit	**Yes (%)**	**No (%)**
Smoking	30.5	69.5
Alcohol consumation	47.3	52.7
Regular physical activity	73.4	26.6

Diet and anthropometric data:
The majority of respondents reported daily consumption of vegetables (88.2%) and fruit (65%). Regarding body weight, 33% of participants had a body weight between 71–90 kg, while overweight and obese individuals (>90 kg) accounted for 45.3%. BMI was not calculated, nor was waist circumference, a marker of abdominal obesity.
Hypertension and family history:
Hypertension was present in 43 participants (21.2%), while a positive family history of hypertension was reported in 68.5% of respondents. Among those with hypertension, 17 individuals (40.5%) had been on therapy for a shorter period (up to 5 years), while 35.7% had been receiving pharmacological treatment for more than 10 years (Figure 2)..

Chart 2. Distribution of respondents as a function of time of initiation of therapy for blood pressure regulation



COVID-19 infection and hypertension: A total of 144 participants (70.9%) had previously had COVID-19 infection, while only 13 (9.0%) experienced a more severe form of the disease. Hospitalization was reported in only 4 participants.

Among the 43 participants with hypertension (100%), 17 (40.5%) had newly diagnosed hypertension after recovering from COVID-19, suggesting a possible association (Table 2). It is particularly noteworthy that 40.5% of hypertensive patients initiated therapy after the pandemic.

Table 2. Association between COVID-19 infection and hypertension (HTA

Parameter	Number of respondents	%
Recovered from COVID-19	144	70.9
HTA total	43	21.2
HTA <5 years and COVID+	17	8.4

A statistically significant association between previous COVID-19 infection and the presence of hypertension was analyzed using the χ^2 test: the relationship between COVID-19 infection and the occurrence of hypertension. The contingency table (COVID +/− × HTA +/−) showed a significant correlation: $\chi^2 = 21.3$; df = 1; $p < 0.001$, indicating that individuals who had previously had COVID-19 were significantly more likely to develop new-onset hypertension and initiate treatment after the pandemic compared to those who were not infected (Table 3).

Table 3. Contingency table

	Hypertension (+)	Hypertension (–)	Total
COVID-19 recovered	43	101	144
No history of COVID-19 infection	0	59	59
Total	43	160	203

(This includes the 17 newly diagnosed cases after COVID-19 infection, as all HTA+ participants are included in this row.).)

There is a statistically significant association between COVID-19 infection and newly diagnosed hypertension ($p < 0.001$).

Vaccination and adverse effects: A total of 59.1% of participants (120 individuals) were vaccinated, most commonly with the Pfizer vaccine (56.7%). Adverse effects were reported in only 8.3% of participants, most of which were mild in nature (fatigue, pain at the injection site).

Figure 3. Graphical representation of the distribution of administered COVID-19 vaccines by manufact

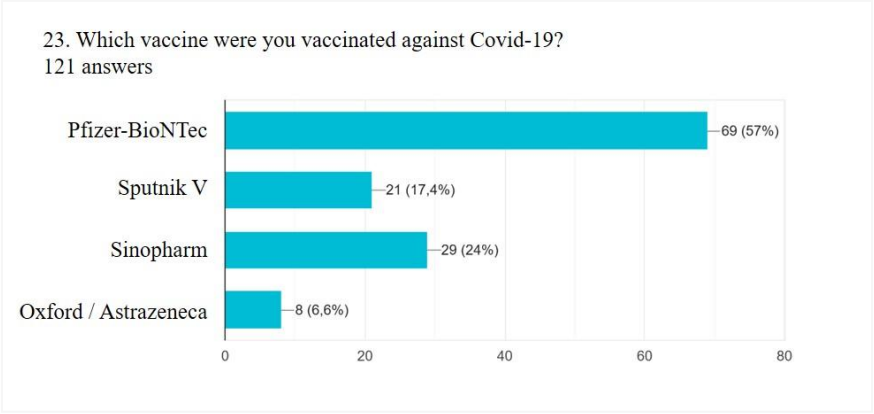


Table 4. Contingency table (derived from text)

	HTA (+)	HTA (–)	Total
Vaccinated	26	94	120
Unvaccinated	17	66	83
Total	43	160	203

(The distribution was estimated based on proportions; no difference in the frequency of adverse effects was observed.)

Gender and age could not be analyzed numerically.

DISCUSSION

Results indicate that there is a statistically significant association between previous COVID-19 infection and the occurrence of hypertension, particularly new-onset arterial hypertension (defined as hypertension diagnosed within less than 5 years). These findings are consistent with other studies suggesting that the SARS-CoV-2 virus affects ACE2 receptors, leading to endothelial dysfunction and increased blood pressure [13,14]. Notably, 40.5% of hypertensive patients initiated therapy after the pandemic, which is statistically significant and may indicate post-COVID hypertension. Most participants in the newly developed post-COVID hypertension group had a mild form of the disease, suggesting that even subclinical damage may have long-term consequences [15]. According to the survey data, vaccination did not have a statistically significant impact on the occurrence of hypertension—most vaccinated participants did not report adverse effects, nor was an increase in blood pressure observed following immunization. This is consistent with published meta-analyses showing that COVID-19 vaccines do not increase the risk of hypertension [16,17]. The results of this study indicate a clear trend toward increased incidence of newly diagnosed hypertension in the post-COVID period. The fact that 40% of hypertensive participants initiated therapy within the last five years, all of whom had a history of COVID-19 infection, supports the hypothesis of a possible pathophysiological link between SARS-CoV-2 and long-term vascular changes. This finding aligns with an increasing body of evidence suggesting that infection may induce persistent alterations in blood pressure regulation, including endothelial inflammation, ACE2 receptor disruption, RAAS activation, increased arterial stiffness, and autonomic dysfunction. Such findings support the concept of “silent endothelial injury,” where viral infection causes subclinical damage that becomes clinically evident over time. Additionally, studies indicate that post-COVID syndrome may include autonomic dysregulation, characterized by blood pressure variability, palpitations, and tachycardia, which may also contribute to the development of hypertension. Regarding vaccination, our data suggest that no significant increase in hypertension was observed following immunization in the studied population. This is consistent with the majority of published meta-analyses showing that episodes of elevated blood pressure after vaccination are most often transient, mild, and without long-term consequences. It is also important to emphasize the significant influence of lifestyle and anthropometric factors. In our sample, obesity was relatively common, while physical activity was present in most participants but often only of moderate intensity. These parameters, along with a

positive family history, are well-known risk factors for hypertension and may partially explain the increased prevalence, particularly during periods of reduced physical activity and increased stress during the pandemic. When all factors are considered together, it may be assumed that in many individuals a combined effect of infection, stress, altered lifestyle habits, and pre-existing predisposition contributed to the manifestation of hypertension. The findings of this study complement existing literature and highlight the need for further multidisciplinary approaches, including cardiological, endocrinological, and immunological perspectives.

CONCLUSION

The results of this study confirm that there is a statistically significant association between previous COVID-19 infection and an increased incidence of newly diagnosed hypertension in the post-pandemic period. In a substantial number of participants, hypertension developed after 2020, which temporally corresponds to the pandemic and supports findings from international studies on the long-term cardiovascular consequences of SARS-CoV-2 infection. According to our results, vaccination does not play a role in the development of hypertension. These findings are consistent with current evidence indicating that the risk of hypertension associated with vaccination is low and most often transient. In the context of risk factors, the presence of obesity, a positive family history, and unhealthy lifestyle habits such as smoking and increased alcohol consumption, as is well established, may further contribute to the development of hypertension. Overall, the data suggest that COVID-19 infection is a significant health event that, in predisposed individuals, may accelerate or precipitate the onset of hypertension. Further, larger-scale and longitudinal studies are necessary to more precisely define the relationships between viral infection, immune response, vascular regulation, and long-term cardiovascular outcomes.

Acknowledgment: The authors thank Gordana Mundrić, Professor of English Language and Literature, for proofreading the English version of the manuscript..

LITERATURE:

1. WHO. Hypertension fact sheet. World Health Organization; 2023.
2. Guzik TJ., Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, et al. COVID-19 and the cardiovascular system: Implications for risk assessment. Eur Heart J.2020;41(19):1792–1801.
3. South AM, Brady TM, Flynn JT, ACE2, COVID-19, and hypertension: What is the connection? Hypertension. 2020;76(1):16–23.
4. Teymourzadeh A, Abramov D, Norouzi S, Grewal D, Heidari-Bateni G, Infection to hypertension: a review of postCOVID-19 new-onset hypertension prevalence and potential underlying mechanisms, 2025; Front. Cardiovasc. Med. 12:1609768.
5. Beladiya J, Kumar A, Vasava Y, Parmar K, Patel D, Patel S, Dholakia S, Sheth D, Boddu SHS, Patel C. Safety and efficacy of COVID-19 vaccines: A systematic review and meta-analysis of controlled and randomized clinical trials. Rev Med Virol. 2024;34(1):e2507.
6. Boparai MS, Gordon J, Bajrami S, Alamuri T, Lee R, Duong TQ, Incidence and risk factors of new-onset hypertension up to 3 years post SARS-CoV-2 infection. Sci Rep. 2025;15(1):28728.
7. Trimarco V, Izzo R, Pacella D, Trama U, Manzi MV, Lombardi A, Piccinocchi R, Gallo P, Esposito G, Piccinocchi G, Lembo M, Morisco C, Rozza F, Santulli G, Trimarco B. Incidence of new-onset hypertension before, during, and after the COVID-19 pandemic: A 7-year longitudinal cohort study in a large population. BMC Med. 2024;22(1):127.
8. Ebinger J.E, Driver M, Joung S, Tran T, Barajas D, Wu M, et al. Hypertension and Excess Risk for Severe COVID-19 Illness Despite Booster Vaccination, Hypertension. 2022;79(10):132-134.
9. Marozzi, M.S., Fucile, I., Panettieri, I. et al. COVID-19 induces greater difficulty in blood pressure control due to increased arterial stiffness. Intern Emerg Med. 2025; PMID: 41191289.
10. Angeli F, Reboldi G, Trapasso M, Santilli G, Zappa M, Verdecchia P. Blood Pressure Increase following COVID-19 Vaccination: A Systematic Overview and Meta-Analysis. J Cardiovasc Dev Dis. 2022;9(5):150.
11. Syrigos N, Kollias A, Grapsa D, Fyta E, Kyriakoulis KG, Vathiotis I, Kotteas E, Syrigou E. Significant Increase in Blood Pressure Following BNT162b2 mRNA COVID-19 Vaccination among Healthcare Workers: A Rare Event. Vaccines (Basel). 2022;10(5):745.
12. Ecin SM, Okur T. The relationship between hypertension and COVID-19 vaccine in the long term and occupational evaluation. Acta Medica. 2024;55(4):255-261.
13. Lanza K, Perez LG, Costa LB, Cordeiro TM, Palmeira VA, Ribeiro VT, et al. Covid-19: The renin-angiotensin system imbalance hypothesis. Clin Sci (Lond). 2020;134(11):1259-1264.
14. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nat Med. 2022 Mar;28(3):583-590.
15. Tsampasian V, Back M, Bernardi M, Cavarretta E, Dębski M, Gati S, et al. Cardiovascular disease as part of Long COVID: a systematic review, European Journal of Preventive Cardiology. 2025;32(6):485–498.
16. Azami P, Vafa RG, Heydarzadeh R, et al. Evaluation of blood pressure variation in recovered COVID-19 patients at one-year follow-up: a retrospective cohort study. BMC Cardiovasc Disord. 2024;24:240.
17. Buso G, Agabiti-Rosei C, Muiesan ML. The relationship between COVID-19 vaccines and increased blood pressure: A word of caution. Eur J Intern Med. 2023;111:27-29.

Author contributions: Concept and design: Teodora Filipović and Dalibor Perić. Data collection: Teodora Filipović and Dalibor Perić. Statistical analysis: Dalibor Perić. Data interpretation: Teodora Filipović. Drafting of the manuscript: Teodora Filipović. Critical revision and final approval of the manuscript: Teodora Filipović, Dalibor Perić, and Natalija Jovanović.

COMPARATIVE ANALYSIS OF ADOLESCENT PREGNANCIES COMPLETED BY DELIVERY AT THE ZAJEČAR MATERNITY HOSPITAL IN 2007 AND 2025

Vera Najdanović Mandić

ORDINANCE "HARMONY, ZAEČAR, SERBIA

Summary: Introduction: Adolescence (from the Latin adolescere, meaning "to become mature, to grow up") lasts from 10 to 19 years according to the definition of the World Health Organization. Adolescent pregnancy represents a significant medical and social challenge. The aim of this study was to compare epidemiological parameters and perinatal outcomes at the maternity ward in Zaječar over an 18-year period, specifically to analyze and compare the frequency and outcomes of deliveries among adolescent girls in Zaječar, and to present the incidence of adolescent births, newborn birth weight, mode of delivery, and employment status of adolescent mothers in 2007 compared to 2025 in Zaječar. METHODS: A retrospective analysis of delivery records and medical histories of women who gave birth at the Gynecology and Obstetrics Department of the Health Center Zaječar, along with statistical data analysis. RESULTS: The results show that the total number of deliveries almost halved from 2007 to 2025, from 555 to 298. The number of adolescent mothers also decreased from 46 (8.29%) in 2007 to 11 (3.69%) in 2025, which is statistically significant (χ^2 = 4.72; p = 0.029). The majority of newborns of adolescent mothers in 2007 were eutrophic, 39 (84.78%), with a mean birth weight of 2850 g ± 410, while in 2025 all newborns were eutrophic with a mean birth weight of 3100 g ± 350 g, but without a statistically significant difference (t = 1.41; p = 0.16). In both observed periods, deliveries were predominantly vaginal, although the frequency of cesarean sections was higher in 2025, without statistical significance (χ^2 = 1.56; p = 0.21). Adolescent mothers were predominantly unemployed in both periods. CONCLUSION: Comparative analysis shows that the proportion of adolescent deliveries significantly decreased from 8.28% in 2007 to 3.69% in 2025 (χ^2 = 4.72; p = 0.029). No statistically significant difference was found in birth weight (t = 1.41; p = 0.16). The frequency of cesarean sections was higher in 2025, but without statistical significance (χ^2 = 1.56; p = 0.21). In both 2007 and 2025, adolescent mothers were unemployed and economically dependent. One of the major tasks for obstetricians and gynecologists is to identify adolescents at risk and prevent behaviors leading to unintended pregnancy. Further work on primary prevention in local communities of eastern Serbia is necessary.

Keywords: adolescent pregnancy, childbirth, vaginal delivery, caesarean section, eutrophic newborn, birth weight, reproductive health

Introduction Adolescence (from the Latin adolescere, meaning "to become mature, to grow up"), as we understand it today, is the result of physical, physiological, and psychological development, as well as the social and cultural conditions of the environment. According to the definition of the World Health Organization from 1980, it lasts from 10 to 19 years (1). Earlier physical maturation, accompanied by early sexual experience and non-use of contraceptive methods, leads to accidental, unplanned, and unwanted pregnancy (2). For safe motherhood, in addition to physical capability, which older adolescents possess, emotional stability, maturity, and experience are also necessary (3). Adolescent pregnancies are a global public health issue. Since 2019, adolescent girls aged 15–19 years in low- and middle-income countries have had an estimated 21 million pregnancies annually, resulting in 12 million births, while 55% of unintended pregnancies end in abortion, which is often unsafe. Adolescent mothers face a higher risk of eclampsia, puerperal endometritis, and systemic infections compared to women aged 20–24 years, while infants of adolescent mothers face a higher risk of low birth weight, preterm birth, and severe neonatal conditions. Data on births among girls aged 10–14 years are becoming increasingly available. Globally, the birth rate among girls aged 10–14 years in 2023 was estimated at 1.5 per 1,000 women, with higher rates in sub-Saharan Africa and Latin America

and the Caribbean. Preventing pregnancy among adolescents, as well as pregnancy-related mortality and morbidity, is fundamental for achieving positive lifelong health outcomes and is imperative for meeting sustainable development goals related to maternal and newborn health (4–6). Aim of the study: To analyze and compare the frequency and outcomes of deliveries among adolescent girls in Zaječar across two time periods, specifically to present the incidence of adolescent births, newborn birth weight, mode of delivery, and employment status of adolescent mothers in 2007 versus 2025 in Zaječar.

Participants and Methods

The study was designed as a comparative retrospective study. Data were collected from delivery records and medical histories of women who gave birth at the Gynecology and Obstetrics Department of the Health Center Zaječar in 2007 and 2025. The following parameters were analyzed: total number of deliveries, maternal age, mode of delivery, and newborn birth weight. Statistical analysis was performed using SPSS software, applying the chi-square (χ^2) test for categorical variables and Student's t-test for independent samples. A retrospective review of delivery records and medical histories in the Gynecology and Obstetrics Department of the Health Center Zaječar showed that in 2007, out of 555 women who gave birth, 46 were adolescents aged 14–19 years, while in 2025, out of 298 women who gave birth, only 11 belonged to this age group..

RESULTS

Table 1: Frequency and parity of women who gave birth in the GA department in ZC Zaječar in 2007.

Paritet / God. života	I	II	III	IV	V	VI	VII	Ukupno
14 -19 god. Adolescentkinje	40	6	/	/	/	/	/	46
20 - 34 god. Optimalan period rađanja	233	175	26	12	2	2	/	450
35 - 45 god. Starije porodilje	15	20	13	9	1	/	1	59
Svega	288	201	39	21	3	2	1	555

In 2007, a total of 555 deliveries were recorded at the Gynecology and Obstetrics Department of the Health Center Zaječar. The majority of women, 450 (81.08%), were aged between 20 and 34 years, i.e., in the optimal reproductive age. Primiparous women predominated with 288 (51.89%), followed by secundiparous women with 201 (36.22%). There were 59 (10.63%) older parturients, mostly secundiparous (20; 33.89%). The oldest primiparous woman was 42 years old, while the oldest women who gave birth were 45 years old (fourth- and seventh-time mothers). In the adolescent age group, there were 46 (8.29%) parturients..

Table 2: Frequency and parity of women giving birth in the GA department in ZC Zaječar in 2025.

Paritet / Godine života	I	II	III	IV	V	VI	VII	VIII	Ukupno
14 -19 god. Adolescentkinje	10	1	/	/	/	/	/	/	11
20 - 34 god. Optimalan period rađanja	112	77	21	5	5	/	2	1	223
35 - 46 god. Starije porodilje	16	25	13	6	2	1	1	/	64
Svega	138	103	34	11	7	1	3	1	298

In 2025, a total of 298 deliveries were recorded at the Gynecology and Obstetrics Department of the Health Center Zaječar. The majority of women, 223 (74.83%), were aged between 20 and 34 years, i.e., in the optimal reproductive age. Primiparous women predominated with 138 (46.31%), followed by secundiparous women with 103 (34.56%). There were 64 (21.48%) older parturients, mostly secundiparous women (25; 39.06%). The oldest primiparous woman was 44 years old, while the oldest woman who gave birth was 46 years old (a third-time mother). In the adolescent age group, there were 11 (3.69%) parturients..

Table 3: Age and parity of adolescent mothers in the GA department of ZC Zaječar in 2007.. .

God. života / Paritet	14	15	16	17	18	19	Ukupno
I	1	3	2	8	6	20	40
II	/	/	/	1	2	3	6
Σ	1	3	2	9	8	23	46

In 2007, there were 46 adolescent parturients (8.28%). The youngest was 14 years old. The majority were 19-year-olds, 23 (50%). Forty women were primiparous, while 6 were secundiparous..

Table 4: Age and parity of adolescent mothers in the GA department of ZC Zaječar in 2025.

God. života / Paritet	14	15	16	17	18	19	ukupno
I	/	/	/	1	4	5	10
II	/	/	/	/	1	/	1

In 2025, there were 11 adolescent parturients (3.69%). The youngest was 17 years old. Ten were primiparous, while only one was secundiparous, aged 18. The total number of deliveries almost halved from 2007 to 2025, from 555 to 298, while the number of adolescent parturients also decreased from 46 (8.29%) in 2007 to 11 (3.69%) in 2025, which is statistically significant ($\chi^2 = 4.72$; $p = 0.029$).

Table 5: Presentation of the body weight of newborns of adolescent mothers born in the GA department of ZC Zaječar in 2007

God. života / Telesna težina	14	15	16	17	18	19	Ukupno
1000 - 1499 gr	/	/	1	1	/	/	2
1500 - 2499 gr	1	1	/	1	/	2	5
2500 - 3999 gr	/	2	1	7	8	21	39
≥ 4000 gr	/	/	/	/	/	/	/
Свега	1	3	2	9	8	23	46

Newborns by birth weight are classified as follows: normal weight (2500–3999 g), low birth weight (1500–2499 g), very low birth weight (1000–1499 g), and macrosomic (>4000 g) (5). Birth weight is an indicator not only of the mother's health and nutritional status, but also a prognostic factor for the newborn's survival, growth, long-term health, and psychosocial development. In our 2007 sample, 39 (84.78%) newborns were eutrophic, with a birth weight ranging from 2500 to 3999 g. Low birth weight was recorded in 5 (10.87%) newborns, while 2 (4.35%) had very low birth weight. In 2025, all 11 newborns were eutrophic. The majority of newborns of adolescent mothers in 2007 were eutrophic (39; 84.78%), with a mean birth weight of 2850 g ± 410, while in 2025 all newborns were eutrophic, with a mean birth weight of 3100 g ± 350 g, with no statistically significant difference ($t = 1.41$; $p = 0.16$). Our sample is too small to confirm the widely accepted findings in the literature that newborns of adolescent mothers are more frequently of low birth weight..

Table 6: Method of childbirth in adolescent pregnant women in the GA department of ZC Zaječar in 2007.

GODINE ŽIVOTA/ /NAČIN PORAĐAJA	14	15	16	17	18	19	Ukupno
Vaginalni porođaj	1	2	1	9	4	20	37
Carski rez	/	1	1	/	4	3	9
Svega	1	3	2	9	8	23	46

In 2007, 37 adolescent mothers (80.43%) delivered vaginally, while 9 adolescents (19.57%) underwent cesarean section. In the control group of women older than 19 years, the rate of cesarean delivery was higher, with 170 cases (30.63%).

Table 7: Method of childbirth among adolescent pregnant women in the GA department of ZC Zaječar in 2025.

God. života / **Način porođaja**	17	18	19	Ukupno
Vag. porođaj	1	3	3	7

Carski rez	/	2	2	4
Svega	1	5	5	11

In 2025, 7 adolescent mothers (63.64%) delivered vaginally, while 4 (36.36%) underwent cesarean section. In the control group, the rate of cesarean delivery was higher, at 53.02%. Of the 11 newborns, 7 were female and 4 were male. In both observed time periods, deliveries were predominantly vaginal, although the frequency of cesarean section was higher in 2025, without statistical significance ($\chi^2 = 1.56$; $p = 0.21$)..

Table 8: Comparative overview of the category of insurance and employment among adolescent girls and the control group of other women who gave birth in the GA department of ZC Zaječar in 2007.

Ispitanice / Vid osiguranja	Adolescentkinje	Kontrolna grupa	Ukupno
Nezaposleno lice	26	150	176
Radnik	2	182	184
Član porodice radnika	13	121	134
Član porodice penzionera	/	2	2
Poljoprivredni proizvođač	3	30	33
Samostalna delatnost	/	14	14
Izbeglice	/	5	5
Privatno lice	2	5	7
Ukupno	46	509	555

The majority of adolescent mothers are unemployed or dependents, while in the control group the number of employed women is significantly higher. Adolescent pregnancy and childbirth significantly reduce the possibility of continuing education and completing schooling, and consequently limit employment opportunities. All of this contributes to their lower socio-economic status and, therefore, lower standard of living. This, as well as unintended pregnancy, leads adolescent mothers more often than women in the control group to leave their newborns in the maternity ward. In 2025, out of 11 adolescent mothers, one was still a student, 6 were registered with the employment agency, and 4 were insured through family members.

DISCUSSION

The results indicate a significant trend of decreasing adolescent births in Zaječar, which may be attributed to better education and improved access to contraception, in line with global trends and World Health Organization data [4]. From 1999 to 2003 at the Gynecology and Obstetrics Department of the Health Center Zaječar, the cesarean section rate among adolescents was 13.54%, which is lower than our rate in 2007 (3). However, the higher cesarean section rate in 2025, similar to findings by Tomić et al. [8], reflects modern medical trends and defensive obstetrics in younger primiparous women. The higher birth weight of newborns in the more recent sample suggests better quality prenatal care and nutrition of pregnant women compared to the period two decades earlier [5,6]. Regional studies (Kosovska Mitrovica, Zemun) also show a decline in adolescent births, although with variability depending on socio-economic conditions. In Kosovska Mitrovica, over a 10-year period from 2000 to 2009, there were 6,335 deliveries and 396 (6.2%) adolescent mothers aged 12–19 years (7). In Zemun, from January 2016 to December 2022, there were 124 adolescent mothers, representing 1% of total deliveries (8). Socio-economic factors remain crucial—adolescent mothers are predominantly unemployed and economically dependent. Although an increasing trend in newborn birth weight was observed, the difference was not statistically significant due to the small sample

size. According to data from the Institute of Public Health of Serbia "Dr Milan Jovanović Batut" [9], significant changes in reproductive trends in Serbia were observed between 2007 and 2023/2024. Specifically, the total number of births decreased by 14.70%, which is less pronounced than in Zaječar, where a 46.31% decrease was observed between 2007 and 2025. However, adolescent births in Serbia decreased from 6.5% to 3.8% (a reduction of about 51.1%), while the reduction in Zaječar was more pronounced at approximately 76.1%. The Batut data also show a decrease in stillbirths (overall), while risks in adolescent pregnancies remain higher and low birth weight is still more common among young mothers [9] (Table 9).

Table 9. Analysis of adolescent pregnancies and perinatal outcomes in all of Serbia (2007–2024)[9]

Pokazatelj	2007	2023	2024*
Ukupan broj porođaja	~68.000	~60.000	~58.000
Adolescentni porođaji	~4.500	~2.500	~2.300
Učešće (%)	~6.5%	~4%	~3.8%
Mrtvorođenost (на 1000)	~6–7	~4–5	~4
Niska porođajna težina(%)	~7–8%	~6–7%	~6–7%

(Low birth weight <2500 g) *2024 - preliminary data

According to the UNICEF report and analysis from 2023 [10], global adolescent birth rates have decreased by more than 40% since 2000, with the rate among the 15–19 age group falling to 39 births per 1,000 girls. However, significant inequalities in these rates still exist, particularly in sub-Saharan Africa. Although progress is evident, early childbearing remains highly prevalent among vulnerable groups, often driven by child marriage and limited access to contraception. Key trends and data from the 2023 analysis indicate regional disparities: sub-Saharan Africa has the highest adolescent birth rate (93 births per 1,000 girls aged 15–19), while Western Europe and North America report the lowest rates. The decline by age group since 2000 shows that among girls aged 10–14 years, birth rates have decreased by approximately 70%, while among those aged 15–19 years the decrease is about 40%. Around 76% of first births among girls under 18 occur within marriage, which is often associated with a higher risk of violence and health complications. When socioeconomic factors are considered, adolescent pregnancy is more common among girls with lower educational attainment and poorer economic status. Due to the small sample of adolescents in the Gynecology and Obstetrics Department of the Health Center Zaječar, it is not possible to assess the risk of stillbirth; however, according to a report on health outcomes [11], newborns of adolescent mothers have a 50% higher risk of stillbirth, neonatal death in the first week of life, and severe morbidity compared to children of mothers in their twenties. Despite improvements and a reduction in adolescent births, if current trends continue, significant inequalities related to socioeconomic status in adolescent childbearing will persist, according to a 2023 study for Latin America and the Caribbean [10].

CONCLUSION

In 2025, there was a significant reduction in the total number of deliveries at the Zaječar maternity ward compared to 2007, with a particularly pronounced decrease in adolescent births to only 11 cases (3.69%). Comparative analysis shows that the proportion of adolescent deliveries significantly decreased from 2007 (46 parturients – 8.28%) to 2025 (11 parturients – 3.69%) ($\chi^2 = 4.72$; $p = 0.029$). No statistically significant difference was found in birth weight ($t = 1.41$; $p = 0.16$). The increased rate of cesarean sections indicates a change in obstetric practice. Although the frequency of cesarean delivery was higher in 2025, this difference was not statistically significant ($\chi^2 = 1.56$; $p = 0.21$). In both 2007 and 2025, adolescent mothers were unemployed and economically dependent. One of the key tasks for obstetricians and gynecologists is to identify adolescents at risk and prevent behaviors leading to unintended pregnancy

Literature

1. Rot N, Radonjić S. Psihologija. Beograd: Zavod za udžbenike; 2007. p. 138-43.
2. Sedlecky K, et al. Reproduktivno zdravlje i polno ponašanje adolescenata. In: Obnavljanje stanovništva i zaštita reproduktivnog zdravlja. Beograd: Zavod za udžbenike i nastavna sredstva i Institut za zdravstvenu zaštitu majke i deteta Srbije; 1999. p. 137-55.
3. Kalinović D. Učestalost porođaja kod adolescentkinja u Zaječaru u periodu 1999–2003. god. In: Zbornik radova 50. Ginekološko akušerske nedelje SLD; 2006; Beograd. p. 421-4.
4. World Health Organization. Adolescent pregnancy [Internet]. 2024 [cited 2026 Apr 8]. Available from: https://www.who.int/news-room/fact-sheets/detail/adolescent-pregnancy
5. Melekoğlu NA, Saraç U. Evaluation of the effect of maternal adolescent age on neonatal outcomes. Cumhuriyet Med J. 2022;44:192-7.
6. Maheshwari MV, Khalid N, Patel PD, Alghareeb R, Hussain A. Maternal and Neonatal Outcomes of Adolescent Pregnancy: A Narrative Review. Cureus. 2022;14:e25921.
7. Relić G, Relić M. Porođaj adolescentkinja i informisanost učenika o rizičnom seksualnom ponašanju na severu Kosova. In: Zbornik radova 66. Ginekološko akušerske nedelje SLD; 2023; Beograd. p. 160-4.
8. Tomić I, Majić I, Dević A, et al. Broj adolescentnih porođaja u KBC Zemun tokom poslednjih šest godina - naše iskustvo. In: Zbornik radova 66. Ginekološko akušerske nedelje SLD; 2023; Beograd. p. 212-6.
9. Institut za javno zdravlje Srbije „Dr Milan Jovanović Batut“. Zdravstveno-statistički godišnjak Republike Srbije 2023. Beograd; 2024.
10. UNICEF. Early childbearing and adolescent pregnancy: global trends report. New York: UNICEF; 2023.
11. Worku SA, Tesema GA, Tessema ZT. Adverse obstetric and perinatal outcomes of adolescent pregnancy: a systematic review and meta-analysis. Front Reprod Health. 2024;6:1356402.

CHARACTERISTICS OF PATIENTS WITH BURNOUT SYNDROME

Aleksandar Tričković (1), Miljana Mladenović-Petrović (2)

(1) Health center Nis, Department of General Medicine; (2) Health center Bela Palanka, Department of General Medicine

Apstrakt: Introduction: Burnout syndrome is a state of chronic stress associated with emotionally demanding work that a person is unable to cope with using their own self-help resources, resulting in exhaustion. The syndrome is always related to work and, in addition to emotional exhaustion, also includes depersonalization and a sense of reduced professional efficacy. The causes of burnout include: imbalance between an individual's personal psychological resources and unfavorable working conditions; lack of autonomy in the workplace and control over work; work that conflicts with ethical and personal values; absence of recognition or support from the team or supervisors; and situations in which work goals do not align with the individual's intrinsic motivations. Characteristics of burnout by profession: Among general practitioners, burnout is an increasingly common phenomenon with serious consequences for professional efficiency. Nurses are also significantly burdened by workload. In recent years, many studies have been published on burnout among employees in the telecommunications sector. Clinical picture: Symptoms of burnout include mental and psychological fatigue, reduced immune response leading to more frequent illnesses, recurrent headaches, back pain, muscle pain, feelings of anxiety when going to work, irritability and anger, as well as feelings of helplessness, failure, hopelessness, and loneliness. Individuals often require more time to complete routine tasks. Diagnosis: As many as 75–90% of all doctor visits are related to chronic stress, and patients often consult multiple specialists in search of a definitive diagnosis. A detailed medical history is essential, followed by physical examination and laboratory tests to exclude other clinical conditions. Burnout syndrome may also present with cardiac symptoms, neurological manifestations, or psychiatric disorders. Principles of treatment: Treatment focuses on managing the symptoms and signs of occupational burnout. Depending on the predominant symptoms, appropriate therapeutic approaches are prioritized. In developed centers, employees have access to art therapy, music therapy, mindfulness training, and counseling services. Role of psychiatrists and psychotherapists: Literature data indicate that some hospitals offer free mental health support and counseling services for their employees. Individuals experiencing burnout may hesitate to seek help and instead progressively deteriorate. Preventive measures: Promotion of a supportive work culture, psychological support, workload rationalization, and team collaboration. Conclusion: This paper presents the etiological factors contributing to burnout syndrome and highlights the characteristics of its clinical presentation to facilitate recognition of the condition. It outlines principles of treatment and emphasizes the importance of psychotherapeutic support in education and patient care. Burnout should be viewed as a systemic warning signal, and more flexible working hours should be considered for employees. Strategies aimed at improving work–life balance should be further developed.

Key words: burnout, burning, profession, doctor, prevention

Introduction

Burnout syndrome, or burnout syndrome in Anglo-Saxon literature, is a phenomenon in modern medicine that was described in the seventies of the twentieth century. It was first introduced into medical use by Freudenberger [1], and then elaborated by Maslach et al. [2, 3]. It is the chronic stress associated with an emotionally draining job that a person cannot cope with with their self-help resources, resulting in burnout. The syndrome is always associated with work, and in addition to emotional exhaustion, it also implies depersonalization and the impression of insufficient efficiency. There are many works on this topic. It is described by professions.

Doctors feel exhausted with the impression of being used up at the end of the shift and that they cannot provide the same quality service to patients. The depersonalization of doctors means that they view patients as an object, not

as a human being, and they become increasingly unkind. This is especially reflected in the inability to help patients with their problems as well as in health care. The professional progress of doctors also suffers [4,5,6,7].

"Managerial disease" is a term that can be synonymous with burnout, and represents a set of symptoms that arise as a result of long-term exposure to stress at work. Although the profession of director-manager is associated with great responsibility and duties, work overload leads to physiological and later psychosomatic reactions. Deterioration of the health condition is accompanied by extreme physical and psychological exhaustion [8,9,10].

Cause of burnout

The causes of burnout syndrome are: -imbalance between the individual's personal psychological strengths and unfavorable conditions at work: lack of autonomy in the workplace and work control; work that conflicts with ethical and personal feelings; lack of praise or support from the team or superiors; to strive even though the goals are not what the individual deeply desires[11].

Dullness towards professions

Burnout syndrome among general practitioners is an increasingly common phenomenon with serious consequences for professional efficiency, the quality of health care, and the personal mental health of health workers. Doctors often feel emotional isolation, overwhelm and loss of meaning in their work.

Nurses are also a work load. Nurses in intensive care or who work at an oncology clinic are particularly exposed to this syndrome [12].

Managers, directors, and especially employees in banking have been a frequently studied occupational group in the literature. In recent years, numerous studies have also been published on burnout among employees in the telecommunications sector. These jobs are highly exhausting, as the performance targets that employees must achieve on the one hand, and very limited interpersonal interaction among employees on the other, create a favorable environment for the development of burnout syndrome. These are sedentary jobs with very little physical activity. It is considered that this profession involves all three dimensions of burnout: job demands, lack of adequate managerial control, and reduced interaction among employees [13, 14].

Clinical picture

Stress is experienced and processed differently by each individual, so symptomatology also varies.

Symptoms of burnout include mental and psychological fatigue, reduced immune response leading to more frequent illness, recurrent headaches, back pain, muscle pain, feelings of fear when going to work, anger and irritability, as well as feelings of helplessness, failure, hopelessness, and loneliness. Individuals often require more time to complete assigned tasks.

All professions with high levels of responsibility and workload, in which physiological and later psychosomatic reactions occur due to overload, may lead to deterioration of health status and eventual physical and mental exhaustion. The most common manifestations include tachycardia, palpitations, excessive sweating, elevated blood glucose levels, increased cholesterol, and elevated blood pressure. The so-called “managerial disease” can be considered an epidemic of the modern era, increasingly affecting people of younger and middle age. The condition more frequently affects men than women. In men, it most commonly leads to cardiac problems, while women more often suffer from anxiety, apathy, and depression.

If acute health problems and symptoms are not treated adequately and in time, they may become chronic. This is a syndrome of chronic occupational stress, manifested as emotional exhaustion, depersonalization, and a reduced sense of personal accomplishment [15].

Among general practitioners, the incidence of this syndrome is increasing due to excessive workload during the working day, including scheduled and unscheduled patients, as well as detailed documentation of each visit. Workload, rigid organizational structure, a work policy that penalizes mistakes but does not reward success, along with lack of personal resources, all contribute to burnout syndrome.

Emotional support is often lacking. Burnout should be viewed as a systemic warning signal that exhausts the employee, rather than a personal weakness. Burnout is not merely job dissatisfaction or fatigue due to workload; it manifests as a combination of stress and depressive symptoms [16]. However, in some cases, these symptoms may be absent.

Burnout has been described as closely related to depression, but the presence of depersonalization and reduced professional

achievement clearly distinguishes it from depression and other psychiatric conditions.
Consequences include reduced empathy, impaired patient relationships, and deterioration of both physical and mental health [17,18]. Table 1 presents the difference between stress and burnout..

Table 1. Difference between stress and burnout

stress	burnout
Over-engagement at work	Usually withdrawing into oneself
Excessive emotional response	Decreased emotional response, numbness
Overcrowding with work and dates	Slowness with a feeling of hopelessness and helplessness
Lack of energy	Decreased motivation, ideas and hopes
Usual individual response	Usual individual response

Diagnosis of burnout syndrome

As many as 75–90% of all medical visits are related to chronic stress, and patients often consult multiple available specialists in order to reach a definitive diagnosis.
First, a detailed medical history is required, followed by a physical examination and available laboratory tests to exclude other clinical conditions. Burnout syndrome may also present with cardiac symptoms, neurological manifestations, or psychiatric disorders [19].

Principles of therapy

The principles of treatment are based on managing the symptoms and signs of occupational burnout. Depending on which symptoms are predominant, greater attention is given to their treatment.
In developed centers such as the Healthcare System, employees have access to art therapy, music therapy, and mindfulness training sessions through counseling services [20].
Role of psychiatrists and psychotherapists in patient care
Literature data indicate that some hospitals offer free mental health support and counseling services for their employees.
Psychotherapy should not be an instrument for adapting individuals to an exhausting system, but rather a means of preserving humanity, empathy, and professional ethics. Individuals experiencing burnout may sometimes hesitate to seek help and instead sink deeper into the condition.
A study conducted in Singapore reported a donation-funded program providing support to individuals facing various problems such as work-related stress, relationship issues, and personal or family dilemmas [21].

Preventive measures

Today, awareness of the importance of prevention is growing, and employers increasingly recognize the value of investing in employee health. Many encourage regular medical check-ups and provide voluntary health insurance for workers. Regular systematic examinations are an important preventive measure.
Preventive strategies include promoting a supportive workplace culture, psychological support, workload rationalization, and teamwork.
Common preventive measures include regular physical activity (as it stimulates endorphin release), a well-balanced diet rich in fruits and vegetables, boiled meat and fish rich in omega-3 fatty acids, and regular sleep (to allow body recovery), as well as avoiding harmful habits such as smoking, excessive alcohol consumption, and caffeine intake. It is important to be aware of one's own emotions and strengthen self-confidence in order to recognize early signs of burnout before they become severe. Finding meaning and satisfaction in the work environment is also important. Flexible working hours may also be considered.
A meta-analysis by Williams et al. indicated that physicians may benefit from stress-reduction interventions, including changes in organizational strategies, as the root of burnout lies in the balance between work environment and private life [22].

Conclusion

This paper presents the etiological factors contributing to burnout syndrome and highlights the characteristics of its clinical presentation to facilitate disease recognition, as well as the principles of treatment. The

importance of psychotherapeutic support in patient education and care is emphasized.

Burnout should be viewed as a systemic warning signal, and more flexible working hours for employees should be considered. Strategies for improving work–life balance should be further developed. Interdisciplinary collaboration represents a key step toward a healthier and more humane working environment and society as a whole..

Literature:

1. Freudenberger HJ. Staff burnout. J Soc Issues 1974; 30:159–65.
2. Maslach C, Jackson SE, Leiter MP. Maslach Burnout Inventory Manual, 3rd ed. Palo Alto, CA: Consulting Psychologists Press, 1996.
3. Schaufeli WB, Leiter MP, Maslach C. Burnout: 35 years of research and practice. Career Dev Int 2009; 14: 204–20.
4. Schaufeli W, Bakker A, Hoogduin K, Schaap C, Kladler A. On the clinical validity of the Maslach burnout inventory and the burnout measure. Psychol Health 2001; 16: 565–82.
5. Bianchi R, Schonfeld IS, Laurent E. Burnout-depression overlap: a review. Clin Psychol Rev 2015; 36: 28–41.
6. Leiter M, Durup J. The discriminant validity of burnout and depression: a confirmatory factor analytic study. Anxiety Stress Coping 1994; 7: 357–73.
7. Wurm W, Vogel K, Holl A et al. Depression-burnout overlap in physicians. PLoS ONE 2016; 11.
8. Bridgeman PJ, Bridgeman MB, Barone J. Burnout syndrome among healthcare professionals. Am J Health Syst Pharm. 2018;75(3):147-152.
9. D Coghlan. Phases of burnout among Irish professionals. J Health Hum Serv Adm 1999;22(1):16-23.
10. CP West, LN Dyrbye, TD Shanafelt . Physician burnout: contributors, consequences and solutions. J Intern Med; 2018; 283(6): 516- 529.
11. Isabelle Roy Burnout syndrome: definition, typology and management.iscrpljenost Soins Psychiatr.2018; 39 (318): 12-19.
12. De Simone S, Vargas M, Servillo G. Organizational strategies to reduce physician burnou: a systematic review and meta-analysis. Aging Clin Exp Res. 2021;33(4): 883-894.
13. Malinauskas R, Grinevicius G, Malinauskiene V. Burnout among Telecommunication Sales Managers. Int J Environ Res Public Health;19 (18) :11249.
14. Tehrani Sh, , Keshtkar A, Ramasamy A, Fadaei M. The worldwide prevalence of burnout syndrome among bank employees: a systematic review and meta-analysis protocol Syst Rev; 2021 ;10 (1): 283.
15. Wuttipat Kiratipaisarl, Vithawat Surawattanasakul, Wachiranun Sirikul. Individual and organizational interventions to reduce burnout in resident physicians: a systematic review and meta-analysis. BMC Med Educ 2024; 24:1234.
16. Tamara D Street, Sarah J Lacey, Klaire Somoray. Employee Stress, Reduced Productivity, and Interest in a Workplace Health Program: A Case Study from the Australian Mining Industry Int J Environ Res Public Health. 2018 Dec 31;16(1): 94.
17. Gómez-Urquiza HL, De la Fuente-Solana E, Albendín-García L, Vargas-Pecino C, Ortega-Campos E, Cañadas-De la Fuente G . Prevalence of Burnout Syndrome in Emergency Nurses: A Meta-Analysis. 2017; 37(5): 1-9.
18. Ying Y, Hayes J. Causes and consequences of burnout among mental health professionals: A practice-oriented review of recent empirical literature Psychotherapy 2020;57(3):426-436.
19. Parker G, Tavella G. The Diagnosis of Burnout: Some Challenges J Nerv Ment Dis; 2021;210 (7): 475-478.
20. Woo T, Ho R, Tang A, Tam W. Global prevalence of burnout symptoms among nurses: A systematic review and meta-analysis; J Psychiatr Res; 2020; 123: 9-20.
21. Williams ES, Manwell LB, Konrad TR, Linzer M. The relationship of organizational culture, stress, satisfaction, and burnout with physician-reported error and suboptimal patient care: results from the MEMO study. Health Care Manage Rev 2007; 32: 203–12.
22. Ovchinniko YV, Palchenkova MV, Kalachev OV. Burnout syndrome: diagnosis, principles of treatment, prophylaxis. Voen Med Zh; 2015; 336 (7): 17-24.

CONTEMPORARY DIAGNOSTICS, CLASSIFICATION, AND TREATMENT OF DYSLIPIDEMIAS ACCORDING TO INTERNATIONAL GUIDELINES 2025–2026

Silvana Babić (1), Mila Bastać (2), Pavle Nešović (3)

(1) CLINIC FOR OTORHINOLARYNGOLOGY, UNIVERSITY CLINICAL CENTER OF SERBIA, BELGRADE; (2) MEDSCAN TADIĆ DIJAGNOSTIKA, ZAJEČAR; (3) INTERNAL MEDICINE PRACTICE "DR BASTAĆ" ZAJEČAR

Summary: Dyslipidemias represent one of the key modifiable risk factors for atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease, cerebrovascular ischemia, and peripheral arterial disease. Epidemiological data show a clear linear relationship between low-density lipoprotein cholesterol (LDL-C) levels and the incidence of cardiovascular events, confirming LDL-C as the primary causal factor in atherogenesis. In apparently healthy individuals, the risk of developing ASCVD is most often the result of the interaction of multiple risk factors, which forms the basis for assessing and managing overall cardiovascular (CV) risk. Risk factor screening should include lipid profiling in men over 40 years of age and in women over 50 years of age or after early menopause. Risk estimation systems such as SCORE2 and SCORE2-OP (used to calculate the 10-year risk of fatal and non-fatal cardiovascular events, with OP referring to older persons) can contribute to rational therapeutic decisions in order to avoid under- or overtreatment. Certain individuals classified as high or very high cardiovascular risk do not require SCORE risk assessment but instead require immediate management of all risk factors. This applies to patients with established cardiovascular disease, diabetes, or chronic kidney disease (CKD). In the last decade, and particularly in the period 2023–2026, significant changes have occurred in international guidelines. According to recommendations of the European Society of Cardiology (ESC), European Atherosclerosis Society (EAS), American College of Cardiology (ACC), American Heart Association (AHA), and American Diabetes Association (ADA), there has been a clear shift toward more aggressive LDL-cholesterol lowering, personalized therapy, and broader use of combination treatment strategies. Early diagnosis and aggressive lipid control remain central components of ASCVD prevention. All these guidelines emphasize the need for earlier, more intensive, and combination therapy to achieve very low levels of atherogenic lipoproteins, with special focus on LDL-C, non-HDL-C (total cholesterol minus HDL cholesterol; includes all atherogenic fractions: LDL, VLDL, IDL, lipoprotein(a)), and apolipoprotein B (ApoB). Advances in understanding lipid metabolism and the availability of new therapies have significantly improved treatment options. This review systematically presents modern principles of diagnosis, classification, treatment, and prognosis of dyslipidemias, along with a comparison of key guideline recommendations. Special attention is given to novel therapeutic modalities, including proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Particular emphasis is also placed on RNA interference gene therapy, where cells can “silence” specific genes via small interfering RNA (siRNA), which represents the mechanism of action of inclisiran.

Key words: dyslipidemia, LDL cholesterol, PCSK9 inhibitors, atherosclerosis, guidelines.

INTRODUCTION

Dyslipidemias encompass disorders of lipid metabolism that significantly contribute to the development of atherosclerotic cardiovascular disease (ASCVD). Elevated low-density lipoprotein cholesterol (LDL-C) represents the main causal factor of atherogenesis. Dyslipidemias are a heterogeneous group of lipid metabolism disorders characterized by increased or decreased concentrations of plasma lipoproteins. They are a key modifiable risk factor for ASCVD, including coronary heart disease, cerebrovascular disease, and peripheral vascular disease. Epidemiological data demonstrate a clear linear relationship between LDL cholesterol (LDL-C) levels and the incidence of cardiovascular events, confirming LDL-C as the primary causal factor in atherogenesis [1–7].

In apparently healthy individuals, the risk of developing ASCVD is most often the result of the interaction of multiple risk factors. This forms the basis for assessment and management of

overall cardiovascular (CV) risk. Risk factor screening should include lipid profiling in men over 40 years of age and in women over 50 years of age or after menopause. The updated electronic risk assessment system HeartScore (www.heartscore.org
), including SCORE2 and SCORE2-OP, supports clinical decision-making in order to avoid under- or overtreatment with lipid-lowering therapy. Certain individuals presenting with high, very high, or extreme cardiovascular risk do not require formal risk scoring but instead require immediate management of all risk factors. This applies to patients with established ASCVD, diabetes mellitus (DM), or chronic kidney disease (CKD) stage G3b–G4 or overt chronic renal failure. It should be noted that all risk scoring systems are relatively rigid and require additional clinical judgment when making final therapeutic decisions. Additional risk modifiers are included in electronic systems such as HeartScore (www.heartscore.org
). This comprehensive approach allows flexibility, as failure to achieve optimal risk reduction through one factor can be compensated by more intensive control of other risk factors.

According to current global, American, and European guidelines (ADA, AHA/ACC, ESC/EAS 2023–2026), early diagnosis and aggressive lipid control remain central components of ASCVD prevention [3–5].

In the period 2023–2026, new versions of major international dyslipidemia guidelines were published, including those of the European Society of Cardiology and European Atherosclerosis Society (ESC/EAS), the American Heart Association (AHA), the American College of Cardiology (ACC), and the American Diabetes Association (ADA).

All these guidelines emphasize the need for earlier, more intensive, and combination therapy in order to achieve lower levels of atherogenic lipoproteins, with special focus on LDL-C, non-HDL-C, and apolipoprotein B (ApoB) [3–5] (Table 1).

Table 1. Comparative overview of key ADA vs ESC/EAS recommendations (2023–2026)

ADA (2024–2026)	ESC/EAS (2023–2026)
LDL-C targets for diabetic patients: more stringent (often <1.4 mmol/L)	LDL-C targets based on risk: very strict (<1.4 mmol/L for high risk; <1.0 mmol/L for extreme risk)
Recommends measurement of ApoB in most patients with type 2 diabetes	ApoB and non-HDL-C levels are considered equally important therapeutic targets
Inclisiran recommended in cases of poor adherence	Inclisiran included in standard therapeutic algorithms
Favors early combination therapy	Emphasizes a "stepwise + combination" approach
Personalized therapeutic approach	Matrix-based risk stratification approach

AIM OF THE STUDY

The aim of this review article is to comprehensively present contemporary principles of diagnosis, classification, early screening, assessment of 10-year cardiovascular risk using SCORE2 and SCORE2-OP tools, and therapeutic management of dyslipidemias in accordance with the latest international standards and guidelines (ESC/EAS, ADA, AHA, ACC).

CLASSIFICATION OF DYSLIPIDEMIAS

Primary dyslipidemias

Familial hypercholesterolemia (FH)

Familial combined hyperlipidemia

Polygenic hyperlipidemia

Secondary dyslipidemias

Most commonly caused by:

Diabetes mellitus

Obesity and metabolic syndrome

Chronic kidney disease

Hypothyroidism

Liver diseases

Medications (corticosteroids, antipsychotics, retinoids, immunosuppressants) [15–17]

DIAGNOSIS OF DYSLIPIDEMIAS

Standard diagnostic approach

Diagnosis includes measurement of the standard lipid profile: total cholesterol, LDL-C, HDL-C, and triglycerides; calculation of non-HDL-C and ApoB; assessment of secondary causes; evaluation of global cardiovascular risk; and review of family history.

Dyslipidemia screening is always indicated in patients with clinical manifestations of cardiovascular disease (CVD), in clinical

conditions associated with increased cardiovascular risk, and whenever risk factor screening is warranted. In several clinical conditions, dyslipidemia may contribute to an increased risk of developing CVD. Chronic autoimmune inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), and psoriasis are considered conditions associated with increased cardiovascular risk. In addition, in women, gestational diabetes and hypertension during pregnancy are important risk indicators, while in men, erectile dysfunction is considered a risk marker. Patients with chronic kidney disease and overt renal failure also have increased cardiovascular risk, and dyslipidemia screening is indicated in these individuals.

It is always necessary to identify clinical manifestations of genetic dyslipidemias, such as xanthomas, xanthelasmas, and early corneal arcus (before the age of 45), as these are indicators of severe lipoprotein disorders, primarily familial hypercholesterolemia (FH), which is most often a monogenic disorder associated with premature ASCVD. Screening for dyslipidemia is also indicated in patients with peripheral arterial disease (PAD) or in the presence of increased carotid intima-media thickness (IMT) or carotid plaques.

Screening should also be considered in all adult men aged ≥40 years or women aged ≥50 years or in early postmenopause, especially in the presence of additional risk factors. Screening is also indicated in the offspring of patients with severe dyslipidemia, with follow-up in specialized clinics if necessary. Furthermore, screening of family members of patients with premature ASCVD is recommended [2].

Evaluation of Lipid and Apolipoprotein Laboratory Parameters [2]

The proposed lipid analyses used for assessment include total cholesterol (TC), triglycerides (TG), HDL-C, and LDL-C. Blood samples collected in the fasting state and those collected after meals provide similar results for total cholesterol (TC), LDL cholesterol, and HDL cholesterol. Triglycerides (TGs), however, are influenced by food intake.

There is significant intra-individual variability in serum lipid levels. Variations of 5–10% for TC and >20% for TG, particularly in patients with hypertriglyceridemia (HTG), are not uncommon. This is partly due to analytical variation, but also to external factors such as diet, physical activity level, and seasonal variation, including higher TC and HDL cholesterol levels during winter.

LDL cholesterol

In most clinical studies, LDL cholesterol is calculated using the Friedewald formula [2]:

LDL-C = TC − HDL-C − TG / 2.2 (mmol/L)
LDL-C = TC − HDL-C − TG / 5 (mg/dL)

Methodological errors may accumulate because this calculation is based on three parameters: total cholesterol (TC), triglycerides (TG), and HDL cholesterol. Direct methods for LDL-C measurement are available and are now widely used. In general, direct and calculated LDL-C values show good agreement.

New LDL-C estimation formulas, such as the Martin/Hopkins and Sampson equations, are particularly recommended in ADA and AHA/ACC guidelines [3–4]. Direct methods for measuring HDL-C and LDL-C are widely used and are reliable in patients with normal lipid profiles. However, in hypertriglyceridemia (HTG), they may be unreliable, and results can vary between commercial assays.

Lipoprotein(a) [Lp(a)]

Lipoprotein(a) [Lp(a)] has been identified in several studies as an independent risk factor in the pathophysiology of atherosclerotic cardiovascular disease and aortic stenosis. Lp(a) shares similarities with LDL but contains a unique protein, apolipoprotein(a) [apo(a)], which is structurally homologous to plasminogen.

Lp(a) measurements are relatively stable over time. Statins do not reduce Lp(a) levels; however, a reduction of approximately 30% has been observed with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors and nicotinic acid. However, a clear reduction in cardiovascular outcomes through direct Lp(a) targeting has not yet been conclusively demonstrated. Emerging therapies targeting the Lp(a) gene can reduce circulating Lp(a) levels by more than 80%.

Lipid parameters in cardiovascular risk estimation

Most cardiovascular risk assessment systems use TC and LDL-C, while other markers such as apoB and non-HDL-C, although physiologically logical, are mainly supported by post-hoc analyses. TC and LDL-C remain primary therapeutic targets, while non-HDL-C and apoB

are considered secondary targets. In patients with elevated triglycerides, additional risk is contributed by triglyceride-rich lipoproteins, which must be taken into account.

Total cholesterol (TC) is recommended for cardiovascular risk estimation using the SCORE system. However, in individual cases, TC may be misleading. This is particularly relevant in women, who often have elevated HDL-C levels, and in patients with diabetes or elevated triglycerides, who frequently have reduced HDL-C levels.

Overall risk assessment is not required in individuals with familial hyperlipidemia (including FH) or in those with TC >7.5 mmol/L (290 mg/dL), as these patients are always considered high risk and require special clinical attention.

Non-HDL cholesterol

Non-HDL cholesterol is used to estimate the total amount of atherogenic lipoproteins in plasma, including VLDL, VLDL remnants, intermediate-density lipoproteins (IDL), LDL, and Lp(a), and it shows a strong correlation with ApoB levels. It is easily calculated as:

non-HDL-C = TC − HDL-C

According to the updated ESC dyslipidemia guidelines [3], SCORE2 and SCORE2-OP recommend non-HDL-C as a better risk indicator than LDL-C. In several analyses, non-HDL-C has shown superiority over other measures, while in others it provides similar information to LDL-C. Compared with LDL-C, non-HDL-C has the advantage of simplicity and does not require additional testing. It also includes triglyceride-rich atherogenic lipoproteins (VLDL, IDL, and remnants), which are increasingly recognized as important in atherogenesis based on genetic (GWAS) evidence.

LDL-C remains the primary treatment target; however, non-HDL-C is recommended as a secondary target once LDL-C goals are achieved. The non-HDL-C target can be estimated by adding 0.8 mmol/L (30 mg/dL) to the LDL-C target value.

High-density lipoprotein cholesterol (HDL-C)

Low HDL-C is an important independent cardiovascular risk factor and is included in most risk scoring systems, including HeartScore. Very high HDL-C levels are not necessarily protective. Epidemiological studies define increased risk thresholds as:

Men: HDL-C < 1.0 mmol/L (40 mg/dL)

Women: HDL-C < 1.2 mmol/L (48 mg/dL)

The protective role of HDL-C has been questioned in several Mendelian randomization studies. Recent evidence suggests that dysfunctional HDL particles may be more relevant to atherosclerosis development than absolute HDL-C levels.

Triglycerides (TG)

Triglycerides are measured using enzymatic methods. Rare analytical errors may occur in patients with extreme hypertriglyceridemia, particularly at very high TG levels. Elevated TG levels are often associated with low HDL-C and increased numbers of small dense LDL particles.

Multiple meta-analyses suggest that TG may represent an independent cardiovascular risk factor. Genetic studies further support the role of triglycerides in directly contributing to cardiovascular disease. Recent data also suggest that non-fasting TG levels may provide important information regarding remnant lipoproteins associated with increased cardiovascular risk.

APOLIPOPROTEINS

There are reliable immunochemical methods for the determination of apolipoproteins using conventional autoanalyzers. Analytical performance is generally good, and these assays do not require fasting conditions and are not affected by elevated triglyceride (TG) levels.

Apolipoprotein B (ApoB)

Apolipoprotein B (ApoB) is the main apolipoprotein of the atherogenic lipoprotein family (VLDL, IDL, and LDL). ApoB is useful for estimating the total number of these particles in plasma. This feature is particularly important in cases of elevated low-density lipoprotein (LDL) concentrations. Several prospective studies have shown that ApoB performs similarly to LDL cholesterol and non-HDL cholesterol in predicting cardiovascular risk. Although ApoB has not been established as a primary treatment target in clinical trials, several post-hoc analyses suggest that it may be used not only as a risk marker but also as a potential therapeutic target.

Apolipoprotein A1 (ApoA1)

Apolipoprotein A1 (ApoA1) is the main protein component of HDL cholesterol and provides a reliable estimate of HDL particle concentration. However, each HDL particle may carry between one and five ApoA1 molecules.

Apolipoprotein CIII (ApoCIII)

Apolipoprotein CIII (ApoCIII) is recognized as a potentially important emerging

cardiovascular risk factor. ApoCIII is a key regulator of triglyceride metabolism, and elevated serum ApoCIII levels are associated with increased concentrations of VLDL and serum triglycerides. In addition, loss-of-function mutations in ApoCIII are associated with low triglyceride levels and reduced cardiovascular risk.

GENETIC DIAGNOSTICS [4]

Genetic testing is recommended in cases of suspected familial hypercholesterolemia (FH), extremely elevated LDL-C levels (>4.9 mmol/L or >190 mg/dL), and a family history of premature ischemic heart disease.

THERAPEUTIC APPROACHES

The treatment of dyslipidemias is based on a combination of non-pharmacological and pharmacological strategies, primarily aimed at reducing LDL cholesterol, but also at controlling triglycerides, increasing HDL cholesterol, and reducing overall atherogenic burden. Contemporary guidelines are consistent with the key principle: "the lower, the better" for LDL-C, especially in patients at high and very high cardiovascular risk [1–9].

1. Non-pharmacological approaches

Lifestyle modification

These interventions represent the foundation of therapy in all patients with dyslipidemia, regardless of risk level. The most important measures include:

Reduction of saturated fat and trans fat intake

Mediterranean or DASH dietary pattern

Increased intake of dietary fiber and plant sterols

Aerobic physical activity ≥150 minutes per week

Weight reduction of ≥5–7% in overweight and obese patients

Smoking cessation

Reduction of alcohol intake in hypertriglyceridemia

Although lifestyle changes can reduce LDL-C by approximately 5–15%, they are usually insufficient as monotherapy in patients at high cardiovascular risk [16–22].

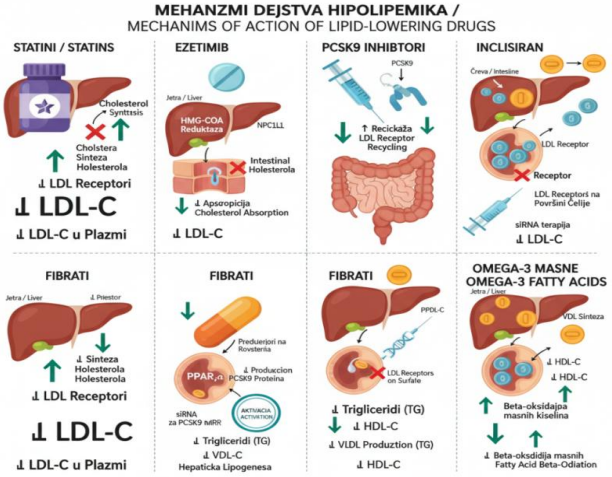
2. Pharmacological treatment of dyslipidemia

(Table 2 and Figure 1)

Table 2. Therapeutic Drug Classes — Comparison of Guideline Recommendations

Therapy	ADA	AHA/ACC	ESC/EAS
Statins	Mainstay of therapy; aim for the lowest possible LDL-C	First-line therapy	First and essential line of therapy
Ezetimibe	Second-line or add-on therapy	Add-on to statins	Mandatory in high-risk patients
PCSK9 inhibitors	Used when targets are not achieved	Preferred after ACS	Required in high and very high risk
Inclisiran	For poor adherence	Alternative to PCSK9 inhibitors	Integrated into treatment algorithms
Fibrates	For TG > 5.6 mmol/L	For severe hypertriglyceridemia	For TG > 5.6 mmol/L
Omega-3 (EPA)	For residual cardiovascular risk	REDUCE-IT population	Additional therapeutic option

Scheme 1. Graphical representation of the mechanism of action of lipid-lowering drugs



Statins (HMG-CoA reductase inhibitors)

Statins remain the first-line therapy in most patients. They are classified into high-intensity statins (atorvastatin 40–80 mg, rosuvastatin 20–40 mg) and moderate-intensity statins (simvastatin, pravastatin, lovastatin, pitavastatin). Effects include LDL-C reduction of 30–60% depending on dose and a reduction in the risk of myocardial infarction, stroke, and cardiovascular (CV) mortality by 25–40% [8–10].n

Adverse effects include myopathy, elevated liver enzymes, and very rarely rhabdomyolysis.

Ezetimibe (cholesterol absorption inhibitor)

Ezetimibe inhibits the NPC1L1 transporter in the small intestine, thereby reducing cholesterol absorption.

Its clinical importance lies in its recommendation as second-line therapy in patients whose LDL-C remains above target despite maximal statin therapy. It provides an additional LDL-C reduction of 20–25% and is safe and well tolerated [13].

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors

PCSK9 inhibitors are monoclonal antibodies, including evolocumab and alirocumab. They block the PCSK9 protein, thereby increasing LDL receptor recycling and reducing LDL-C levels by 50–65%.

Indications include:

Patients at very high risk (previous myocardial infarction, polyvascular disease)

Patients with familial hypercholesterolemia (FH)

Patients who do not achieve target LDL-C levels despite maximal statin + ezetimibe therapy [10–11]

Major clinical trials (FOURIER, ODYSSEY Outcomes) demonstrated a significant reduction in cardiovascular mortality and myocardial infarction.

Inclisiran (siRNA therapy)

Inclisiran is a small interfering RNA (siRNA) that inhibits hepatic synthesis of PCSK9 in hepatocytes.

Advantages include administration only twice yearly and sustained LDL-C reduction of approximately 50%, making it particularly suitable for patients with poor adherence.

Guideline integration: ESC/EAS 2023–2026 includes inclisiran in standard treatment algorithms for very high-risk patients, while ADA recommends it in cases of poor therapeutic adherence [5–7].

Fibrates

Fenofibrate and bezafibrate are used in specific lipid disorders.

Indications include:

Triglycerides >5.6 mmol/L (>500 mg/dL)

Prevention of pancreatitis

Residual hypertriglyceridemia in type 2 diabetes mellitus (DM2)

Omega-3 fatty acids (EPA formulations)

High-dose EPA (2–4 g/day) is used to reduce triglyceride levels and stabilize atherosclerotic plaque.

The REDUCE-IT trial demonstrated a reduction in cardiovascular outcomes in patients with elevated triglycerides [39].

NEW DEVELOPMENTS IN THE 2023–2026 GUIDELINES (ADA, ESC/EAS, AHA/ACC)

In the past three years, several important changes have occurred that significantly impact everyday clinical practice. (Table 3 and Scheme 2).

Scheme 2. Graphical representation of the therapeutic algorithm and comparison of guidelines

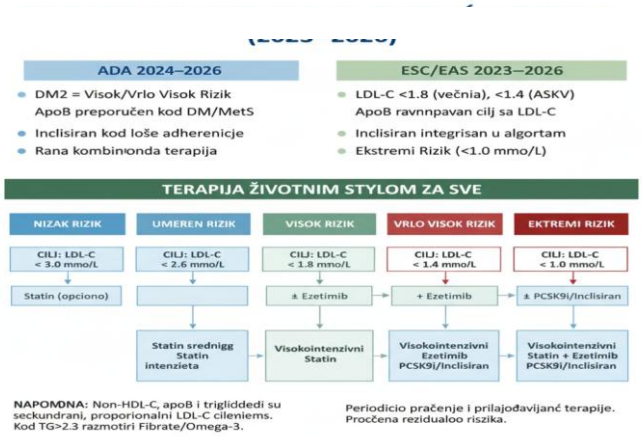


Table 3. Comparative LDL-C targets according to guidelines (ADA, AHA/ACC, ESC/EAS)

Risk category	ADA 2024–2026	AHA/ACC 2023–2025	ESC/EAS 2023–2026
Moderate risk	LDL-C < 2.6 mmol/L	LDL-C < 2.6 mmol/L	LDL-C < 2.6 mmol/L
High risk	LDL-C < 1.8 mmol/L	LDL-C < 1.8 mmol/L	LDL-C < 1.8 mmol/L
Very high risk	LDL-C < 1.4 mmol/L	LDL-C reduction as much as possible (often <1.4 mmol/L)	LDL-C < 1.4 mmol/L
Extreme risk	—	—	LDL-C < 1.0 mmol/L
FH (heterozygous)	≥50% LDL-C reduction target	≥50% LDL-C reduction	<1.8 mmol/L; if ASCVD <1.4 mmol/L
FH (homozygous)	specialized centers	PCSK9 + lomitapide	PCSK9 + lomitapide/evinacumab

1. ADA 2024–2026 – Diabetes and dyslipidemia

Patients with type 2 diabetes mellitus (DM2) are automatically classified as having high or very high cardiovascular risk. The LDL-C target in most diabetic patients is <1.8 mmol/L, while in patients with ASCVD the target is <1.4 mmol/L. Measurement of apoB is recommended in individuals with obesity, metabolic syndrome, and high triglycerides. Inclisiran is recommended in cases of poor adherence. The emphasis is on early initiation of combination therapy.

2. AHA/ACC 2023–2025 – Personalized therapeutic approach

PCSK9 inhibitors are increasingly used even after the first myocardial infarction. The LDL-C goal is "the lower, the better," although in some situations there is no strict numerical target. Lifelong LDL-C monitoring is emphasized in patients with familial hypercholesterolemia (FH). Non–HDL-C has an important role in patients with elevated triglycerides.

3. ESC/EAS 2023–2026 – Most aggressive LDL-C approach

A new "extreme risk" category has been introduced (e.g., polyvascular disease, recurrent ACS). LDL-C targets are: high risk <1.8 mmol/L, very high risk <1.4 mmol/L, extreme risk <1.0 mmol/L. LDL-C, non–HDL-C, and apoB are considered equal target parameters. Inclisiran is formally included in the therapeutic algorithm. There is a stronger focus on reduction of remnant lipoproteins and triglycerides.

The comparative therapeutic algorithm according to cardiovascular risk level is shown in Tables 4 and 5.

Table 4. Comparative therapeutic algorithm according to cardiovascular risk level

Risk	ADA	AHA/ACC	ESC/EAS
Low risk	Lifestyle ± statin	Lifestyle	Lifestyle ± statin
Moderate risk	Moderate-intensity statin	Statin based on clinical judgment	Moderate-intensity statin

Risk	ADA	AHA/ACC	ESC/EAS
High risk	High-intensity statin	High-intensity statin	High-intensity statin + ezetimibe
Very high risk	Statin + ezetimibe; PCSK9 if needed	High-intensity statin + early ezetimibe + PCSK9	Statin + ezetimibe + mandatory PCSK9
Extreme risk	—	—	Statin + ezetimibe + PCSK9 ± inclisiran
FH	Maximal combination therapy	Statin + ezetimibe, PCSK9	Statin + ezetimibe + PCSK9

Table 5. Recommendations for specific populations

Population	ADA	AHA/ACC	ESC/EAS
Diabetes	Automatically high risk	Most patients at high risk	Strict LDL-C targets (<1.4 mmol/L)
CKD	LDL-C <1.8 mmol/L	Caution with statins when GFR <30	Focus on apoB and non–HDL-C
Elderly	Benefit proportional to absolute risk	Individualization	Statins recommended up to age 75
FH	Statin + ezetimibe + PCSK9	Early family screening	Most aggressive approach
Post-ACS	Rapid LDL-C reduction <1.4 mmol/L	PCSK9 after first ACS	PCSK9 as first-line after ACS

1. Effect of LDL cholesterol reduction on cardiovascular outcomes

In a large meta-analysis by the Cholesterol Treatment Trialists' Collaboration, including over 170,000 patients, it was shown that each reduction of LDL-C by 1 mmol/L (~39 mg/dL) reduces the risk of major vascular events by approximately 22% [23]. This effect is consistent across men and women, younger and older individuals, patients with diabetes, those with prior myocardial infarction, and in both primary and secondary prevention. LDL-C reduction is beneficial in almost all clinical populations.

2. Statins – evidence from clinical trials

High-intensity statins have been shown to reduce myocardial infarction by 25–35%, ischemic stroke by 20–30%, and cardiovascular mortality by 15–20% [6–8]. In addition to LDL reduction, statins exert pleiotropic effects, including plaque stabilization, anti-inflammatory action, and improvement of endothelial function [24].

3. Ezetimibe – clinical outcomes

The IMPROVE-IT trial (ezetimibe + statin) demonstrated an additional LDL-C reduction of ~23% and a 6% relative reduction in primary cardiovascular outcomes (p=0.016) [11]. This supports the importance of combination therapy.

4. PCSK9 inhibitors – greatest benefit in highest-risk patients

The FOURIER trial (evolocumab) showed LDL-C reduction to ~0.8 mmol/L, a 15% reduction in cardiovascular events, and a 27% reduction in myocardial infarction risk [10]. The ODYSSEY Outcomes trial (alirocumab) demonstrated a significant reduction in cardiovascular mortality after acute coronary syndrome [11]. The key principle is: the lower the LDL-C, the greater the benefit.

5. Inclisiran – a new era of long-term lipid control

Inclisiran, an siRNA-based therapy, provides sustained and stable LDL-C reduction. Its advantages include dosing every 6 months, improved adherence, and approximately 50% LDL-C reduction [12]. Large outcome trials are still ongoing, but current data are promising.

6. Triglycerides and residual risk

Elevated triglycerides and remnant lipoprotein particles significantly increase cardiovascular risk, particularly in patients with diabetes and metabolic syndrome [19–20]. The REDUCE-IT trial (EPA 4 g/day) demonstrated a 25% reduction in major cardiovascular events and a 20% reduction in cardiovascular mortality [39]. This confirms that residual risk is important and that LDL-C reduction alone is not sufficient.

LATEST AMERICAN RECOMMENDATIONS FOR THE MANAGEMENT OF DYSLIPIDEMIA (2026)

The new American recommendations [40] reintroduce a focus on LDL cholesterol target values: for patients with borderline or intermediate risk, the target is <2.6 mmol/L; for high-risk patients <1.8 mmol/L; and for very high-risk patients (i.e., in secondary prevention), LDL-C should be reduced to <1.4 mmol/L.

The PREVENT-ASCVD calculator has been adopted, which estimates both 10-year and 30-year risk of adverse cardiovascular events (myocardial infarction, stroke, or cardiovascular mortality). Key patient characteristics used for risk estimation include age, sex, systolic blood

pressure, antihypertensive therapy, presence of diabetes, smoking status, and laboratory markers (total and LDL cholesterol). These variables are required for the basic model. The expanded model additionally includes body mass index (BMI) and kidney function, while the full model also incorporates albuminuria and HbA1c [40].

A notable innovation is the assessment of both 10-year and 30-year cardiovascular risk in individuals aged 30 to 59 years. The new recommendations also strengthen the use of additional biomarkers for assessing residual cardiovascular risk, such as lipoprotein(a), which is recommended to be measured at least once in a lifetime, and apolipoprotein B, which is particularly useful in patients with diabetes and hypertriglyceridemia.

Greater emphasis is placed on the assessment of coronary artery calcium (CAC) score [40], especially in situations where the decision to initiate statin therapy is uncertain—most commonly in patients with borderline or intermediate risk.

An important aspect of the new recommendations is earlier and more intensive LDL-C reduction. This is based on the concept that cumulative exposure to elevated LDL-C determines cardiovascular risk. Therefore, earlier initiation of therapy reduces lifetime exposure to high LDL-C levels and leads to a greater reduction in cardiovascular risk.

Accordingly, a complementary recommendation is universal lipid screening and lifelong prevention. Rather than waiting for cardiovascular events to occur, periodic assessment of lipid status is advised, with particular attention to screening in patients with diabetes, cardio-renal-metabolic syndrome, and in children [40].

PROGNOSIS

Dyslipidemias, if not properly diagnosed and treated, significantly increase the risk of atherosclerotic cardiovascular disease, premature disability, and mortality. However, contemporary therapeutic approaches allow for a substantial improvement in prognosis.

1. Prognosis

Prognosis depends on baseline LDL-C levels, the presence of comorbidities, degree of adherence, genetic factors (especially in familial hypercholesterolemia), and the timeliness of therapy initiation. In patients who achieve LDL-C target levels according to ESC/EAS guidelines (<1.4 mmol/L for high-risk patients), the risk of new cardiovascular events can be reduced by up to 50% [5].

2. Clinical implications

Recent guidelines (2023–2026) emphasize the following principles: LDL-C is the primary therapeutic target; lower LDL-C equals better prognosis. Combination therapy is the rule rather than the exception (statin + ezetimibe + PCSK9 inhibitor / inclisiran). ApoB and non–HDL-C are equally important as LDL-C, particularly in patients with elevated triglycerides and diabetes. Personalization of therapy is essential, with different targets for different risk categories..

CARDIOVASCULAR BENEFITS AND OUTCOMES

Reduction of atherogenic lipoproteins, particularly LDL cholesterol, represents the most effective pharmacological strategy in the prevention of atherosclerotic cardiovascular disease (ASCVD). Numerous randomized clinical trials, genetic analyses, and meta-analyses demonstrate a clear causal relationship between LDL-C reduction and decreased risk of major cardiovascular events [8–12,25–34].

1. Effect of LDL cholesterol reduction on cardiovascular outcomes

In a large meta-analysis by the Cholesterol Treatment Trialists' Collaboration, including over 170,000 patients, each 1 mmol/L (~39 mg/dL) reduction in LDL-C was associated with approximately a 22% reduction in major vascular events [25]. This effect is consistent across men and women, younger and older individuals, patients with diabetes, those with prior myocardial infarction, and in both primary and secondary prevention. LDL-C lowering is beneficial in nearly all clinical populations.

2. Statins – evidence from clinical trials

High-intensity statins have been shown to reduce myocardial infarction by 25–35%, ischemic stroke by 20–30%, and cardiovascular mortality by 15–20% [8–10]. In addition to LDL-C reduction, statins exert pleiotropic effects, including plaque stabilization, anti-inflammatory action, and improvement of endothelial function [26].

3. Ezetimibe – clinical outcomes

The IMPROVE-IT trial (ezetimibe + statin) demonstrated an additional LDL-C reduction of ~23% and a 6% relative reduction in primary cardiovascular outcomes (p=0.016)

[11], supporting the importance of combination therapy.

4. PCSK9 inhibitors – greatest benefit in highest-risk patients

The FOURIER trial (evolocumab) showed LDL-C reduction to ~0.8 mmol/L, a 15% reduction in cardiovascular events, and a 27% reduction in myocardial infarction risk [8]. The ODYSSEY Outcomes trial (alirocumab) demonstrated a significant reduction in cardiovascular mortality after acute coronary syndrome [9]. The key principle is: the lower the LDL-C, the greater the benefit.

5. Inclisiran – a new era of long-term lipid control

Inclisiran, as an siRNA-based therapy, provides sustained and stable LDL-C reduction. Its advantages include administration every 6 months, improved adherence, and approximately 50% LDL-C reduction [12]. Large outcome trials are still awaited, but current data are promising.

6. Triglycerides and residual risk

Elevated triglycerides and remnant lipoprotein particles significantly increase cardiovascular risk, particularly in patients with diabetes and metabolic syndrome [19–20]. The REDUCE-IT trial (EPA 4 g/day) demonstrated a 25% reduction in major cardiovascular events and a 20% reduction in cardiovascular mortality [39]. This confirms that residual risk is important and that LDL-C reduction alone is not sufficient.

GENE THERAPY AND FUTURE PERSPECTIVES [41]

In vivo gene or base editing represents a novel therapeutic strategy currently being investigated for the treatment of dyslipidemia, targeting genes such as PCSK9 and ANGPTL3. VERVE-101 is an experimental CRISPR-based therapy that includes mRNA encoding an adenine base editor targeting the PCSK9 gene, with the aim of permanently "silencing" (inactivating) this gene [42].

In non-human primates, a single infusion of VERVE-101 resulted in a 69% reduction in LDL-C, with sustained effects lasting up to 476 days post-dose, without significant adverse events. Following confirmed efficacy in primates, the first human study included 10 patients with heterozygous familial hypercholesterolemia (HeFH) and a mean LDL-C level of 201 mg/dL. A single intravenous infusion of CRISPR-based gene therapy delivered via targeted lipid nanoparticles resulted in up to a 55% reduction in LDL-C [43].

A next-generation therapy, Verve-102, represents an improved PCSK9 base-editing approach with enhanced liver targeting and redesigned lipid nanoparticles, and is currently in clinical development.

Today, numerous effective strategies are available to manage lipid-related cardiovascular risk factors. Even more promising innovations suggest continued progress in this field. However, the implementation of proven therapies, patient acceptance, adherence to treatment, and ensuring equitable access to modern therapeutic advances remain key challenges that must be addressed [4]..

CONCLUSION

Dyslipidemias remain one of the most important risk factors for atherosclerosis and cardiovascular mortality. Reduction of atherogenic lipoproteins, particularly LDL cholesterol, represents the most effective pharmacological strategy for the prevention of atherosclerotic cardiovascular disease (ASCVD). Numerous randomized clinical trials, genetic analyses, and meta-analyses demonstrate a clear causal relationship between LDL-C reduction and a decreased risk of major cardiovascular events.

Advances in the understanding of lipid metabolism and the availability of novel therapies have significantly improved treatment options. The integration of recommendations from ADA, AHA/ACC, and ESC/EAS enables an optimal and individualized approach, particularly in patients at high and very high risk.

A key novelty of the 2026 ACC/AHA guidelines is the assessment not only of 10-year cardiovascular risk (fatal and nonfatal), but also of 30-year risk in individuals aged 30 to 59 years. The new recommendations further emphasize the use of additional biomarkers for assessing residual cardiovascular risk, such as lipoprotein(a), apolipoprotein B, non–HDL cholesterol, coronary artery calcium score, body mass index, and HbA1c. Apolipoprotein B is particularly useful in patients with diabetes and hypertriglyceridemia.

Continued research in lipidology, the development of new therapeutic agents, and

advances in genetic diagnostics will contribute to even more effective prevention of ASCVD in the future..

REFERENCE:

1. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR /AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guidel ine on the Management of Blood Cholesterol. *Circulation.* 2019; 139(25):e1082–1143.
2. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to r educe cardiovascular risk. *Eur Heart J.* 2020;41(1):111–188.
3. Farkouh KE, Srivatsa S, Farkouh EM. The limitations of biomar kers in addressing bias in alcohol and cardiovascular disease re search. *Eur Heart J.* 2025;46(48):5296–5297.
4. Tokgözoğlu L, Libby P. Lipoprotein disorders and cardiovascul ar diseases. In: Libby P, Bonow RO, Mann DL, Tomaselli GF, Bha tt DL, Solomon SD, et al., editors. *Braunwald's Heart Disease: A T extbook of Cardiovascular Medicine.* 12th ed. Philadelphia: Else vier; 2027.
5. American Diabetes Association. Standards of Medical Care in Di abetes – 2024. *Diabetes Care.* 2024;47(Suppl 1):S1–S221.
6. Virani SS, Morris PB, Agarwala A, et al. AHA/ACC Guideline on t he Management of Lipids – 2023 Update. *J Am Coll Cardiol.* 2023;81:184–218.
7. Visseren FLJ, Mach F, Smulders YM, et al. 2023 ESC/EAS Guideli nes on cardiovascular disease prevention. *Eur Heart J.* 2023;44: 1–111.
8. Ference BA, Ginsberg H, Graham I, et al. Low-density lipoprotei ns cause atherosclerotic cardiovascular disease. *JAMA.* 2017;31 8:1655–1663.
9. Collins R, Reith C, Emberson J, et al. Interpretation of the evide nce for the efficacy and safety of statin therapy. *Lancet.* 2016;3 88:2532–2561.
10. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and cli nical outcomes in patients with cardiovascular disease (FOURI ER). *N Engl J Med.* 2017;376:1713–1722.
11. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiova scular outcomes after acute coronary syndrome (ODYSSEY Out comes). *N Engl J Med.* 2018;379:2097–2107.
12. Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisi ran in patients with elevated LDL cholesterol. *Lancet.* 2020;396 :797–806.
13. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes (IMPROVE-IT). *N Engl J Med.* 2015;372:2387–2397.
14. Nicholls SJ, Lincoff AM, Garcia M, et al. Effects of high-dose eico sapentaenoic acid on coronary plaque. *Eur Heart J.* 2022;43:10 16–1024.
15. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA Guid eline for the management of high blood pressure. *Hypertension.* 2018;71:e13–e115.
16. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guideline s on cardiovascular disease prevention. *Eur Heart J.* 2016;37:2 315–2381.
17. Toth PP, Banach M. Statin intolerance. *J Clin Lipidol.* 2021;15:4 15–431.
18. Ganda OP, Bhatt DL, Mason RP. Clinical utility of reducing trigly cerides in patients with diabetes. *Diabetes Care.* 2021;44:2185 –2195.
19. Miller M, Cannon CP, Murphy SA, et al. Triglycerides and cardio vascular disease: A scientific statement from the AHA. *Circulati on.* 2011;123:2292–2333.
20. Borén J, Chapman MJ, Krauss RM, et al. Triglyceride-rich lipopr oteins and atherosclerotic cardiovascular disease. *Eur Heart J.* 2020;41:99–109.
21. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS G uideline for the management of overweight and obesity. *Circul ation.* 2014;129:139–143.
22. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics – 2021 update. *J Am Coll Cardiol.* 2021;77:159–240.
23. Kahn R, Cooper ME, Del Prato S. Pathophysiology and treatmen t of insulin resistance. *Diabetes Care.* 2022;45:188–199.
24. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association r ecommendations for patient-centered management of dyslipid emia. *J Clin Lipidol.* 2022;16:394–427.
25. Silverman MG, Ference BA, Im K, et al. LDL-cholesterol reductio n and the impact on cardiovascular outcomes: A systematic rev iew and meta-analysis. *Lancet.* 2016;388:643–651.
26. Ridker PM, Everett BM, Thuren T, et al. Anti-inflammatory ther apy with canakinumab (CANTOS). *N Engl J Med.* 2017;377:111 9–1131.
27. Brown MS, Goldstein JL. A receptor-mediated pathway for chol esterol homeostasis. *Cell.* 1986;46:1–10.
28. Tavori H, Fan D, Blakemore J, et al. PCSK9 and LDL receptor reg ulation. *Circulation.* 2015;132:164–176.
29. Laufs U, Parhofer KG, Ginsberg HN. Contemporary lipid-loweri ng strategies. *Eur Heart J.* 2021;42:2215–2223.
30. Ademi Z, Park H, Lee J. Cost-effectiveness of PCSK9 inhibitors. *P harmacoeconomics.* 2021;39:981–994.
31. Lloyd-Jones DM, Braun LT, Ndumele CE, et al. Lifetime risk asse ssment and its significance. *Circulation.* 2022;145:e1085– e1143.
32. Arnett DK, Blumenthal RS, Albert MA, et al. ACC/AHA Guideline on the primary prevention of cardiovascular disease. *Circulati on.* 2019;140:e596–e646.
33. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associat ed with lipids and coronary disease. *N Engl J Med.* 2009;361:13 83–1392.
34. Holmes MV, Asselbergs FW, Palmer TM, et al. Mendelian rando mization of apoB. *Eur Heart J.* 2018;39:3389–3396.
35. Reiner Ž, Guardamagna O, Nair D, et al. Diagnosis and manage ment of familial hypercholesterolaemia. *Clin Lipidol.* 2018;13:1 –12.
36. Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial h ypercholesterolaemia – screening and diagnosis. *Eur Heart J.* 2013;34:3478–3490.
37. Santos RD, Gidding SS, Hegele RA, et al. Lipid management in cli nical practice. *J Am Coll Cardiol.* 2020;76:1397–1414.
38. Wiviott SD, Raz I, Bonaca MP, et al. SGLT2 inhibition and cardio vascular outcomes (DECLARE-TIMI 58). *N Engl J Med.* 2019;38 0:347–357.
39. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl (REDUCE-IT). *N Engl J Med.* 2019;380:11– 22.
40. Blumenthal RS, Morris PB, Gaudino M, Johnson HM, Anderson TS, Bittner VA, et al. 2026 ACC/AHA/AACVPR/ABC/ACPM/AD A/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia. *Circulation.* 2026;153:e00– e00. doi:10.1161/CIR.0000000000001423.
41. Rosenthal N, Ylä-Herttuala S. Gene therapy and future perspect ives. In: Libby P, Bonow RO, Mann DL, Tomaselli GF, Bhatt DL, S olomon SD, et al., editors. *Braunwald's Heart Disease: A Textboo k of Cardiovascular Medicine.* 12th ed. Philadelphia: Elsevier; 20 27.
42. Lee RG, Mazzola AM, Braun MC, et al. Efficacy and safety of an i nvestigational single-course CRISPR base-editing therapy targe ting PCSK9 in nonhuman primates and mouse models. *Circulati on.* 2023;146(3):242–253.
43. Naddaf M. First trial of base editing in humans lowers cholester ol – but raises safety concerns. *Nature.* 2023;623(7988):671– 672.

Vol. 51 (2026) No. 1 TIMOK MEDICAL GAZETTE Review article

UPDATES IN THE 2025 ESC GUIDELINES FOR MYOCARDITIS AND PERICARDITIS: AN INTEGRATIVE APPROACH TO INFLAMMATORY MYOPERICARDIAL SYNDROMES AND IMPLICATIONS FOR CLINICAL PRACTICE

Dušan Bastać (1), Zoran Joksimović (1), Mila Bastać (2), Pavle Nešović (1)

(1) INTERNAL MEDICINE PRACTICE "DR BASTAĆ" ZAJEČAR; (2) MEDSCAN TADIĆ DIJAGNOSTIKA, ZAJEČAR

Apstrakt: Introduction: Myocarditis is an inflammatory disease of the myocardium that can present with highly heterogeneous clinical manifestations, ranging from asymptomatic forms to fulminant heart failure and sudden cardiac death. The aim of this review paper is to present contemporary diagnostic and therapeutic approaches according to the latest ESC recommendations, integrating clinical experience and emphasizing the need for further research. LITERATURE REVIEW: In 2025, the European Society of Cardiology (ESC) published the first integrated guidelines addressing the diagnosis and treatment of myocarditis and pericarditis, introducing the new concept of inflammatory myopericardial syndrome (IMPS). This umbrella term recognizes the frequent clinical overlap between these two entities and their shared pathophysiological mechanisms. The paper analyzes key updates in classification, diagnostics, genetic evaluation, and therapeutic approaches, with particular emphasis on revised cardiac magnetic resonance (CMR) criteria (Lake Louise criteria), expanded indications for endomyocardial biopsy (EMB), and innovations in the treatment of pericarditis, including interleukin-1 inhibitors. The diagnostic paradigm for myocarditis has been changed. The discussion includes a comparison of ESC recommendations with American ACC/AHA guidelines, as well as contributions from domestic literature, particularly studies in the field of diastolic stress testing and inflammatory cardiomyopathies. The COVID-19 pandemic has further highlighted myocarditis as a potential complication of viral infections. CONCLUSION: The contemporary approach to myocarditis is shifting the paradigm by introducing the concept of inflammatory myopericardial syndrome and involves integrated diagnostics and therapy in accordance with the latest ESC guidelines, recognizing this syndrome as a clinically significant entity. Advances in the use of cardiac magnetic resonance imaging, broader indications for endomyocardial biopsy, and the introduction of targeted therapies, including interleukin-1 inhibitors, enable more precise diagnosis and individualized treatment strategies. Despite these advances, the heterogeneity of clinical presentation remains a challenge in everyday practice. Further research is necessary to improve understanding of the pathophysiology and to optimize the treatment of these patients..

Key words: Myocarditis, pericarditis, inflammatory myopericardial syndrome, ESC guidelines, cardiac magnetic resonance imaging, COVID-19, endomyocardial biopsy.

INTRODUCTION

The 2025 ESC guidelines represent a turning point in the approach to inflammatory heart diseases, unifying myocarditis and pericarditis within a single framework [1]. This decision stems from an increasingly clear understanding that these two entities are functionally, anatomically, and pathophysiologically closely related, and that treating them separately often leads to fragmentation in diagnosis and therapy. The new concept of inflammatory myopericardial syndrome (IMPS) serves as an umbrella term encompassing a clinical continuum ranging from isolated myocarditis, through combined myopericarditis and perimyocarditis, to isolated pericarditis, including complex mixed forms, up to chronic inflammatory cardiomyopathy and constrictive pericarditis [2–5, 6–8]. Such an integrative approach aims to improve collaboration among specialists and guide future research.

The term inflammatory cardiomyopathy has also been introduced, referring to chronic myocarditis associated with cardiac dysfunction and ventricular remodeling with a hypokinetic phenotype, with or without dilation. The role of cardiac magnetic resonance (CMR) is now central in diagnostics [9–11]. In the domestic literature, among others, contributions by the

authors of this review and their collaborators have advanced the understanding of diastolic dysfunction and echocardiographic parameters in inflammatory cardiomyopathies [12–14], while endomyocardial biopsy is recommended in high-risk cases [1, 15–21]..

EPIDEMIOLOGY AND CLASSIFICATION

The guidelines report an incidence of pericarditis ranging from 3 to 32 cases per 100,000 inhabitants per year, while the incidence of myocarditis is between 6 and 8 cases per 100,000 inhabitants [1,15]. Higher rates have been observed in men and younger adults. A particular challenge is the fact that a large number of subclinical and mild cases, including those diagnosed within the context of MINOCA (myocardial infarction with non-obstructive coronary arteries), remain undiagnosed [6,9], which may lead to underestimation of the true incidence and prevalence of chronic forms of the disease.

IMPS is classified into the following clinical entities: isolated pericarditis, isolated myocarditis, myopericarditis (predominant pericarditis with mild myocardial involvement), perimyocarditis (predominant myocarditis with pericardial features), and chronic inflammatory cardiomyopathy (chronic myocarditis with structural remodeling, dysfunction, and an arrhythmogenic substr [1].

ETIOLOGY AND PATHOPHYSIOLOGY

The etiology of myocarditis and pericarditis is heterogeneous. In developed countries, viral infections predominate (enteroviruses, adenoviruses, parvovirus B19, human herpesvirus 6, influenza virus, hepatitis C virus) [5,16,17], whereas in endemic regions tuberculosis remains an important cause of pericarditis, particularly in predisposed individuals with HIV infection. Bacterial causes (diphtheria, borreliosis, staphylococcal infections) are less common. Autoimmune mechanisms may lead to inflammation in the context of systemic diseases (lupus, sarcoidosis, vasculitis), while toxic agents (anthracyclines, alcohol, cocaine) and drugs (checkpoint inhibitors) can also induce myocarditis. A genetic basis plays an important role in susceptibility to viral infections and in determining the severity of the clinical presentation, with variants in sarcomeric and desmosomal genes being associated with myocarditis, and autoinflammatory diseases with recurrent pericarditis [6,8,15].

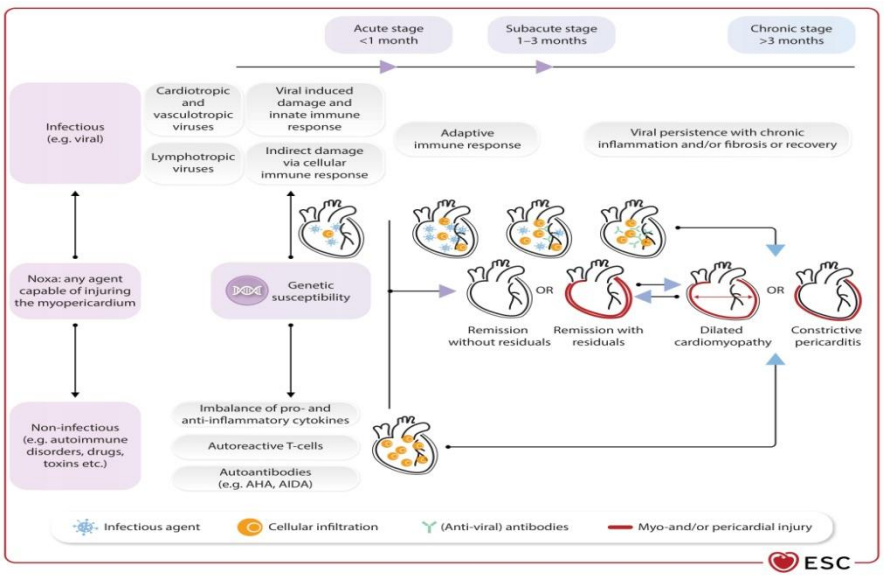
The pathophysiology of myocarditis is complex and involves acute, immune-mediated, and chronic phases of inflammation [5,6,17], progressing through several stages (Figure 1):

Acute phase: Direct myocardial injury caused by pathogen entry (e.g., viruses) into cardiomyocytes, leading to cell necrosis.

Immunological phase: Activation of the innate and adaptive immune response (macrophages, T-lymphocytes) with the release of cytokines and inflammatory mediators, resulting in further myocardial damage. Genetic variants in sarcomeric and desmosomal genes are increasingly being identified [1,18–20].

Chronic phase: In some patients, the inflammatory response persists, leading to progressive myocardial fibrosis, ventricular remodeling, and the development of dilated cardiomyopathy..

Figure 1. Stages of inflammatory myopericardial syndrome. AHA – anti-cardiac antibodies; AIDA – antibodies against the intercalated disc. Adapted from: *Eur Heart J*, Volume 46, Issue 40, 21 October 2025, Pages 3952–4041, https://doi.org/10.1093/eurheartj/ehaf192



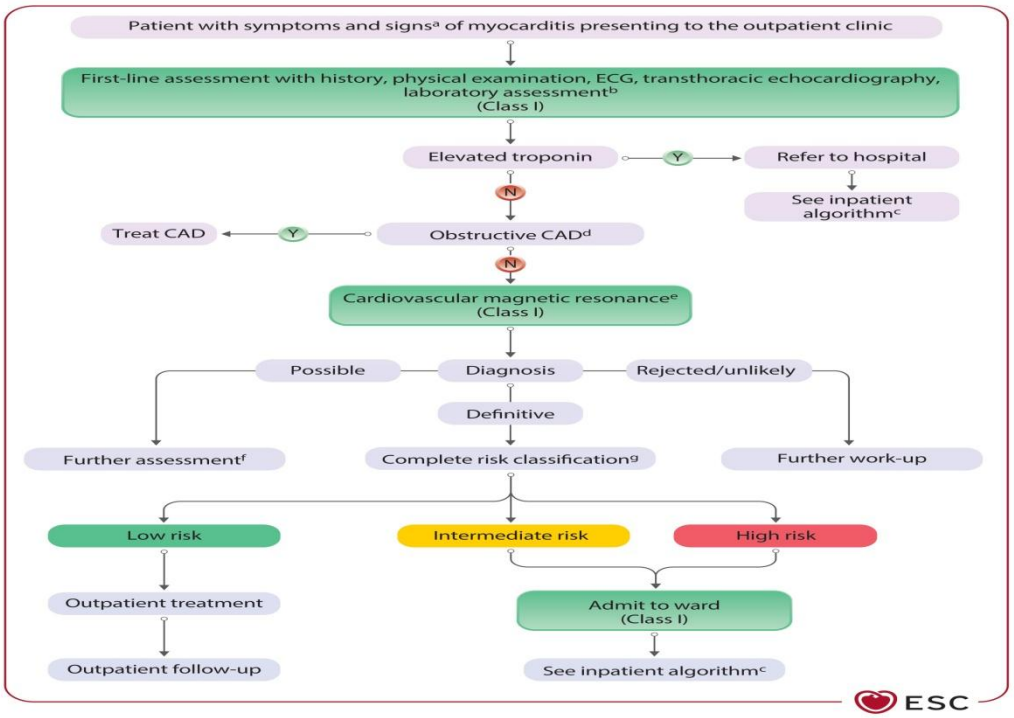
CLINICAL PRESENTATION

The clinical presentation of IMPS is highly variable. According to the time course, myocarditis is classified into: acute (≤4 weeks), subacute (4–12 weeks), and chronic (>3 months, with persistent inflammation and remodeling).

Myocarditis may present with a wide spectrum of clinical manifestations, ranging from mild or asymptomatic forms to heterogeneous clinical phenotypes, including asymptomatic mild myocarditis, chest pain, perimyocarditis, heart failure, arrhythmic presentation, sudden cardiac death, and fulminant myocarditis with fulminant heart failure and cardiogenic shock [6,18–20].

Myocarditis is considered complicated when there is LVEF <50%, acute heart failure, ventricular arrhythmias, or high-degree atrioventricular (AV) block. Complicated forms may be associated with ventricular arrhythmias, AV blocks, and significantly reduced ejection fraction [7–9,18–20] (Figure 2).

Figure 2. Diagnostic algorithm and triage for outpatients with myocarditis. Adapted from: *Eur Heart J*, Volume 46, Issue 40, 21 October 2025, Pages 3952–4041, https://doi.org/10.1093/eurheartj/ehaf192



The term fulminant myocarditis [21] is reserved for patients presenting with cardiogenic shock and the most severe form of the disease, which often requires intensive treatment and mechanical circulatory support.

Pericarditis clinically manifests as dry (fibrinous), effusive, as an impending or acute cardiac tamponade, reversible partial constriction, or a chronic constrictive form [2,4]. Timely differentiation between inflammatory and non-inflammatory phenotypes is crucial.

DIAGNOSTIC APPROACH

The 2025 ESC recommendations significantly reshape the essence of the diagnostic pathway and disease staging, reflecting a paradigm shift in the diagnostic process. This is largely driven by the major role of cardiac magnetic resonance imaging (CMR), which has become the gold standard for diagnosing myocarditis. At the same time, the role of endomyocardial biopsy has been refined and is now mainly reserved for severe, unclear, or high-risk cases, as well as for guiding appropriate therapy based on pathological and histological characterization with immunohistochemistry and PCR detection of viral genomes in the myocardium.

Previously, diagnostic categories included: suspected, confirmed, and proven myocarditis. In the new framework, classification has been updated to: unlikely/excluded, possible, and definite myocarditis (Figure 3 and Tables 1 and 2)..

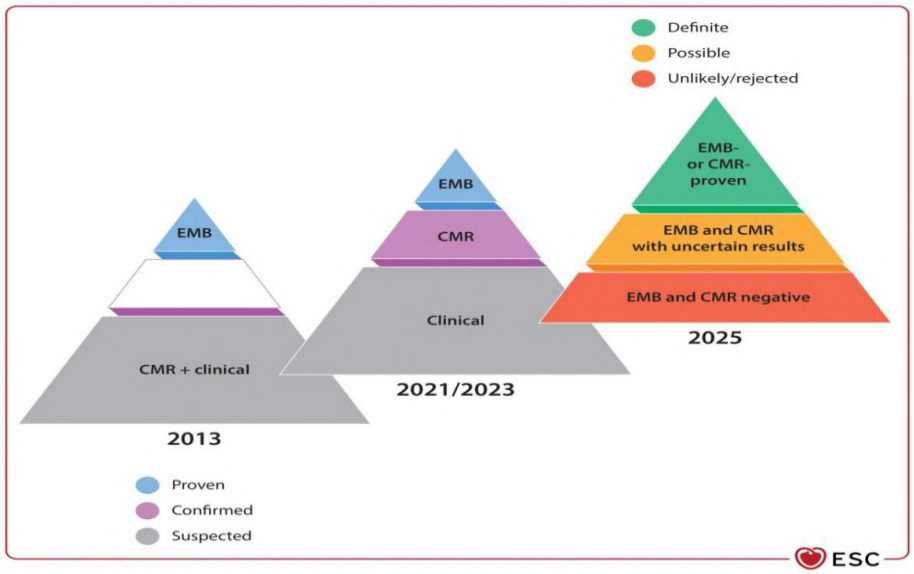
Table 1. Diagnostic criteria and classification for inflammatory myopericardial syndrome (IMPS)
If diagnostic criteria for myocarditis and/or pericarditis are fulfilled

Category	Myocarditis	Pericarditis
Definite	Clinical presentation + confirmation by CMR or EMB	Clinical presentation with >1 additional criterion
Possible	Clinical presentation with at least 1 additional criterion; CMR or EMB inconclusive or unavailable	Clinical presentation with 1 additional criterion
Unlikely / Excluded	Clinical presentation only, without additional criteria	Clinical presentation only, without additional criteria

Table 2. Additional criteria (in addition to clinical presentation)

Criterion	Myocarditis	Pericarditis
Clinical	Nonspecific findings	Pericardial friction rub
ECG	ST–T changes	PR depression, diffuse ST-segment elevation
Biomarkers	Elevated troponin	Elevated CRP
Imaging	Abnormal strain, wall motion abnormalities, reduced ejection fraction (EF)	New or worsening pericardial effusion
CMR findings	Myocardial edema and/or LGE (late gadolinium enhancement)	—

Figure 3. Paradigm shift in the clinical diagnosis of myocarditis



Basic diagnostic elements

Initial evaluation – biomarkers: Mandatory measurement of troponin (marker of myocardial injury/necrosis), high-sensitivity C-reactive protein (hsCRP, marker of inflammation), and natriuretic peptides BNP/NT-proBNP (markers of heart failure). Routine viral serologies are not recommended [1,3,5,19–20].

Electrocardiography (ECG): May show nonspecific ST-segment changes [5] (ST elevation/depression, T-wave changes, AV block, arrhythmias). There is no typical ECG pattern for myocarditis; however, ECG is rarely completely normal and is considered heterogeneous across different IMPS forms. Diffuse, concave upward ST-segment elevation is typical of pericarditis.

Echocardiography: A basic imaging modality for assessment of ventricular function (LVEF), presence of pericardial effusion, tamponade, and regional wall motion abnormalities. However, it often cannot definitively confirm inflammation [12–14].

If troponin is normal and LVEF is preserved, this indicates a favorable prognosis.

Non-invasive imaging – Cardiac Magnetic Resonance (CMR)

Cardiac magnetic resonance imaging is a key modality according to the revised Lake Louise criteria [1,10,11] and has become central in the diagnostic work-up of IMPS.

Diagnosis is established based on the revised Lake Louise criteria, which require at least one abnormality based on T1 mapping (indicating interstitial fibrosis or edema) and at least one abnormality based on T2 mapping (indicating myocardial edema) [11].

CMR enables detection of edema, necrosis, and fibrosis through late gadolinium enhancement (LGE), typically in an epicardial or mid-myocardial distribution, which helps differentiate inflammatory disease from myocardial ischemia and coronary artery disease.

The 2025 ESC recommendations emphasize an individualized approach based on clinical presentation and risk assessment (Table 3).1].

Table 3. Risk stratification algorithm and triage of patients with suspected myocarditis and pericarditis in outpatient settings. Hospitalization is recommended for all patients with myocarditis and high-risk pericarditis.

Risk	High risk	Intermediate risk	Low risk
Myocarditis	• Acute HF/cardiogenic shock • Dyspnoea NYHA III–IV refractory to medical therapy • Cardiac arrest/syncope[a] • Ventricular fibrillation/sustained ventricular tachycardia[a] • High-level AV block[a]	• New/progressive dyspnoea • Non-sustained ventricular arrhythmias • Persistent release or relapsing troponin	Stable symptoms or oligosymptomatic
	Imaging criteria:	**Imaging criteria:**	**Imaging criteria:**
	• Newly reduced LVEF (<40%)[a] • Extensive LGE on CMR[a]	• Newly mildly reduced LVEF (41%–49%) and/or WMA • Preserved LVEF (≥50%) and LGE ≥2 segments on CMR	• Preserved LVEF (≥50%) without LGE or limited LGE (<2 segments) on CMR
Pericarditis	• Signs and symptoms of cardiac tamponade • Fever (temperature >38°C) • Effusive–constrictive pericarditis • Failure of NSAID therapy • Incessant pericarditis	• Signs and symptoms of right HF	• Response to adequate therapy within 1–2 weeks
	Imaging criteria:	**Imaging criteria:**	**Imaging criteria:**
	• Large PEff (>20 mm end-diastole) • Cardiac tamponade • Extensive pericardial LGE on CMR	• Moderate–large PEff (10–20 mm end-diastole) • Constrictive physiology regardless of the size of the effusion	• Absence or mild PEff • Absence of pericardial LGE on CMR

Invasive diagnostics – Endomyocardial biopsy (EMB)

Endomyocardial biopsy (EMB) is considered the gold standard in severe forms of disease [17,21,22], providing definitive diagnosis and etiological classification. Indications have been expanded compared with previous guidelines and are now reserved for high-risk cases (Table 4). Molecular biological (PCR) analysis for viral genomes is mandatory prior to initiation of immunosuppressive therapy [21–23]].

TABLE 4. Indications for endomyocardial biopsy (EMB) according to ESC 2025 [21]

Clinical situation	Level of recommendation
Fulminant myocarditis with cardiogenic shock	Strong indication
Suspected giant-cell myocarditis	Strong indication
Suspected eosinophilic myocarditis	Strong indication
Acute heart failure of unknown etiology (<2 weeks duration)	Recommended
Heart failure (2 weeks–3 months) with left ventricular (LV) dilation and new ventricular arrhythmias	Recommended
Suspicion of cardiac sarcoidosis or autoimmune myocarditis	Recommended
Refractory ventricular arrhythmias of unknown etiology	Consider
Persistent left ventricular dysfunction without clear cause (LVEF <40%, extensive LGE on CMR)	

GENETIC TESTING

There is increasing evidence of an association between myocarditis and inherited cardiomyopathies. The ESC 2025 guidelines recommend genetic testing in selected patients with familial forms and recurrent pericarditis [1]. Studies highlight mutations in desmosomal genes as part of an inherited predisposition [1], particularly in patients with high diagnostic yield, such as those with:

Family history of cardiomyopathy or sudden cardiac death

Arrhythmic presentation of disease

Presence of septal or "ring-like" LGE on CMR

Persistent systolic dysfunction without recovery

Recurrent myocarditis or pericarditis (a genetic cause is identified in approximately 15% of patients with recurrent pericarditis) [1]

THERAPY OF MYOCARDITIS

Therapeutic management is individualized and depends on etiology, clinical presentation, and hemodynamic status [1,6] (Table 5). In stable patients, analgesics and NSAIDs are used, with the addition of colchicine when pericardial symptoms are present [1,31]. In heart failure, standard HF guideline-directed medical therapy is applied (ACE inhibitors/ARNI, beta-blockers, mineralocorticoid receptor antagonists, SGLT2 inhibitors) [6,29].

Immunosuppressive therapy is reserved for virus-negative forms [21] or specific entities such as giant-cell and eosinophilic myocarditis [22–24]. In fulminant myocarditis, mechanical circulatory support (VA-ECMO) is recommended [1,20].

The treatment of myocarditis is systematized into five key domains:

1. General measures and symptomatic therapy

Restriction of physical activity for 3–6 months. In the acute phase, in hemodynamically stable patients, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), and colchicine are used if pericardial symptoms are present.

2. Heart failure therapy

In patients with heart failure, standard guideline-directed therapy is used: ACE inhibitors or ARNI, beta-blockers, mineralocorticoid receptor antagonists (MRA), sodium-glucose cotransporter-2 inhibitors (SGLT2i), and diuretics in cases of congestion.

3. Immunosuppressive therapy

Used only in non-infectious etiologies and after exclusion of active viral infection in the myocardium by PCR analysis of EMB samples. Indications include:

Virus-negative inflammatory (autoimmune) myocarditis

Giant-cell myocarditis (strong recommendation)

Eosinophilic myocarditis (strong recommendation)

Myocarditis associated with systemic autoimmune diseases (e.g., sarcoidosis)

Commonly used agents include corticosteroids (prednisone), azathioprine, mycophenolate mofetil, and cyclosporine [1].

4. Antiarrhythmic therapy and devices

Antiarrhythmic drugs are used for symptomatic arrhythmias. Implantable cardioverter-defibrillator (ICD) implantation is considered in patients with persistent LV dysfunction after at least 3 months of optimal therapy. A wearable defibrillator (vest-type device) may be used as a temporary option for 3–6 months [1].

5. Mechanical circulatory support (MCS)

In fulminant myocarditis with cardiogenic shock, MCS serves as a "bridge to recovery" or "bridge to transplantation." Recommended modalities include intra-aortic balloon pump (IABP) and veno-arterial ECMO (VA-ECMO) as the most effective support strategies [20–21].].

Table 5. Therapeutic recommendations for myocarditis according to ESC 2025

Therapeutic approach	Recommendation
Restriction of physical activity for 3–6 months	Recommended (Class II)
Standard heart failure therapy	Recommended (Class II)
Immunosuppressive therapy in virus-negative autoimmune myocarditis	Recommended (Class II)
Corticosteroids in giant-cell or eosinophilic myocarditis	Strong recommendation (Class I)
Antiviral therapy in confirmed viral etiology	Selective
Mechanical circulatory support in cardiogenic shock	Recommended

TREATMENT OF PERICARDITIS

First-line therapy: Aspirin or NSAIDs in combination with colchicine for at least 3 to 6 months (Class I A recommendation) [1–4].

Second-line therapy:

Corticosteroids are considered second-line treatment for refractory forms [2]. They are

used only when first-line therapy fails or is contraindicated.

Refractory pericarditis:

Interleukin-1 (IL-1) inhibitors represent a novel therapeutic option for treatment-refractory and/or recurrent pericarditis, particularly in patients with markedly elevated hsCRP levels (Class I A recommendation in highly inflammatory phenotypes) (Figure 4 and Table 6)..

Figure 4. Proposed algorithm for pharmacological treatment of pericarditis in adults (excluding interventional procedures and pericardiectomy). Adapted from: *Eur Heart J*, Volume 46, Issue 40, 21 October 2025, Pages 3952–4041, https://doi.org/10.1093/eurheartj/ehaf192

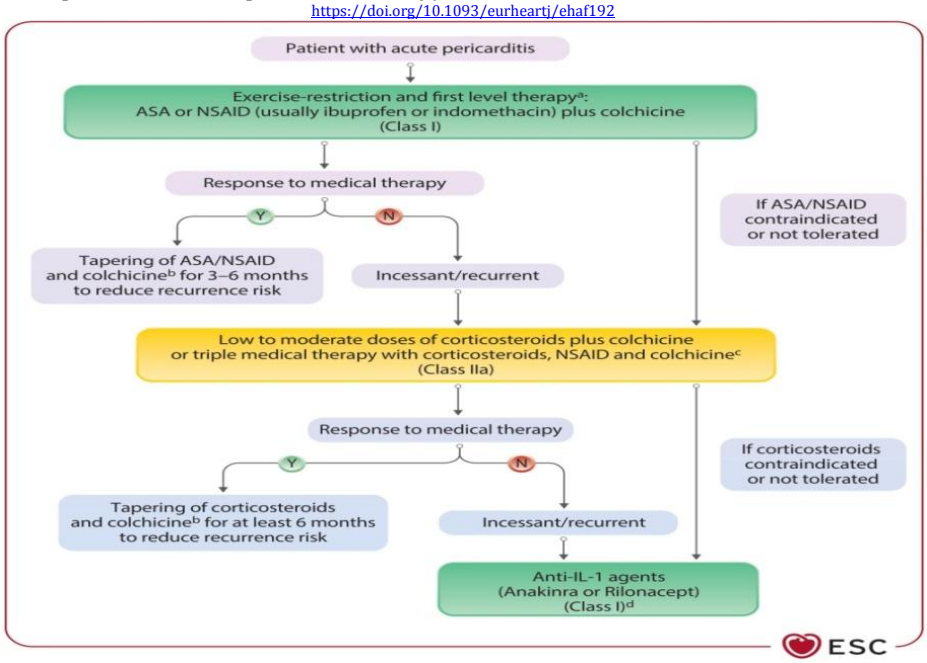


TABLE 6. Therapeutic protocol for the treatment of pericarditis. Adapted from: *Eur Heart J*, Volume 46, Issue 40, 21 October 2025, Pages 3952–4041, https://doi.org/10.1093/eurheartj/ehaf192

Therapy	Dosing	Duration[a]	Tapering[a]
Aspirin[b]	750–1000 mg 3 times daily	1–2 weeks	Decrease by 250 mg every 1–2 weeks
Ibuprofen[b]	600–800 mg 3 times daily	1–2 weeks	Decrease by 200 mg every 1–2 weeks
Indomethacin	25–50 mg 3 times daily	1–2 weeks	Decrease by 25 mg every 1–2 weeks
Colchicine[b]	0.5 mg once daily (<70 kg or severe renal impairment) or 0.5 mg twice daily	3–6 months	Not required
Prednisone	0.2–0.5 mg/kg/day	2–4 weeks	Several months
Treatment for recurrences only:			
Azathioprine	Starting with 1 mg/kg/day then gradually increased to 2–3 mg/kg/day	Several months	Several months
IVIG	400–500 mg/kg i.v. daily for 5 days	5 days	Not required
Anakinra	1–2 mg/kg/day up to 100 mg/day in adults	At least 6 months/ >12 months	Needed (at least 3–6 months)/ unknown
Rilonacept[c]	320 mg once daily followed by 160 mg weekly		

TABLE 7. SUMMARY OF ESC RECOMMENDATIONS FOR THE TREATMENT OF INFLAMMATORY MYOPERICARDIAL SYNDROME (IMPS)

Recommendations	Class[a]	Level[b]
Management of symptoms		
NSAIDs (together with proton pump inhibition) should be considered in patients with associated symptoms of pericarditis to reduce symptoms.	IIa	C
Colchicine should be considered in patients with myopericarditis to reduce recurrences.[263]	IIa	B
Management of heart failure		
Adherence to the ESC HF guidelines is recommended in cases of myocarditis with LV systolic dysfunction and/or HF to reduce symptoms and to improve LV function.[12]	I	C
HF therapy should be considered in patients with myocarditis and LV systolic dysfunction for at least 6 months upon complete LV functional recovery to stabilize LV function.	IIa	C
Management of arrhythmias		
β-Blockers, with a continuation for at least 6 months, should be considered in patients with acute myocarditis, especially those with troponin elevation, to control symptoms and prevent arrhythmias.	IIa	C
Anti-arrhythmic treatment should be considered in post-myocarditis patients with recurrent, symptomatic VT to reduce arrhythmic burden.[58]	IIa	C
Immunosuppressive therapy		
Corticosteroids should be considered in patients with fulminant, non-infectious forms of myocarditis to stabilize the patients.	IIa	C
Corticosteroids may be considered in patients with acute myocarditis with impaired LVEF if refractory to standard HF therapy to stabilize patients.	IIb	C
Routine use of immunosuppressive therapy is not recommended in acute myocarditis with preserved LV function because no outcome benefit has been shown.	III	C

ESC, European Society of Cardiology; HF, heart failure; LV, left ventricle; LVEF, left ventricular ejection fraction; NSAID, non-steroidal anti-inflammatory drug; VT, ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.

SPECIAL POPULATIONS

Post-COVID myocarditis: May occur as a result of direct viral infection, systemic inflammatory response, or immune dysregulation (25–26). Diagnosis is often established by CMR, and therapy is mainly supportive. Post-COVID myocarditis and post-vaccination forms have been analyzed in several studies [23–28]. Rare cases of post-vaccination myocarditis after mRNA vaccines have been reported, most commonly in young males within several days after the second dose. The clinical course is usually mild, and the prognosis is favorable. The benefits of vaccination far outweigh the risks [27–30].

Children: Similar diagnostic criteria are applied, but caution is required with corticosteroid use due to potential effects on growth.

Pregnancy: Colchicine may be used for recurrence prevention in pericarditis (Class IIb C recommendation).

Elderly patients:

Dose adjustment of colchicine is necessary, along with monitoring of renal function.

PROGNOSIS AND FOLLOW-UP

Prognosis depends on initial clinical presentation and etiology. The most important predictor of adverse outcome is biventricular dysfunction. Most patients with mild disease achieve full recovery. In a minority of cases, progression to dilated cardiomyopathy and chronic heart failure may occur [14,15].

Follow-up after acute myocarditis is systematic over the first 6–24 months and includes: clinical assessment, ECG, Holter monitoring, biomarkers (troponin, CRP), echocardiography, exercise testing, and CMR in selected cases [1].

Prognosis is influenced by the degree of left ventricular dysfunction and the presence of fibrosis on CMR [6,10,11]. Diastolic dysfunction may persist even after clinical recovery [12–14].

DISCUSSION

The ESC 2025 guidelines represent a significant conceptual advance with the introduction of IMPS, but also raise several controversies.

The most debated issues include: Central role of CMR: Although CMR has become indispensable, its position as a "new gold standard" carries the risk of overdiagnosis and limited accessibility.

Controversial beta-blocker recommendation [1,6]: The recommendation for beta-blocker use in all myocarditis patients for at least 6 months, regardless of EF, is based on limited evidence and is one of the most debated points in the guideline.

Genetic testing approach: Also controversial, being more limited in ESC guidelines compared with broader recommendations in ACC/AHA documents [3,4].

Nedovoljna posvećenost u raščišćavanju etiopatogeneze kod MINOCA populacije: Smernice propuštaju priliku da preciziraju definiciju IMPS kod pacijenata sa MINOCA-om, gde je miokarditis jedan od najčešćih konačnih nalaza.

Razlike u odnosu na američke preporuke (ACC/AHA) [1,3]: Evropski pristup je konzervativniji po pitanju genetskog testiranja (samo selektovani pacijenti naspram svih), ranije primene IL-1 inhibitora kod perikarditisa (kasnije u odnosu na ACC) i ne uključuje mikroaksijalne pumpe (npr. Impella) u algoritme mehaničke potpore, za razliku od američkih smernica.

Table 8. Comparison of ESC 2025 and ACC/AHA 2024 guidelines

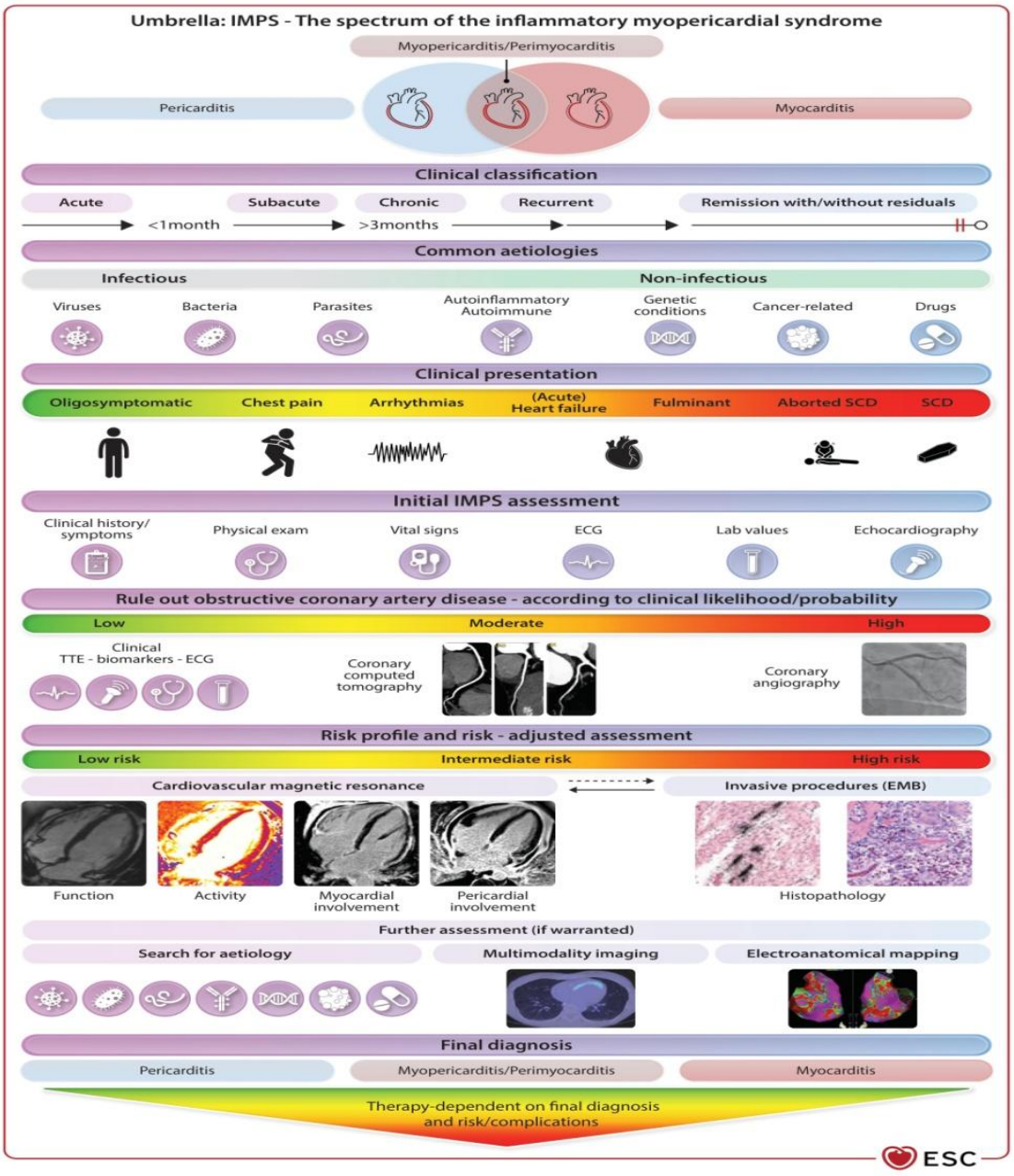
Topic	ESC 2025	ACC/AHA consensus
Genetic testing	Only in selected patients	Recommended in all patients with myocarditis
Beta-blockers	Recommended for ≥6 months in all patients	No universal recommendation
IL-1 inhibitors	More conservative approach (after corticosteroids)	Earlier use after failure of NSAIDs + colchicine
Mechanical support	Emphasis on VA-ECMO	More detailed inclusion of microaxial pumps (e.g., Impella)

The ESC 2025 guidelines introduce the IMPS concept, emphasize the role of CMR, and expand indications for EMB [1,10,17]. In the context of local clinical practice, the studies by the author of this literature review, Dr Dušan Bastać, significantly help bridge gaps in the practical application of diagnostic methods for inflammatory myopericardial syndrome in Serbia [12–14].

His research on diastolic stress testing and echocardiographic markers indicates that diastolic dysfunction and elevated left ventricular filling pressures may persist even after recovery of systolic function (LVEF). This finding is consistent with the concept of inflammatory cardiomyopathy and the HFpEF phenotype (heart failure with preserved ejection fraction) in these patients.

These observations highlight the need for careful, multimodal follow-up even in patients with normalized ejection fraction..

Figure 5. Central illustration of the ESC guidelines on myocarditis and pericarditis. Adapted from: *Eur Heart J*, Volume 46, Issue 40, 21 October 2025, Pages 3952–4041, https://doi.org/10.1093/eurheartj/ehaf192



CONCLUSION

The ESC 2025 recommendations and guidelines represent the most comprehensive document to date, unifying myocarditis and pericarditis into a single concept—inflammatory myopericardial syndrome (IMPS), as illustrated in the figure (Figure 5: Central illustration of ESC guidelines on myocarditis and pericarditis).

The emphasis is on a multimodal diagnostic approach, with a central role of cardiac magnetic resonance imaging (CMR), rational use of endomyocardial biopsy (EMB), selective application of immunosuppressive therapy, and overall personalization of treatment strategies.

Despite significant progress, many recommendations are still based on expert consensus, highlighting the need for further

high-quality research, particularly in areas such as optimal use of beta-blockers, novel antiviral therapies, genetic testing, and biological treatments.

The integration of domestic clinical experience shows that the guidelines are largely compatible with current practice, but also open new questions and research opportunities aimed at improving outcomes in patients with inflammatory heart diseases.

REFERENCE :

1. European Society of Cardiology. ESC Guidelines for the Management of Myocarditis and Pericarditis. *Eur Heart J.* 2025.
2. European Society of Cardiology. 2015 ESC Guidelines on Pericardial Diseases. *Eur Heart J.* 2015;36:2921–2964.
3. American College of Cardiology. ACC Expert Consensus Decision Pathway on Myocarditis. *J Am Coll Cardiol.* 2024.
4. American College of Cardiology. ACC Consensus on Pericardial Diseases. *J Am Coll Cardiol.* 2024.
5. Caforio ALP, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis and therapy of myocarditis. *Eur Heart J.* 2022;43:399–421.
6. Ammirati E, Frigerio M, Adler ED, et al. Management of acute myocarditis and chronic inflammatory cardiomyopathy. *Circulation.* 2022;145:1722–1737.
7. Cooper LT. Myocarditis. *N Engl J Med.* 2009;360:1526–1538.
8. Tschöpe C, Ammirati E, Bozkurt B, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol.* 2021;18:169–193.
9. Kindermann I, Barth C, Mahfoud F, et al. Update on myocarditis. *J Am Coll Cardiol.* 2022;79:1326–1342.
10. Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC White Paper. *J Am Coll Cardiol.* 2009;53:1475–1487.
11. Ferreira VM, Schulz-Menger J, Holmvang G, et al. CMR mapping techniques for myocarditis: consensus statement. *JACC Cardiovasc Imaging.* 2018;11:155-169.
12. Bastać D, Marković Z, Vasić B, et al. Dijastolni stres test u proceni bolesnika sa srčanom insuficijencijom. *Zbornik radova Zdravstvenog centra Zaječar.* 2017;1:45–49.
13. Bastać D, Vasić B, Nešović P, et al. Ehokardiografska procena dijastolne funkcije kod bolesnika sa miokarditisom. *Timočki medicinski glasnik.* 2018;43(2):73–78.
14. Bastać D, Vasić B, Marković Z, et al. Srčana insuficijencija sa očuvanom ejekcionom frakcijom – dijagnostički izazovi. *Timočki medicinski glasnik.* 2020;45(1):23–28.
15. Heymans S, Cooper LT, De Smet B, et al. Inflammatory cardiomyopathy. *Eur Heart J.* 2020;41:1358–1376.
16. Schultheiss HP, Kühl U, Cooper LT. Viral myocarditis. *Nat Rev Cardiol.* 2021;18:145–161.
17. Imazio M, Klingel K, Kindermann I, et al. Myocarditis management – current trends and future perspectives. *Eur Heart J.* 2022;43:1012–1027.
18. Kühl U, Pauschinger M, Noutsias M, et al. Viral persistence in myocardium is associated with progressive cardiac dysfunction. *Circulation.* 2005;112:1965–1970.
19. Ammirati E, Veronese G, Bottiroli M, et al. Contemporary management of myocarditis: diagnostic and therapeutic updates. *Eur J Heart Fail.* 2024;26:1–15.
20. Ammirati E, Cipriani M, Lilliu M, et al. Clinical presentation and outcome of myocarditis. *Eur J Heart Fail.* 2020;22:2117–2125.
21. McCarthy RE III, Boehmer JP, Hruban RH, et al. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. *N Engl J Med.* 2000;342:690–695.
22. Blauwet LA, Cooper LT. Myocarditis. *Prog Cardiovasc Dis.* 2010;52:274–288.
23. Frustaci A, Russo MA, Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in virus-negative inflammatory cardiomyopathy. *N Engl J Med.* 2009;360:1526–1538.
24. Cooper LT, Berry GJ, Shabetai R. Giant-cell myocarditis. *N Engl J Med.* 1997;336:1860–1866.
25. Siripanthong B, Nazarian S, Muser D, et al. Recognizing COVID-19–related myocarditis: the possible pathophysiology and proposed diagnostic algorithm. *Heart Rhythm.* 2020;17:1463–1471.
26. Puntmann VO, Carerj L, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from COVID-19. *JAMA Cardiol.* 2020;5:1265–1273.
27. Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 mRNA COVID-19 vaccination. *N Engl J Med.* 2021;385:2140–2149.
28. Witberg G, Barda N, Hoss S, et al. Myocarditis after COVID-19 vaccination in patients under 40 years. *N Engl J Med.* 2021;385:1813–1822.
29. Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA vaccines. *Circulation.* 2021;144:471–484.
30. Oster ME, Shay DK, Su JR, et al. Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US. *JAMA.* 2022;327:331–340.

Vol. 51 (2026) No. 1 TIMOK MEDICAL GAZETTE Review article

IRRITABLE BOWEL SYNDROME: CLINICAL APPROACH AND THERAPEUTIC STRATEGIES

Zoran Joksimović (1), Dušan Bastać (1), Snežana Pavlović (2)

(1) INTERNAL OFFICE „DR BASTAĆ" ZAJEČAR; (2) SPECIALIST OFFICE FOR INTERNAL MEDICINE "DR PAVLOVIĆ CARDIOLOGIA" BELGRADE

Apstrakt: Irritable Bowel Syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by recurrent abdominal pain associated with changes in stool frequency and consistency. Symptoms vary in both intensity and frequency. IBS is classified into subtypes: IBS-D (diarrhea-predominant), IBS-C (constipation-predominant), mixed IBS (IBS-M), and unclassified IBS (IBS-U). The etiopathogenesis is multifactorial and includes visceral hypersensitivity, alterations in central nervous system pain processing, motility disturbances, immune activation, gut microbiota dysbiosis, and increased intestinal permeability. Psychological factors, stress, and childhood trauma further modulate symptom expression. The prevalence of IBS is estimated at 10–15% of the general population, with higher incidence in women and individuals under 50 years of age. Genetic and familial factors contribute to susceptibility, while acute gastroenteritis and post-infectious states represent important triggers. Epidemiological data suggest relatively stable prevalence over time, with spontaneous remission occurring in a subset of patients. The diagnostic approach is based on the Rome IV criteria and a positive diagnostic strategy, with exclusion of alarm symptoms and selective laboratory evaluation. Treatment is individualized according to subtype, dominant symptoms, and psychosocial burden. Core interventions include patient education, dietary modification, and pharmacotherapy, while neuromodulators, probiotics, and psychological interventions play an important role in patients with marked visceral hypersensitivity or refractory symptoms. Understanding IBS through a biopsychosocial model enables a rational and personalized approach to diagnosis and therapy, aiming to reduce symptoms, improve functional status, and enhance quality of life. Psychological therapies and complementary approaches, including cognitive-behavioral therapy, hypnotherapy, and stress-reduction techniques, contribute to long-term improvement in patients' quality of life.

Key words: irritable bowel syndrome (IBS), abdominal pain, constipation, diarrhea

INTRODUCTION

Irritable Bowel Syndrome (IBS) is a chronic disorder of gut–brain interaction, clinically characterized by recurrent abdominal pain associated with changes in stool frequency and/or consistency. According to the modern classification of functional gastrointestinal disorders, IBS belongs to the group of disorders of gut–brain interaction, in which symptoms occur in the absence of structural, biochemical, or inflammatory abnormalities that would fully explain them. The diagnosis is based on clinical criteria, with exclusion of alarm features suggestive of organic disease [1].

Although traditionally labeled as a "functional" disorder, contemporary research indicates that IBS is not synonymous with the absence of pathophysiological changes, but rather reflects dysregulation at multiple levels—neural, immune, microbiological, and neuroendocrine. The absence of clear morphological findings has often led to underestimation of the severity of the syndrome, despite its impact on quality of life being comparable to that of chronic inflammatory bowel diseases and other long-term conditions [2].

IBS is a chronic condition with a fluctuating course, characterized by periods of exacerbation and remission. Symptoms often include bloating, a sensation of incomplete evacuation, urgency, or straining during defecation, and their severity does not necessarily correlate with objective laboratory or endoscopic findings. This discrepancy between subjective symptom intensity and minimal diagnostic abnormalities represents one of the main challenges in everyday clinical practice.

A particular dimension of the syndrome is the high frequency of extraintestinal manifestations. Patients commonly report chronic pain

syndromes, including fibromyalgia, chronic pelvic pain, and tension-type headaches, as well as chronic fatigue syndrome, temporomandibular joint disorders, non-cardiac chest pain, and urinary symptoms. Anxiety and depressive disorders are also more prevalent in this population. This comorbidity suggests shared mechanisms of central sensitization and altered pain processing, further supporting the systemic nature of the disorder..

The modern approach to IBS shifts the focus from purely gastrointestinal symptoms toward a broader concept of dysregulation of the brain–gut axis. The interaction between the enteric nervous system, autonomic regulation, microbiota, immune response, and psychological factors shapes the individual disease phenotype. This understanding has direct therapeutic implications, as it explains why a universal treatment approach often yields limited results and why personalization of therapy is of particular importance [3].

Although IBS does not increase mortality nor lead to progressive intestinal damage, its public health impact is significant. The syndrome is associated with frequent medical consultations, extensive diagnostic workups, and reduced work productivity. The psychological burden, stigmatization, and chronic nature of symptoms further impair patients' quality of life [4].

Understanding IBS requires an integrative approach that combines clinical criteria, epidemiological data, and contemporary insights into pathophysiological mechanisms. In this context, irritable bowel syndrome should not be viewed as a single disease, but rather as a heterogeneous clinical entity with varying dominant mechanisms, which opens the door to more precise diagnostic and therapeutic strategies.

Epidemiology Irritable Bowel Syndrome (IBS) is one of the most common gastrointestinal disorders in the general population. Population-based studies estimate the prevalence of IBS at 10% to 15%, with an annual incidence of approximately 1–2%. Prevalence varies significantly between countries. The lowest prevalence has been reported in France (1.1%), while the highest has been reported in Mexico (35.5%); a prevalence of 7.1% has been observed in the USA, Europe, Australia, and New Zealand.

Approximately 50% of individuals with IBS report symptom onset before the age of 35. Adolescent girls and young adult women are most commonly affected. In Western countries, women are 2–3 times more likely to develop IBS than men, whereas in the Indian subcontinent men account for 70–80% of IBS patients [5].

Differences in prevalence are partly explained by methodological factors, including the use of different versions of the Rome criteria, as well as cultural and healthcare-seeking behaviors. Geographic variation is evident, with higher prevalence in parts of Asia and some European countries, while lower rates have been reported in other regions. The reasons for these differences likely include hormonal factors, variations in pain perception and processing, and differences in healthcare utilization patterns.

The syndrome is most commonly diagnosed in individuals under 50 years of age, while prevalence is lower in older populations. This may reflect spontaneous remission in some patients, as well as changes in symptom perception or healthcare-seeking behavior. The highest prevalence has been observed among educated individuals, higher-income groups, students, and younger populations [6]. Nevertheless, IBS is a universally present disorder regardless of ethnic or cultural background, confirming its multifactorial nature.

Familial aggregation of IBS suggests a genetic component, but also the influence of shared environmental factors. Studies show that IBS is approximately twice as common in first-degree relatives compared with the general population. However, the exact contribution of genetic factors versus learned behavioral patterns and shared stressors remains under investigation.

A significant epidemiological entity is post-infectious IBS. Following acute gastroenteritis, the risk of developing chronic IBS-like symptoms is markedly increased. This risk is particularly pronounced after severe infections, prolonged symptom duration, and the presence of psychological stressors during recovery. Triggered by bacterial or viral infections, it involves persistent low-grade inflammation, altered intestinal permeability, and microbiota changes, clearly demonstrating the link between inflammation, immune activation, and long-term alterations in neuromuscular gut function [7].

Psychosocial factors also have epidemiological importance. Chronic stress, childhood trauma, and adverse life events are associated with a higher risk of IBS development and a more

severe disease course. These factors do not act in isolation but rather through modulation of the brain–gut axis and visceral signal perception [8].

The natural course of IBS is variable. In population studies, prevalence remains relatively stable over time, but 10–40% of patients experience symptom remission during long-term follow-up. IBS rarely progresses to organic disease and is not associated with increased mortality, but it is linked to significantly reduced quality of life and increased healthcare resource utilization [9].

Etiopathogenesis The etiopathogenesis of irritable bowel syndrome (IBS) is not fully understood, but it is now considered the result of a complex interaction between genetic, neurobiological, immunological, microbiological, and psychosocial factors. The contemporary concept is based on the biopsychosocial model, according to which genetic predisposition, combined with environmental factors such as acute gastrointestinal infections, chronic stress, and adverse early-life events, leads to dysregulation of the brain–gut axis. IBS is therefore viewed as a disorder of regulation rather than structure, with pathophysiological mechanisms varying in intensity and combination among different patient subtypes [10].

One of the central mechanisms is visceral hypersensitivity. In approximately 60% of patients, a reduced threshold for perception of mechanical and chemical stimuli in the gastrointestinal tract has been demonstrated. Peripheral sensitization of enteric neurons, as well as enhanced central pain processing, leads to increased perception of otherwise physiological stimuli. Neuroimaging studies of the central nervous system show increased activation of the anterior cingulate cortex and amygdala—regions involved in emotional pain processing—along with reduced activation of the prefrontal cortex, which is involved in cognitive modulation. These changes indicate central amplification of visceral signals and explain why pain in IBS is not proportional to objective findings [11].

Low-grade immune activation represents another important mechanism. This is particularly evident in post-infectious IBS, where increased infiltration of T lymphocytes and mast cells in the intestinal mucosa has been documented. Mast cells, through the release of histamine, proteases, and cytokines, contribute to peripheral neuronal sensitization and disruption of epithelial barrier function. Increased luminal protease activity further enhances activation of the enteric nervous system. This microinflammation, although mild, may have long-term effects on neuromuscular gut function [12].

Disturbances in the serotonergic system also play a significant role. Serotonin (5-HT), synthesized in enteroendocrine cells, is a key regulator of intestinal motility, secretion, and sensory function. In IBS patients, altered serotonin metabolism has been described, contributing to changes in gastrointestinal transit. Motor disturbances include increased activity in fasting and postprandial states, as well as altered responses to stress. Accelerated transit is present in approximately half of patients with diarrhea-predominant IBS (IBS-D), while delayed transit is characteristic of a subset of patients with constipation-predominant IBS (IBS-C). In about one-quarter of IBS-D patients, increased colonic bile acid exposure has been observed, contributing to enhanced secretion and motility, while reduced bile acid availability is associated with a constipation phenotype [13].

The gut microbiota represents another key element in pathogenesis. Meta-analyses have demonstrated altered gut microbiota composition in IBS patients compared with healthy controls, with reduced diversity and changes in the abundance of specific bacterial taxa. Dysbiosis may affect serotonin synthesis, immune modulation, short-chain fatty acid production, and epithelial barrier integrity. Studies showing symptom improvement after administration of certain antibiotics or probiotics further support the role of the microbiota in the syndrome. Increased intestinal permeability, documented in a subset of patients, represents an important link between stress, microbiota, and immune activation, allowing increased antigen translocation and immune sensitization [14].

Psychological factors and stress have a significant modulatory effect. Chronic stress, childhood trauma, and maladaptive coping mechanisms—such as catastrophic thinking and persistent fear and hypervigilance—are associated with increased symptom perception. Activation of the hypothalamic–pituitary–adrenal (HPA) axis leads to the release of corticotropin-releasing factor (CRF), which influences autonomic regulation, motility,

secretion, and immune response. Experimental models show that acute stress increases visceral sensitivity and intestinal permeability. Dominance of the sympathetic over the parasympathetic nervous system is more frequently observed in patients with more severe symptoms, although a causal relationship remains insufficiently defined [15].

Genetic predisposition represents an additional risk factor. Twin studies show higher concordance of IBS symptoms in monozygotic compared to dizygotic twins. Genome-wide analyses have identified gene variants associated with ion channel function, autonomic regulation, smooth muscle contractility, and mechanical sensitivity. In a smaller subset of patients, mutations in the sucrase–isomaltase gene have been described, leading to carbohydrate malabsorption and a clinical presentation resembling IBS.

Overall, IBS is a heterogeneous syndrome in which neural, immunological, microbiological, and psychoneuroendocrine mechanisms are interrelated. Different combinations and varying dominance of individual pathophysiological pathways likely explain the clinical heterogeneity of the syndrome and the variability in therapeutic response. This understanding of etiopathogenesis opens the possibility for a personalized therapeutic approach based on identifying the dominant mechanism in each individual patient.

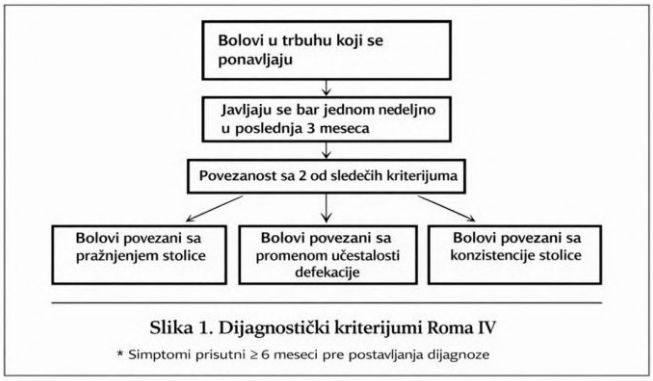
Diagnostic approach

The modern diagnostic approach to irritable bowel syndrome (IBS) is based on the concept of establishing a positive clinical diagnosis rather than relying solely on exclusion. This approach aims to reduce unnecessary diagnostic procedures, shorten the time to treatment initiation, and decrease patient anxiety.

Management of IBS requires a thorough medical history, clinical evaluation, review of previous diagnostic tests, and careful follow-up. Approximately half of IBS patients present with extraintestinal symptoms, including headache (23–45%), back pain (27–81%), fatigue (36–63%), myalgia (29–36%), and urinary symptoms (21–61%). Extraintestinal symptoms are more common in women, particularly during menstruation. Depending on symptom severity and disease burden, patients are divided into three groups according to an IBS symptom severity scale. Patients with mild symptoms are usually managed in primary care, as their quality of life is not significantly impaired. The moderate group is managed at the secondary care level, while patients with severe symptoms are typically treated in tertiary care centers [16].

Diagnosis is based on the Rome IV criteria, which require persistent symptoms over the last 3 months, with symptom onset at least 6 months prior to diagnosis. The sensitivity and specificity of these diagnostic criteria are 62.7% and 97.1%, respectively.

The defining feature is recurrent abdominal pain, occurring on average at least one day per week over the last 3 months, associated with at least two of the following criteria: (1) related to defecation, (2) associated with a change in stool frequency, and (3) associated with a change in stool form/consistency (Figure 1) [9**]**..

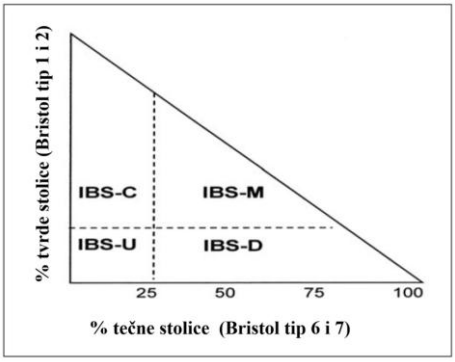


Slika 1. Dijagnostički kriterijumi Roma IV

Other symptoms in addition to abdominal pain include: (1) abnormal stool frequency (<3 bowel movements per week or >3 bowel movements per day), (2) straining during defecation, (3) urgency or a sensation of incomplete evacuation, and mucus discharge [17].

According to the predominant symptoms accompanying chronic abdominal pain over the

last 3 months, IBS is classified into four subtypes:
IBS with predominant constipation (IBS-C) – more than 25% of bowel movements with Bristol Stool Scale types 1 or 2, and less than 25% with types 6 or 7.
IBS with predominant diarrhea (IBS-D) – more than 25% of bowel movements with Bristol Stool Scale types 6 or 7, and less than 25% with types 1 or 2.
Mixed IBS (IBS-M) – more than 25% of bowel movements with Bristol Stool Scale types 1 or 2, and more than 25% with types 6 or 7.
Unclassified IBS (IBS-U) – patients fulfilling diagnostic criteria for IBS that cannot be classified into any of the above subtypes (Figure 2). [9].



Slika 2. Podtipovi sindroma iritabilnog creva

A key component of the initial evaluation is the identification of alarm symptoms that may indicate organic disease. These include unexplained weight loss, gastrointestinal bleeding, anemia, nocturnal symptoms, a family history of colorectal cancer or inflammatory bowel disease, and onset of symptoms after the age of 50. The presence of these features requires an extended diagnostic workup, including endoscopic and radiological investigations.
In patients without alarm symptoms, a limited initial laboratory evaluation is recommended. This typically includes a complete blood count, C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), as well as serological testing for celiac disease, particularly in patients with diarrhea-predominant symptoms. Fecal calprotectin is a useful non-invasive biomarker for differentiating IBS from inflammatory bowel disease, as normal values with high probability exclude active intestinal inflammation [1].
Endoscopic evaluation is not routinely indicated in younger patients without alarm features. However, colonoscopy is recommended in individuals over 50 years of age according to colorectal cancer screening guidelines, as well as in patients with persistent or atypical symptoms. In patients with chronic diarrhea, colonic biopsies should be considered to exclude microscopic colitis, even in the absence of macroscopic abnormalities.
The differential diagnosis of IBS depends on the dominant clinical phenotype. In IBS-D, inflammatory bowel disease, celiac disease, infections, and bile acid malabsorption should be excluded. In IBS-C, differential diagnoses include primary motility disorders, hypothyroidism, and drug-induced constipation. Small intestinal bacterial overgrowth (SIBO) remains a controversial diagnosis but may be considered in patients with prominent bloating and refractoriness to standard therapy.
An important aspect of the diagnostic process is the assessment of psychosocial factors. Anxiety, depression, and chronic stress do not represent merely comorbidities, but can also modulate symptom intensity and therapeutic response. Structured evaluation of psychological burden may help individualize the therapeutic approach. Overdiagnosis may have negative consequences, including increased healthcare costs and heightened health-related anxiety. Therefore, a rational, stepwise approach is of particular importance. After a careful medical history, physical examination, and basic laboratory testing, a reliable diagnosis of IBS can be established in patients without alarm features, allowing treatment initiation without additional invasive procedures.
The modern diagnostic concept of IBS thus reflects an understanding of the syndrome as a disorder of regulation, in which the clinical symptom pattern is of central importance. This

approach enables faster identification of disease subtypes, reduces unnecessary interventions, and forms the basis for a personalized therapeutic plan.

Treatment of Irritable Bowel Syndrome

Therapeutic management of IBS is based on a combination of patient education, dietary measures, pharmacotherapy, and, when necessary, psychological interventions. Due to the heterogeneity of pathophysiological mechanisms, treatment must be individualized and directed toward the dominant subtype (IBS-C, IBS-D, IBS-M, IBS-U), as well as the severity of pain, bloating, and psychosocial factors.

General principles of therapy

Patient education is the cornerstone of treatment. Explaining the benign nature of the condition and the role of the brain–gut axis reduces anxiety and improves adherence. It is important to emphasize that IBS has a chronic, fluctuating course and that the goal of therapy is symptom control and improvement of quality of life, rather than complete cure.

Dietary measures: The assumption that IBS symptoms are strictly diet-related is often overestimated, and elimination diets and fiber supplementation rarely provide long-term symptom improvement. A low-FODMAP diet, which restricts fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, may improve symptoms in about one in five patients by reducing bloating and abdominal pain [18].

Individual assessment of intolerance to lactose, fructose, and other fermentable carbohydrates may be useful. However, overly restrictive diets should be avoided due to the risk of nutritional deficiencies and negative effects on the gut microbiota.

Lifestyle modifications (regular physical activity, adequate sleep, and stress management) may contribute to symptom relief. In patients with moderate to severe symptoms, a combination of pharmacological and non-pharmacological approaches is often required [9].

Pharmacological treatment of IBS-C (constipation-predominant IBS)

The goals of therapy are to increase stool frequency and improve stool consistency, while reducing pain and bloating.

Fiber (psyllium, methylcellulose, calcium polycarbophil) is first-line therapy. Meta-analyses show moderate efficacy. Wheat bran has not demonstrated significant benefit.

Osmotic laxatives (PEG, magnesium-containing mineral waters) improve stool consistency and reduce straining, but have limited effect on pain and bloating. Lactulose and sorbitol are not recommended due to bloating. Stimulant laxatives (senna, bisacodyl) are used short-term.

In patients with persistent symptoms, secretagogues and pro-secretory agents are used:

Lubiprostone (ClC-2 channel activator) improves stool consistency and reduces pain; common adverse effects include nausea and diarrhea.

Plecanatide (guanylate cyclase-C agonist) increases intestinal secretion and reduces visceral hypersensitivity, with beneficial effects on abdominal pain.

Tenapanor (Na^+/H^+ exchanger inhibitor) increases stool water content and reduces abdominal pain.

Tegaserod (5-HT4 agonist) may be considered in women under 65 years without cardiovascular risk.

Prucalopride, a selective 5-HT4 receptor agonist, stimulates colonic peristalsis and is particularly useful in chronic constipation with poor response to previous treatments.

For prominent abdominal pain and visceral hypersensitivity, especially in the presence of anxiety or depression, SSRIs (selective serotonin reuptake inhibitors) or SNRIs (serotonin–norepinephrine reuptake inhibitors) may be used, while TCAs (tricyclic antidepressants) can be beneficial in patients with pain and slow intestinal transit..

Irritable Bowel Syndrome (IBS)

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder characterized by recurrent abdominal pain associated with changes in stool frequency and/or stool consistency. Symptoms vary in intensity and frequency. IBS is classified into subtypes: IBS-D (diarrhea-predominant), IBS-C (constipation-predominant), mixed IBS (IBS-M), and unclassified IBS (IBS-U).

The etiopathogenesis is multifactorial, including visceral hypersensitivity, alterations in central nervous system processing of signals, motility disturbances, immune activation, microbiota dysbiosis, and increased intestinal permeability. Psychological factors, stress, and childhood trauma further modify symptom expression. The prevalence of IBS is estimated at 10–15% of the

general population, with higher frequency in women and individuals younger than 50 years.
Genetic and familial factors contribute to susceptibility, while acute gastroenteritis and post-infectious forms represent important etiological triggers. Epidemiological data suggest a relatively stable prevalence over time, with spontaneous remission occurring in a subset of patients. IBS does not increase mortality but is associated with reduced quality of life and increased healthcare utilization.
Biopsychosocial Model and Clinical Significance
Modern understanding of IBS shifts the focus from purely gastrointestinal symptoms toward a broader concept of brain–gut axis dysregulation. Interactions between the enteric nervous system, autonomic regulation, microbiota, immune responses, and psychological factors shape the individual disease phenotype. This explains why uniform therapeutic approaches often yield limited results and highlights the importance of personalized treatment strategies.
Although IBS does not lead to structural intestinal damage or increased mortality, it represents a significant public health burden due to frequent medical consultations, diagnostic procedures, reduced productivity, and impaired quality of life. Psychological distress, stigma, and the chronic nature of symptoms further contribute to disease burden.
IBS should therefore not be viewed as a single disease entity, but rather as a heterogeneous clinical syndrome with varying dominant mechanisms, allowing for more precise diagnostic and therapeutic approaches.
Epidemiology
IBS is one of the most common gastrointestinal disorders in the general population. Population-based studies estimate a prevalence of 10–15% and an annual incidence of 1–2%.
Prevalence varies significantly across countries, ranging from 1.1% in France to 35.5% in Mexico, while a pooled prevalence of 7.1% has been reported in the USA, Europe, Australia, and New Zealand. Approximately 50% of patients report symptom onset before the age of 35.
IBS is more common in young adult women; in Western countries, women are 2–3 times more likely to be affected than men, whereas in some regions (e.g., the Indian subcontinent), men may predominate among diagnosed cases.
The syndrome is most frequently diagnosed in individuals under 50 years of age. Familial aggregation suggests a genetic contribution, although shared environmental factors also play a significant role. Post-infectious IBS is an important subtype, developing after acute gastroenteritis and involving low-grade inflammation, altered permeability, and microbiota changes.
Psychosocial factors such as chronic stress and early-life trauma significantly influence both risk and symptom severity. The natural course is variable, with symptom remission in 10–40% of patients, while mortality is not increased.
Etiopathogenesis
The etiopathogenesis of IBS is not fully understood, but it is considered the result of complex interactions among genetic, neurobiological, immunological, microbiological, and psychosocial factors. The biopsychosocial model explains IBS as a disorder of regulation rather than structure.
Visceral hypersensitivity is a key mechanism, present in approximately 60% of patients, involving both peripheral sensitization and altered central pain processing. Neuroimaging studies show increased activation of the anterior cingulate cortex and amygdala, with reduced prefrontal modulation.
Low-grade immune activation is particularly relevant in post-infectious IBS, with increased mast cells and T lymphocytes contributing to neural sensitization. Serotonergic dysregulation affects motility and secretion, while bile acid malabsorption contributes to diarrhea in IBS-D.
Alterations in gut microbiota (dysbiosis) influence immune activation, serotonin metabolism, and epithelial barrier integrity. Increased intestinal permeability may allow antigen translocation and immune activation.
Psychological factors, including chronic stress and early-life trauma, modulate symptoms via the hypothalamic–pituitary–adrenal (HPA) axis, leading to altered motility, secretion, and visceral sensitivity.
Genetic studies suggest heritability, with involvement of genes related to ion channels, smooth muscle function, and autonomic regulation.
Diagnosis
The modern diagnostic approach is based on a positive diagnosis using Rome IV criteria, rather than exclusion alone. IBS is defined by recurrent abdominal pain occurring at least 1 day per week over the past 3 months, associated with at least two of the following: relation to defecation,

change in stool frequency, or change in stool form.

Alarm features (weight loss, bleeding, anemia, nocturnal symptoms, family history of colorectal cancer/IBD, or onset after age 50) require further investigation.

Basic evaluation includes blood tests (CBC, CRP/ESR), celiac serology, and fecal calprotectin. Endoscopy is not routinely required in young patients without alarm features.

IBS is classified into IBS-C, IBS-D, IBS-M, and IBS-U based on stool patterns (Bristol Stool Scale).

Psychosocial assessment is an important part of diagnosis, as anxiety, depression, and stress significantly influence symptom severity.

Treatment

Treatment is individualized and based on symptom predominance.

General principles

Education is essential, emphasizing the benign but chronic nature of IBS and the role of the brain–gut axis. Dietary and lifestyle modifications include physical activity, sleep regulation, and stress management.

A low-FODMAP diet may improve symptoms in approximately 20% of patients. Excessively restrictive diets should be avoided.

IBS-C (Constipation-predominant)

First-line therapy includes dietary fiber (psyllium, methylcellulose). Osmotic laxatives (PEG) improve stool consistency. Secretagogues and prokinetics include lubiprostone, plecanatide, tenapanor, tegaserod, and prucalopride.

Antidepressants (SSRIs, SNRIs, TCAs) may be used for pain and visceral hypersensitivity.

IBS-D (Diarrhea-predominant)

Loperamide is first-line therapy. Eluxadoline reduces diarrhea and pain but is contraindicated in patients without a gallbladder.

Rifaximin improves bloating and global symptoms. Bile acid sequestrants are used in suspected bile acid malabsorption.

5-HT3 antagonists (alosetron, ondansetron, ramosetron) are used in refractory cases.

Antispasmodics and neuromodulators are also effective for pain.

IBS-M and IBS-U

Treatment is symptom-driven and flexible. Neuromodulators and antispasmodics play a central role. Probiotics (especially Bifidobacterium strains) may improve symptoms in a subset of patients.

Neuromodulators and Psychological Therapy

Neuromodulators (TCAs, SSRIs, SNRIs) act on the brain–gut axis and reduce visceral hypersensitivity.

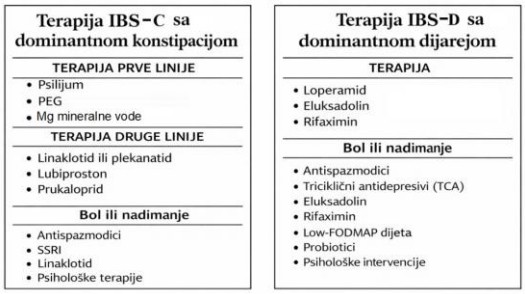
Psychological therapies include cognitive-behavioral therapy (CBT), gut-directed hypnotherapy, relaxation techniques, and stress management programs. CBT is the most extensively studied and has demonstrated significant efficacy in reducing symptom severity and improving quality of life..

Gut-directed hypnotherapy acts through central mechanisms of modulation of visceral perception. Studies demonstrate clinically significant improvement in symptoms after 6–12 weeks of therapy. Relaxation techniques may improve quality of life, although their effect on core IBS symptoms is less consistent.

Due to the chronic course of the disease, many patients turn to complementary medicine. Acupuncture, according to available analyses, is likely not superior to placebo. Evidence for herbal treatments is limited, although some studies suggest potential benefit from individualized approaches.

IBS treatment must be personalized. The foundation consists of patient education, rational dietary intervention, and targeted pharmacotherapy. In cases of pronounced central sensitization and psychological comorbidities, the combination of neuromodulators and psychological interventions often yields the best results. This individualized and combined approach reflects the modern understanding of IBS as a heterogeneous disorder of brain–gut axis regulation and enables optimal symptom control with minimal therapeutic burden for the patient [1].

A schematic overview of the therapeutic approach for IBS-C and IBS-D is shown in Figure 3..



Slika 3. Terapija IBS sa dominantnom konstipacijom i sa dominantnom dijarejom

Conclusion> Irritable bowel syndrome (IBS) is a common and chronic functional gastrointestinal disorder that significantly impairs patients' quality of life. In patients who fulfill the Rome IV diagnostic criteria and do not present alarm features, the diagnosis can be established based on a carefully obtained medical history, analysis of typical clinical symptoms, and physical examination, without the need for extensive diagnostic testing. In contrast, the presence of alarm symptoms, onset after the age of 50, a positive family history of colorectal cancer, or suspicion of celiac disease or chronic inflammatory bowel disease requires additional laboratory, imaging, and endoscopic evaluation.

Management of IBS begins with a clear explanation of the nature of the disorder and reassurance that it is not a malignant or life-threatening condition. Treatment is long-term and individualized, targeting predominant symptoms and their severity. The foundation of therapy includes patient education, dietary measures, and targeted pharmacotherapy, while neuromodulators and psychological interventions play an important role in patients with pronounced visceral hypersensitivity and psychological comorbidities.

Successful management requires continuous and constructive collaboration between the patient and the physician, with involvement of other specialists when necessary. A multidisciplinary and personalized approach reflects the modern understanding of IBS as a disorder of brain–gut axis regulation and enables optimal symptom control while preserving quality of life..

Literature:

1. Huang KY, Wang FY, Lv M, Ma XX, Tang XD, Lv L. **Irritable bowel syndrome: Epidemiology, overlap disorders, pathophysiology and treatment.** World J Gastroenterol. 2023 Jul 14;29(26):4120-4135
2. Videlock EJ, Chang L. **Irritable bowel syndrome, In: Wang TC, Camilleri M, eds. Yamada's Textbook of Gastroenterology: Seventh edition.** New York: Wiley; 2022. p. 1374–407.)
3. Chey WD, Kurlander J, Eswaran S: **Iritable bowel syndrome: a clinical review**. JAMA 2015;313:945–58.
4. Ford AC, et al. **Evidence-based clinical practice guidelines for irritable bowel syndrome.** Nat Rev Gastroenterol Hepatol. 2020;17:458–476.
5. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. *Clin Epidemiol*. 2014. 6:71-80.
6. Husain N, Chaudhry IB, Jafri F, Niaz SK, Tomenson B, Creed F. **A population-based study of irritable bowel syndrome in a non-Western population.** Neurogastroenterol Motil. 2008;20:1022–1029. doi: 10.1111/j.1365-2982.2008.01143.x. *).*
7. Thabane M, Marshall JK. **Post-infectious irritable bowel syndrome.** World J Gastroenterol. 2009 Aug 7;15(29):3591-6.)
8. Ballou S, Bedell A, Keefer L. **Psychosocial impact of irritable bowel syndrome: A brief review.** World J Gastrointest Pathophysiol. 2015 Nov 15;6(4):120-3.
9. Štabuc B. **Sindrom razdražljivega črevesa - najpogosteša funkcionalna črevesna bolezen** Slovenian Journal of Gastroenterology / Gastroenterolog 2024; 3: 52–6
10. Tang HY, Jiang AJ, Wang XY, et al. **Uncovering the pathophysiology of irritable bowel syndrome by exploring the gut-brain axis: a narrative review**. *Ann Transl Med*. 2021 Jul. 9(14):1187).
11. Van den Houte K, Bercik P, Simren M, Tack J, Vanner S. **Mechanisms underlying food-triggered symptoms in disorders of gut-brain interactions**. *Am J Gastroenterol*. 2022 Jun 1. 117(6):937-46.
12. Gao J, Xu K, Liu H, et al. Impact of the gut microbiota on intestinal immunity mediated by tryptophan metabolism. *Front Cell Infect Microbiol*. 2018. 8:13. [
13. 13 Camilleri M. Physiological underpinnings of irritable bowel syndrome: neurohormonal mechanisms. *J Physiol*. 2014 Jul 15. 592(14):2967-80
14. Kim GH, Lee K, Shim JO. **Gut bacterial dysbiosis in irritable bowel syndrome: a case-control study and a cross-cohort analysis using publicly available data sets**. *Microbiol Spectr*. 2023 Feb 14. 11(1):e0212522.
15. Ng QX, Yaow CYL, Moo JR, Koo SWK, Loo EXL, Siah KTH. **A systematic review of the association between environmental risk factors and the development of irritable bowel syndrome**. J Gastroenterol Hepatol. 2024 May 3.
16. Francis CY, Morris J, Whorwell PJ. **The irritable bowel scoring system: a simple method of monitoring IBS and its progress**. Aliment Pharmacol Therapeut 1997;11:395–402.
17. Palsson OS, Whitehead WE, Miranda AL, Chang L, Chey W, Crowel MD. **Development and validation of the Rome IV diagnostic questionnaire for adults. Bowel disorders.** Gastroenterology 2016;150:1481–91.)
18. Bijkerk CJ, de Wit NJ, Muris JWM, Whorwell PJ, Knottnerus JA, Hoes AW. **Soluble or insoluble fibre in irritable bowel syndrome in primary care? Randomised placebo controlled trial**. BMJ 2009;339:b3154.

Vol. 51 (2026) No. 1 TIMOK MEDICAL GAZETTE Review article

CONTEMPORARY APPROACH TO THE DIAGNOSIS AND TREATMENT OF PRECOCIOUS PUBERTY IN CHILDREN: A LITERATURE REVIEW

Bratimirka Jelenković (1), Brankica Vasić (2)

(1) Pediatric Practice "Lazarica Pediatrics", Zaječar; (2) Children's Department, Health Center Zaječar

Summary: Introduction: Precocious puberty (PP) is defined as the onset of secondary sexual characteristics before the age of 8 years in girls and before 9 years in boys. The main clinical challenge is the differentiation between central precocious puberty (CPP), caused by premature activation of the hypothalamic–pituitary–gonadal axis, peripheral precocious puberty (PPP), and benign variants of pubertal development. Aim: To systematize current diagnostic approaches, evaluate the effectiveness of therapeutic protocols, and accurately differentiate pathological conditions from benign developmental variants. Diagnostics: The diagnostic algorithm is primarily based on anthropometric assessment (growth velocity > 7 cm/year) and radiological evaluation of bone maturation, where advanced bone age ≥ 2 SD represents a key indicator of progression. Additional criteria include pelvic ultrasound findings, with uterine volume > 1.8 ml suggestive of pubertal activation. The gold standard for diagnosis remains the gonadotropin-releasing hormone (GnRH) stimulation test, with a peak LH value > 5 IU/L confirming CPP. A special focus is placed on differentiating progressive forms from benign variants such as isolated thelarche and adrenarche, in order to avoid unnecessary therapeutic intervention. Treatment: Modern management of CPP involves the use of GnRH agonists (triptorelin, leuprolide) in depot formulations, which suppress pubertal progression by desensitizing pituitary GnRH receptors. Conclusion: Early diagnosis and timely initiation of therapy result in a significant improvement in final adult height (average gain of 0.63 SDS). Effective management requires an interprofessional approach and clear differentiation between normal developmental variants and pathological entities.

Keywords: Central precocious puberty, GnRH test, GnRH agonists, bone age, Tanner stages.

INTRODUCTION: NEUROENDOCRINE CONTROL AND PHYSIOLOGY

1. Hypothalamic–Pituitary–Gonadal (HPG) Axis

Puberty is the result of reactivation of the hypothalamic–pituitary–gonadal (HPG) axis [1]. This complex process occurs through three key phases:

Fetal activation:

The HPG axis becomes active between the 12th and 14th week of gestation, but is suppressed toward the end of pregnancy by placental hormones [1].

Mini-puberty:

A short-term reactivation of the axis occurs immediately after birth due to the removal of placental inhibition. It lasts up to 6 months in boys, while in girls estradiol levels may fluctuate up to 2–4 years of age, leading to transient breast enlargement [1,2].

True puberty:

Occurs when neuroendocrine mechanisms (primarily the kisspeptin system and leptin) remove central nervous system (CNS) inhibition of GnRH neurons. This triggers pulsatile secretion of gonadotropin-releasing hormone (GnRH), which stimulates the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH), thereby initiating gonadal maturation [1,3–6].

The main components of this regulatory system and their functions are summarized in Table 1..

Table 1. Components and Regulation of the HPG Axis. Source: Adapted from Sharma L, Daley SF [1]

Regulatory level	Hormone / Signal	Function and effect
Hypothalamus	GnRH (pulsatile)	Stimulates the anterior pituitary gland
Pituitary gland	LH and FSH	Stimulate the gonads to produce sex steroids and gametes
Gonads	Estrogen / Testosterone	Development of secondary sexual characteristics
Feedback loop	Negative / Positive	Regulation of hormone secretion at the hypothalamic and pituitary levels

2. Key Terms and Physiological Processes

Understanding pubertal disorders requires a clear distinction between two independent processes:

- Gonadarche:

Activation of the gonads under the influence of the HPG axis. In girls, it leads to ovarian growth and breast development (via estradiol), while in boys it leads to testicular enlargement and spermatogenesis (via testosterone) [2,7].

- Adrenarche:

Increased production of adrenal androgens (DHEA and DHEA-S). It occurs independently of the HPG axis, around 7–8 years of age, and is responsible for the development of pubic hair (pubarche), acne, and body odor.

Hormonal and physical changes in normal development

Physical changes of puberty result from sex steroid production by the gonads, and the onset of gonadarche indicates the beginning of puberty. Gonadarche is initiated by pulsatile secretion of gonadotropin-releasing hormone (GnRH), which activates the HPG axis [1–3].

Adrenarche (i.e., adrenal androgen production leading to pubic and axillary hair, body odor, and mild acne) is a separate but usually concurrent process and, by itself, does not indicate true pubertal onset in either boys or girls [8].

In girls, increased ovarian estradiol secretion leads to breast development at an average age of 10 years (range: 8–12 years). Menarche typically follows approximately 2.5 years after the onset of breast development, at an average age of 12.5 years (range: 9–15 years) [1,2,3,7,9].

In boys, testicular enlargement to at least 4 mL in volume or 2.5 cm in length is the first sign of true puberty and occurs at an average age of 11.5 years (range: 9.5–14 years) [8,10].

Peak height velocity (PHV) occurs earlier in puberty in girls and later in boys, with an average sex difference of approximately two years [11].

At the onset of menarche, approximately 95.3% (SD 1.7) of adult height has already been achieved; the remaining height gain averages 7.8 cm (SD 2.8) [12].

3. Clinical Progression (Tanner Stages)

Pubertal progression follows a predictable sequence of physiological changes that are clinically assessed using the standardized Tanner staging system (I–V) [1,13].

Detailed criteria for assessing breast development and pubic hair in girls are systematized in Table 2, while parameters for evaluating genital development and pubic hair in boys are presented in Table 3..

Table 2. Tanner Classification of Development in Girls

Stage	Breast development (B – Breast)	Pubic hair (P – Pubic hair)
1	Prepubertal: only papilla elevation	No pigmented terminal hair
2	"Breast budding" (thelarche): glandular tissue palpable	Sparse, lightly pigmented hair, mainly along labia
3	Further breast elevation without separation of contours	Darker, coarser hair over the pubic symphysis
4	Secondary mound: areola elevated above breast contour	Adult-type hair, but limited distribution
5	Adult stage: areola flush with breast contour	Adult distribution extending to medial thighs

Table 3. Tanner Classification of Development in Boys

Stage	Genital development (G – Genitals)	Pubic hair (P – Pubic hair)
1	Prepubertal: testicular volume < 4 mL	No terminal hair
2	Enlargement of scrotum and testes (≥ 4 mL)	Sparse, long hair at base of penis
3	Increase in penile length	Darker, coarser, curlier hair
4	Further penile growth in width; glans development	Dense adult-type hair with limited distribution
5	Adult genital size and morphology	Adult distribution pattern

ETIOLOGY AND CLASSIFICATION

Precocious puberty is defined as the appearance of secondary sexual characteristics before the age of 9 years in boys (or before 8 years in girls), corresponding to a chronological age approximately 2–2.5 standard deviations earlier than the average age of pubertal onset in the White population [13,14]. Its incidence ranges between 1:5,000 and 1:10,000, while its prevalence is increasing worldwide [15].

Based on the underlying pathological mechanism, precocious puberty can be classified as follows:

Central Precocious Puberty (CPP)

(Gonadotropin-dependent) – caused by early maturation of the HPG axis. It results from premature activation of the axis (GnRH-dependent) [16,2]. Etiologies include congenital abnormalities (hamartoma, cysts), acquired lesions (tumors, trauma), and genetic mutations (e.g., MKRN3). In girls, up to 90% of cases are idiopathic [2,9].

Peripheral Precocious Puberty (PPP)

(Gonadotropin-independent) – caused by excessive secretion of sex steroids from the gonads or adrenal glands, exogenous exposure to sex steroids, or ectopic production of gonadotropins from germ cell tumors.

Benign Pubertal Variants

These include non-progressive or intermittently progressive forms of CPP, as well as isolated androgen-mediated sexual characteristics in boys resulting from early activation of the hypothalamic–pituitary–adrenal axis (premature adrenarche). Both conditions may represent normal variants of pubertal development [13,14].

Differential characteristics between central and peripheral precocious puberty are summarized in Table 4.

Table 4. Differential diagnosis of central (CPP) and peripheral (PPP) puberty

Characteristic	Central puberty (CPP)	Peripheral puberty (PPP)
HPG axis	Activated (GnRH-dependent process)	Suppressed (GnRH-independent process)
Gonadotropins (LH/FSH)	Elevated or pubertal response to GnRH stimulation	Low or suppressed
Response to GnRH test	Pubertal LH response (positive pubertal pattern)	No significant LH increase
Development pattern	Progressive, consistent with biological sex	May be asynchronous, sometimes discordant with sex
Secondary sexual characteristics	Consistent with HPG axis activation	Dependent on hormone source (gonads, adrenal glands, exogenous hormones)
Most common cause	Idiopathic (especially in girls), CNS lesions, genetic mutations (e.g., MKRN3)	Ovarian/testicular cysts or tumors, congenital adrenal hyperplasia (CAH), exogenous steroid exposure, hCG-secreting tumors

Detailed description of peripheral precocious puberty (PPP):

Peripheral precocious puberty (PPP) is caused by excessive production of sex steroids from the gonads or adrenal glands, secretion of β-hCG–producing tumors, or exposure to exogenous sex hormones. Etiological causes include McCune–Albright syndrome (MAS), functional ovarian cysts (FC), Leydig cell tumors, or familial male-limited precocious puberty. Adrenal sources of androgen excess are most commonly due to adrenal tumors or congenital adrenal hyperplasia [17]. PPP is significantly less common than central precocious puberty (CPP).

Non-classic congenital adrenal hyperplasia (NCAH), most commonly due to 21-hydroxylase deficiency (CYP21A2 gene mutation), is an autosomal recessive disorder. Clinical manifestations reflect androgen excess, including premature pubic hair (pubarche), body odor, and acne before the age of 8 in girls or 9 in boys. Additional features may include accelerated linear growth during childhood and advanced bone maturation, which can ultimately result in reduced adult height due to premature epiphyseal closure [18,19,20].

MFor accurate diagnosis of NCAH, assessment of 17-hydroxyprogesterone (17-OHP) levels—often including basal and ACTH-stimulated values—is essential, as they correlate with disease severity and are used for diagnostic confirmation (see Table 5.

Table 5. Differential diagnosis of NCCAH based on 17-OHP levels. Source: Adapted from White PC, Speiser PW [21]

Category	Basal 17-OHP (ng/dL)	Stimulated 17-OHP (ng/dL)
Healthy children	< 200	< 1000
Heterozygous carriers	< 200	1000 – 3500
NCCAH (non-classic congenital adrenal hyperplasia)	> 200	> 1000 (often > 3500)

BENIGN VARIANTS (PARTIAL PRECOCIOUS PUBERTY)

Benign variants of precocious puberty include premature thelarche, premature adrenarche, and isolated premature menarche. These conditions are characterized by the appearance of isolated pubertal signs without full activation of the hypothalamic–pituitary–gonadal (HPG) axis. Importantly, bone age, growth velocity, and biochemical findings are usually within normal limits [1,8]. Sharma L and Daley SF emphasize the importance of distinguishing these conditions to reduce unnecessary diagnostic procedures [1].

Premature thelarche (PT)

The most common benign variant. It presents as unilateral or bilateral breast development in girls, typically occurring between 0–24 months of age or again around 6–8 years. No other pubertal changes are present. Clinical follow-up is recommended to monitor for progression to central puberty [1,22,23,24].

Premature adrenarche (PA)

Characterized by early adrenal androgen production, leading to pubic or axillary hair, acne, and body odor before the age of 8 years. There is no breast development or testicular enlargement. Exogenous androgen exposure, tumors, and late-onset congenital adrenal hyperplasia (CAH) must be excluded [1,24].

Isolated premature menarche

Defined as vaginal bleeding in girls younger than 8 years in the absence of other pubertal signs. It generally does not affect final adult height. Differential diagnosis must exclude sexual abuse, foreign bodies, genital tract tumors, and infections [1,24].)

Table 6. Differential diagnosis of benign variants

Condition	Main symptom	Hormonal findings	Recommendation
Premature thelarche (PT)	Isolated breast development (glandular tissue)	Estradiol normal or mildly elevated	Clinical follow-up every 3–6 months
Premature adrenarche (PA)	Pubic and/or axillary hair development	Elevated DHEA-S	Exclude NCAH and androgen-secreting tumors
Isolated premature menarche	Vaginal bleeding	Prepubertal hormone levels	Exclude local causes (infection, trauma, foreign body, tumors)
Lipomastia	Excess adipose breast tissue (no glandular proliferation)	Prepubertal hormone levels	Weight reduction and clinical observation

CLINICAL ASSESSMENT AND DIAGNOSTIC APPROACH

1. Medical history and anthropometry

A detailed clinical history is essential to distinguish true precocious puberty (PP) from benign variants. Progressive pubertal development, rapid linear growth, and advanced bone age are characteristic of true PP [1,25].

The evaluation should include:

Neurological symptoms (headache, seizures, episodes of inappropriate laughter – suggestive of hypothalamic hamartoma)

Previous head trauma, brain tumor treatment, or central nervous system (CNS) infections

Physical examination: assessment of pubic and axillary hair, signs of virilization (clitoromegaly, penile enlargement, acne), and full neurological examination

Skin examination: café-au-lait macules (suggestive of Neurofibromatosis type 1 or McCune–Albright syndrome)

Growth velocity: a growth spurt >7 cm/year with breast or testicular enlargement requires urgent evaluation [24]

2. Laboratory and radiological evaluation

Bone age (BA):

Advanced bone age >2 standard deviations (SD) compared to chronological age (CA) requires further diagnostic work-up [1,14].

Hormonal testing:

Measured using ultrasensitive assays (ICMA or ECLIA). Basal serum LH levels >0.2–0.3 IU/L may indicate pubertal activation [1].

GnRH stimulation test (gold standard):

Activation of the pubertal HPG axis is confirmed if peak LH >5 IU/L. An LH/FSH ratio <0.43 suggests a prepubertal state, while a stimulated ratio >0.66 helps differentiate progressive from non-progressive variants [1].

In girls:

Serum estradiol (E2) levels after 24-hour GnRH agonist stimulation (peak >50 pg/mL) improve diagnostic sensitivity [16,22].

In boys:

Measurement of testosterone, DHEA-S, 17-OHP, and early-morning hCG is recommended when PPP is suspected. Certain tumors may secrete hCG, which activates LH receptors and mimics central puberty [1].

Reference tables:

Reference hormone and steroid levels are presented in Table 7 and Table 8

Pelvic ultrasound criteria in girls are shown in Table 8

Differential diagnostic criteria (CPP vs benign variants) are presented in Table 9.

Table 7. Reference serum concentrations of gonadotropins and steroids. Source: Neely EK et al. [26]

Parameter	Prepubertal (Tanner stage I)	Pubertal (Tanner stage II)
LH (basal)	0.03 ± 0.03 IU/L	0.71 ± 1.04 IU/L
Estradiol	< 1.0 ng/dL	1.6 ± 0.7 ng/dL
Testosterone	< 10 ng/dL	42 ± 15 ng/dL

Table 8. Pelvic ultrasound criteria in girls

Parameter	Threshold value	Clinical significance
Uterine volume	> 1.8 mL	Sensitive marker of early CPP
Uterine length	> 3.4 cm	Indicates estrogen exposure
Ovarian volume	> 1.2 mL	Suggests gonadal activation

Table 9. Differential diagnostic criteria (CPP vs benign variants)

Parameter	Central precocious puberty (CPP)	Isolated thelarche	Isolated adrenarche
Bone age	Advanced ≥ 2 SD	Normal	Normal / mildly increased
Growth velocity	Accelerated (> 7 cm/year)	Normal	Normal
Peak LH (GnRH test)	> 5 IU/L	< 4.5 IU/L	< 4.5 IU/L

DIAGNOSTIC ALGORITHMS

ALGORITHM 1. DIAGNOSTIC APPROACH IN GIRLS WITH THELARCHE (Adapted from: Root AW. Pediatr Rev. 2000 [27])

Normal growth velocity and bone age (BA ≈ CA):

Bone age corresponds to chronological age.

Diagnosis: Isolated premature thelarche

Management: Clinical follow-up; no treatment usually required

Accelerated growth velocity and advanced bone age (BA > CA):

Bone age is advanced compared to chronological age.

Indicated test: GnRH stimulation test

Peak LH > 5 IU/L (pubertal response):

Diagnosis: Central precocious puberty (CPP)

Next step: Brain MRI to exclude CNS pathology

Low LH (prepubertal response) with ovarian cysts present:

Suspicion: McCune–Albright syndrome (MAS) or other forms of peripheral puberty

In boys, differential diagnosis requires a systematic approach presented in Algorithm 2.

ALGORITHM 2. DIAGNOSTIC EVALUATION OF BOYS WITH PRECOCIOUS PUBERTY (Adapted from: Root AW. Pediatr Rev. 2000 [27])

I. Clinical triage (growth velocity and bone age assessment)

BA ≈ CA:

Likely isolated premature adrenarche

→ Periodic clinical follow-up recommended

BA > CA:

→ Requires hormonal laboratory evaluation

II. Gonadotropin (LH) assessment

Elevated LH (pubertal response at baseline or after GnRH test):

Diagnosis: Central precocious puberty (CPP)

Mandatory: Brain MRI to exclude hypothalamic hamartoma or CNS tumors

Low LH (suppressed/prepubertal response):

Diagnosis: Peripheral precocious puberty

→ Proceed with etiological work-up

III. Differential diagnosis of peripheral precocious puberty (low LH)

Elevated 17-OHP / DHEA-S:

Suggests congenital adrenal hyperplasia (CAH) or adrenal tumors

Elevated hCG:

Suggests ectopic hCG-secreting tumors (e.g., hepatoblastoma or germ cell tumors)

High testosterone with suppressed gonadotropins and enlarged testes:

Suggests testotoxicosis (familial male-limited precocious puberty, FMPP) or Leydig cell tumor

THERAPY AND MANAGEMENT

1. Central precocious puberty (CPP)

Gold standard treatment: GnRH agonists (GnRHa) [7,24]

Goals: Maximize final adult height and reduce psychosocial stress

Early onset (<6–7 years) with rapid progression → standard indication for treatment

Formulations:

Monthly depot injections (3.75 mg)

Long-acting depot preparations (every 4–12 weeks)

Monitoring:
Clinical evaluation every 3–6 months
Bone age every 6–12 months
Target stimulated LH suppression: <2.5–4.5 IU/L
Discontinuation:
Usually around chronological age 11 years
Or when bone age reaches ~12.5 years in girls and ~14 years in boys [1,7,28]
Safety:
Therapy is considered safe
Meta-analysis shows average gain in final height of ~0.63 SDS [1]
2. Peripheral precocious puberty (PPP)
Surgery: For gonadal or adrenal tumors
NCCAH: Treated with glucocorticoids
MAS: Aromatase inhibitors and selective estrogen receptor modulators
Important note:
Children with PPP may later develop secondary CPP; in such cases, GnRH analogs should be added [1]

CONCLUSION (Practical aspects)

The main clinical sign suggesting precocious puberty is the development of breast tissue in girls and testicular enlargement (> 4 mL) in boys before 8–9 years of age.

Differential diagnosis: The priority is to distinguish benign variants from progressive central precocious puberty (CPP) in order to avoid unnecessary treatment.

Gold standard: The GnRH stimulation test combined with assessment of bone age maturation.

Brain MRI: Recommended in all cases of CPP in boys, and in girls younger than 6 years or in those with neurological symptoms.

Time is a critical factor: The best outcomes are achieved when treatment is initiated before 6 years of age.

Education: A thorough discussion with the family is essential, including explanation of normal pubertal development, treatment goals, and psychosocial aspects (peer interaction, self-esteem, and emotional well-being).

LITERATURE:

1. Sharma L, Daley SF. Precocious Puberty. [Updated 2025 Nov 7]. In: StatPearls [Internet].
2. Cheuiche AV, et al. Diagnosis and management of precocious sexual maturation. Eur J Pediatr. 2021.
3. Alghamdi A. Precocious Puberty: Types, Pathogenesis and Updated Management. Cureus. 2023.
4. Largo RH, Prader A. Somatische Pubertätsentwicklung bei Mädchen. Monatsschr Kinderheilkd. 1987.
5. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969.
6. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970.
7. Bonomi M, et al. Management of andrological disorders. J Endocrinol Invest. 2025.
8. Klein DA, et al. Disorders of Puberty: An Approach to Diagnosis and Management. Am Fam Physician. 2017.
9. Sizonenko PC. Normal sexual maturation. Pediatrician. 1987.
10. Kang E, et al. Etiology and therapeutic outcomes of children with PPP. Ann Pediatr Endocrinol Metab. 2016.
11. Luo X, et al. Long-term efficacy and safety of GnRHa treatment. Clin Endocrinol. 2021.
12. Baek JW, et al. Age of menarche and near adult height after long-term GnRHa treatment. Ann Pediatr Endocrinol Metab. 2014.
13. Wheeler MD. Physical changes of puberty. Endocrinol Metab Clin North Am. 1991.
14. Taranger J, et al. VI. Somatic pubertal development. Acta Paediatr Scand Suppl. 1976.
15. Beştaş A, et al. Evaluation of Clinical and Laboratory Findings. Indian J Endocrinol Metab. 2023.
16. Bangalore Krishna K, Garibaldi L. Critical appraisal of diagnostic laboratory tests. Front Pediatr. 2025.
17. Cavarzere P, et al. Revising LH cut-off for the diagnosis of CPP. Endocrine. 2025.
18. Witchel SF, Azziz R. Nonclassic congenital adrenal hyperplasia. Int J Pediatr Endocrinol. 2010.
19. Witchel SF. Non-classic congenital adrenal hyperplasia. Steroids. 2013.
20. Loli P, et al. Non-classical congenital adrenal hyperplasia: current insights. Endocrine. 2025.
21. White PC, Speiser PW. Congenital adrenal hyperplasia. Endocr Rev. 2000.
22. Cappa M, Chioma L. Disorders of Pubertal Development. Springer; 2021.
23. Della Manna T, et al. Premature thelarche: identification of clinical and laboratory data. Rev Hosp Clin. 2002.
24. Paparella R, et al. Precocious Puberty and Benign Variants in Female Children. Endocrines. 2025.
25. Widek T, et al. Bone age estimation with the Greulich-Pyle atlas using 3T MR images. Forensic Sci Int. 2021.
26. Neely EK, et al. Normal ranges for immunochemiluminometric gonadotropin assay. J Pediatr. 1995.
27. Root AW. Precocious puberty. Pediatr Rev. 2000.
28. Kilberg MJ, Vogiatzi MG. Approach to the Patient: Central Precocious Puberty. J Clin Endocrinol Metab. 2023.

ABBREVIATIONS:

ACTH – Adrenocorticotropic hormone
BMI – Body mass index
CNS – Central nervous system
CPP – Central precocious puberty
DHEA-S – Dehydroepiandrosterone sulfate
FSH – Follicle-stimulating hormone
GnRH – Gonadotropin-releasing hormone
GnRHa – Gonadotropin-releasing hormone agonists
HPG axis – Hypothalamic–pituitary–gonadal axis
CAH – Congenital adrenal hyperplasia
LH – Luteinizing hormone
MAS – McCune–Albright syndrome
MRI – Magnetic resonance imaging
NCAH – Non-classic congenital adrenal hyperplasia
PPP – Peripheral precocious puberty
SDS – Standard deviation score
TSH – Thyroid-stimulating hormone
BA – Bone age
CA – Chronological age
US – Ultrasound

PHLEBECTASIA OF THE INTERNAL JUGULAR VEIN- CONSERVATIVE TREATMENT: CASE REPORTS

Bojan Davidović (1), Dragoljub Živanović (2,3), Maja Zečević (2,3), Goran Janković (2)

1) GENERAL HOSPITAL BOR; 2) CLINIC FOR PEDIATRIC SURGERY, ORTHOPEDICS AND TRAUMATOLOGY, UNIVERSITY CENTER NIŠ; 3) FACULTY OF MEDICINE NIŠ

Abstract: introduction: Phlebectasia of the internal jugular vein is a rare clinical entity characterized by an isolated fusiform or saccular dilatation of the internal jugular vein, without torsion. Clinically, phlebectasia manifests as a cystic soft, painless, partially compressible non-pulsatile mass in the neck, which increases with Valsalva maneuver, during exertion, and spontaneously decreases during rest. To show that conservative treatment is the best modality for the treatment of phlebectasia in children. Results: The first patient presented is a 6-year-old boy who was diagnosed with phlebectasia of the right internal jugular vein by ultrasonography during Valsalva maneuver. The diagnosis was confirmed by magnetic resonance imaging of the neck vessels with contrast. The second patient is also a 10-year-old boy with an identical clinical course, so adequate diagnostics were performed, and the diagnosis of phlebectasia of the internal jugular vein on the right side was confirmed. The third case presented is a 5-year-old girl with a clinical presentation of phlebectasia of the right internal jugular vein, but in her case, radiological evaluation was postponed due to the decision of the parents. All patients presented with phlebectasia of the internal jugular vein were asymptomatic, so after appropriate diagnostics, conservative treatment and periodic monitoring in outpatient conditions were recommended. Conclusion: The decision on the modality of treatment of phlebectasia of the internal jugular vein in asymptomatic and some symptomatic patients involves conservative treatment and regular monitoring.
Key words: treatmant, ectasia, children.

Introduction

Phlebectasia of the internal jugular vein is a rare clinical entity characterized by isolated fusiform or saccular dilatation of the internal jugular vein without torsion (1). Clinically, phlebectasia of the internal jugular vein manifests as a cystic, soft, painless, partially compressible, nonpulsatile mass in the anterior triangle of the neck supraclavicularly anterior to the anterior border of the sternocleidomastoid muscle, which increases with the Valsalva maneuver, during exertion, coughing, crying, sneezing, and spontaneously decreases during rest (2,3).

It can occur in almost any cervicofacial vein, but most often affects the internal jugular vein (4). More often on the right side, in boys in the pediatric population (5). The differential diagnosis of neck swelling that increases with Valsalva maneuver includes laryngocele or external laryngeal diverticulum, jugular phlebectasia, brachial cyst, tumor and cyst of the upper mediastinum, and inflation of the apical bulla of the lung (6).

The diagnostic modality of first choice is ultrasound examination of the soft tissues of the neck at rest, and during the Valsalva maneuver. Magnetic resonance imaging with contrast angiography and venography of the main blood vessels of the neck is reserved for the definitive diagnosis of phlebectasia, especially in pediatric patients (7).

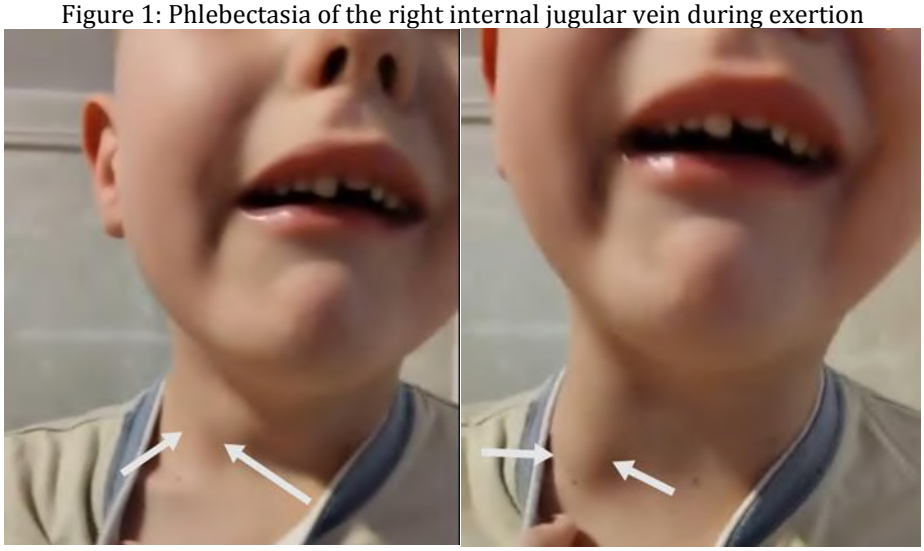
Surgical treatment is reserved for patients with complications, or for cosmetic reasons (8). The decision on the modality of treatment of phlebectasia of the internal jugular vein in asymptomatic and some symptomatic patients involves conservative treatment..

Case report 1:

A 6-year-old boy. He first presented for examination due to swelling on the right side of the neck, the change appears and increases with exertion, coughing or crying for the past month. The mother describes the appearance of a round, soft, painless change in the lower third of the right side of the neck that she noticed when the child cried. Initially, the patient was examined by a pediatrician and an otolaryngologist who, after conducting diagnostics, suspected phlebectasia of the

jugular veins. The patient had no associated diseases that could be one of the causes of phlebectasia.
Clinical examination did not reveal any change in the neck at rest, but during the Valsalva maneuver, an oval change of about 3.5x 5 cm in size appeared in front of the anterior edge of the sternocleidomastoid muscle in the lower third on the right supraclavicular side, painless on palpation, partially compressible, soft consistency, non-pulsatile, the skin above the change unchanged (Figure 1).

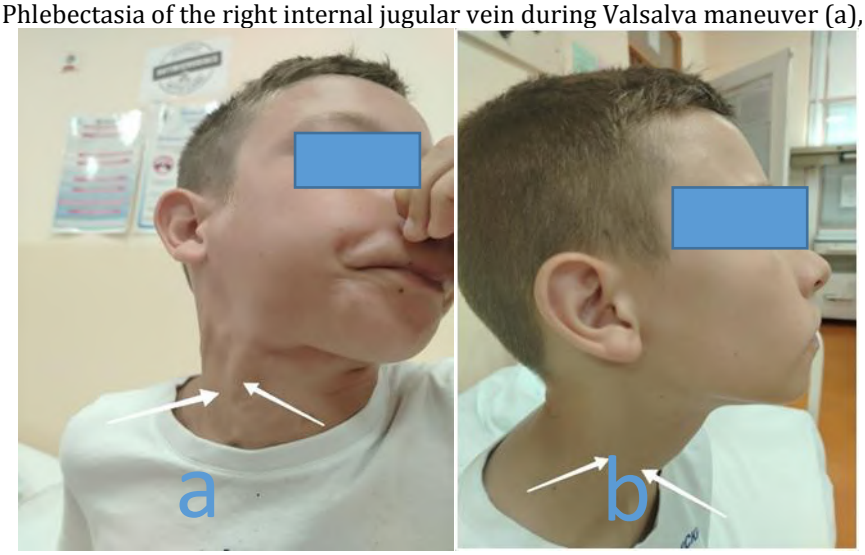
Figure 1: Phlebectasia of the right internal jugular vein during exertion



Ultrasound examination of the soft tissues of the neck at rest and during the Valsalva maneuver shows a dilated right internal jugular vein, without thrombotic masses, without tortuosity. At rest, the diameter is 12 mm, during the Valsalva maneuver it is 34 mm. The right brachiocephalic trunk is dilated to 7.5 mm. The left internal jugular vein is up to 7 mm in diameter with regular characteristics. In hospital conditions, magnetic resonance imaging of the main blood vessels of the neck with contrast was performed, which showed an ectatic right internal jugular vein predominantly in the distal part with a diameter of up to 15 mm, and a left internal jugular vein with a diameter of up to 7 mm. The jugular veins are transient, without signs of thrombosis. Due to the benign course and the absence of complications, the patient was suggested conservative treatment and a normal lifestyle. Home monitoring and periodic outpatient check-ups were suggested.

Case report 2:
A 10-year-old boy. He first presented for examination due to a tumor lesion on the outer side of the right neck, the lesion appearing and increasing predominantly during exertion for the past six months. The mother describes the appearance of a round, soft, painless lesion in the lower third of the right side of the neck that she noticed when the child was straining. The patient had no associated diseases that could be one of the causes of phlebectasia. He denies any other significant complaints (Figure 2a)

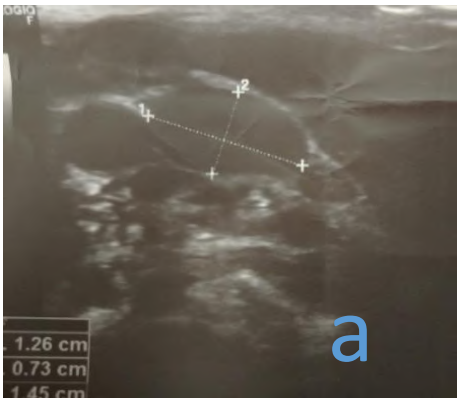
Figure 2: Phlebectasia of the right internal jugular vein during Valsalva maneuver (a), at rest (b)

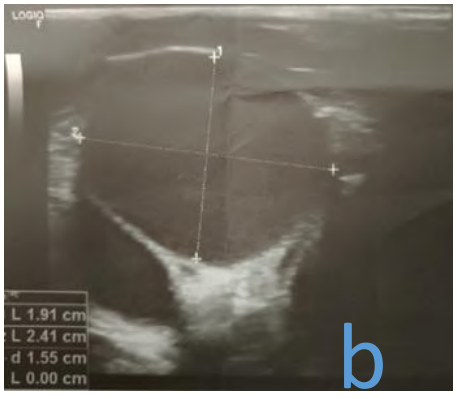


Clinical examination at rest does not reveal any changes in the neck, but during the Valsalva maneuver, an oval lesion measuring approximately 3 x 4 cm appears in front of the anterior border of the sternocleidomastoid muscle in the lower third of the right supraclavicular side, painless on palpation, partially compressible, soft consistency, non-pulsatile, the skin over the lesion unchanged (Figure 2b).

asound examination of the soft tissues of the neck at rest and during the Valsalva maneuver shows a dilated right internal jugular vein, with preserved hemodynamic flow. During the Valsalva maneuver, the maximum lumen width is 24.1 x 19.1 mm (US Figure 3a), and at rest, the lumen width is 12.6 x 7.3 mm (US Figure 3b).

Figure 3: (UZ) Ultrasonography of the main blood vessels of the neck (v. jugularis interna dex.). Cross-section during Valsalva maneuver (a), at rest (b)

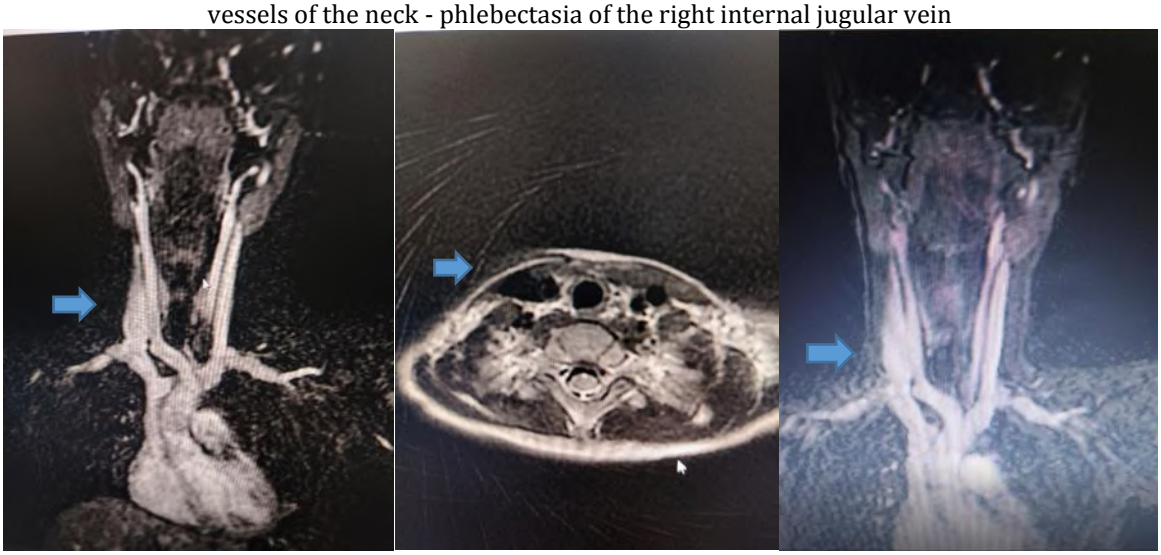




Left internal jugular vein with normal characteristics. In hospital conditions, magnetic resonance imaging of the main blood vessels of the neck was performed, which showed that the right internal jugular vein was wider along its entire length, with a maximum diameter of up to

11 mm, and the left internal jugular vein was reduced in diameter to 4 mm. The jugular veins were transient, without signs of thrombosis (MRI image 4).

Figure 4: (MR) Magnetic resonance imaging with contrast angiography and venography of the main blood vessels of the neck - phlebectasia of the right internal jugular vein



Due to the benign course and absence of complications, the patient was recommended conservative treatment and a normal lifestyle. Home monitoring and periodic outpatient check-ups were suggested.

Case report 3:

A 5-year-old girl. The parents report a change in the right side of the neck in the lower third that increases with exertion. The change is painless and does not interfere with normal life, and has been present for the past three years. The patient had no associated diseases that could be one of the causes of phlebectasia. Heteroanamnestic data are available on right-sided phlebectasia in a younger child, also female, in whom the change was seen at birth. Given the child's early infant age and the fact that the change is asymptomatic, the child has not yet had a radiological evaluation. The girl's mother was diagnosed with varicose veins in both lower legs.

Clinical examination at rest does not show any changes in the neck, but during the Valsalva maneuver, an oval change of about 2 x 3 cm in size appears in front of the anterior edge of the sternocleidomastoid muscle in the lower third on the right supraclavicular side, painless on palpation, partially compressible, soft consistency, non-pulsatile, the skin over the change unchanged.

Further diagnostics are recommended, ultrasonography of the soft tissues of the neck at rest, and during the Valsalva maneuver, as well as color Doppler of the blood vessels of the neck. It was explained to the parents that this is most often a benign condition that requires periodic monitoring in outpatient settings and parental supervision at home, in case of any complications, surgical treatment should be considered.

Discussion

Jugular vein flexure was first described by Harris in 1928 (1), and anomalous reduplication of the internal jugular vein was described by Zukschewerdh in 1929 (2). In 1952, Gerwing coined the term “phlebectasia” to describe an abnormal fusiform or saccular dilatation of the vessel (3).

Internal jugular vein phlebectasia is a rare type of vascular abnormality characterized by an isolated fusiform or saccular dilatation of the internal jugular vein without tortuosity. It is distinguished from varicosity by the absence of tortuosity, and from aneurysm by the fact that the dilatation uniformly involves the entire circumference of the vessel.

Clinically, phlebectasia of the internal jugular vein manifests as a cystic, soft, painless, partially compressible, non-pulsatile mass in the anterior triangle of the neck, visible supraclavicularly in front of the anterior edge of the sternocleidomastoid muscle. It increases with the Valsalva maneuver, during exertion, coughing, crying, sneezing, and spontaneously decreases during rest. It is most often asymptomatic and benign, more often affecting boys in a ratio of 2:1. Dysphonia or aphonia caused by pressure on the laryngeal nerve is rare, there is a feeling of humming due to turbulent blood flow in the dilated venous segment, headache, difficulty swallowing, cough on exertion, shoulder pain, phlebectasia of the internal jugular vein when moving the right arm, inability to speak loudly, pain in the root of the tongue, a feeling of tightness, suffocation and discomfort on exertion, and a feeling of a foreign body in the neck. Thrombosis, phlebitis, congestive heart failure, massive bleeding due to traumatic rupture, and Horner's syndrome are rare (9). Spontaneous rupture of phlebectasia has not been reported in pediatric patients (10).

Phlebectasia of the internal jugular vein occurs more frequently on the right side in a ratio of 5.2:1. Bilateral phlebectasia of the internal jugular vein is less common, somewhat more common in boys in a ratio of 1.4:1 (11). Possible causes of venous ectasia in the neck include gross anatomical abnormality, congenital structural defects in the vein wall, mechanical compression, or trauma, but are most often idiopathic (12). The most commonly affected internal jugular vein is the internal jugular vein, followed in descending order of occurrence by the external and anterior jugular veins, the jugular bulb, the facial vein, and the superficial communicating neck veins (13). The more frequent involvement of the right internal jugular vein is explained by anatomical differences: the shorter right brachiocephalic trunk, the higher position of the bulb of the right jugular vein, and the position and size of the valves (14). La Monte et al. hypothesized that phlebectasia of the internal jugular vein generally tends to the right because the right brachiocephalic vein is in close contact with the right apical pleura, and therefore the increase in intrathoracic pressure could be transmitted to the right internal jugular vein (15). A venous valve is almost never observed in the right brachiocephalic vein, in contrast to the left where the incidence of competent valves is 4 to 8% (16). Paleri and Gopalakrishnan presented their hypothesis that the increased intrathoracic pressure is transmitted predominantly to the right internal jugular vein due to the higher anatomically positioned valve and larger diameter of the right internal jugular vein, the shorter right brachiocephalic vein that follows the course of the superior vena cava, the greater number of competent valves in the right subclavian vein, and the greater number of valves in the left brachiocephalic vein (17). Other possible less likely causes include tracheomalacia and tracheoesophageal fistula, exposure to elevated positive intrathoracic pressure, internal jugular vein cannulation, internal jugular vein duplication, congenital primary weakness of the venous muscular layer, or loss of normal connective tissue of the vein wall. An association between internal jugular vein phlebectasia and Menkes disease has been suggested (18).

Histopathological studies have shown loss of the elastic layer and hypertrophy of connective tissue with focal intimal thickening. Histologically, diffuse fibrosis and disrupted elastic tissue architecture suggest a mechanical effect (19). Histopathological studies of surgically removed specimens show a normal varicose vein pattern in most cases, but in some cases there is loss or disruption of the arrangement of smooth muscle cells, elastic fibers, and connective tissue (20). In 1962, after surgical removal of a phlebectatic portion of the internal jugular vein, Leighton observed that smooth muscle fibers were randomly distributed in the vessel wall and that there was an island of adipose tissue extending into the tunica intima between the fibers. He called the phlebectasia a vascular hamartoma (21).

Ultrasonography is the diagnostic modality of first choice, the diagnosis of phlebectasia of the internal jugular vein is confirmed by the variation in size during rest and during Valsalva maneuver - anteroposterior diameter of more than 15 mm. During Valsalva maneuver, the diameter of the affected vein can increase up to 2.2 times compared to the measurement during rest (22). Color Doppler ultrasonography confirms the presence or absence of thrombosis in the vein lumen. Neck and chest radiography, magnetic resonance imaging of the main blood vessels of the neck and contrast-enhanced computed tomography additionally provide

even more information about the size of the lesion, anatomical relationships with other structures, and are indispensable for the definitive diagnosis of phlebectasia of the internal jugular vein, especially in pediatric patients (7). Chest and neck radiography can raise suspicion of laryngocele, or exclude the presence of air, as well as changes in the upper mediastinum. Laryngoscopy is recommended to complete the diagnosis and confirm the diagnosis of laryngocele. Invasive diagnostic radiological procedures and surgical explorations are rarely used in children, as noninvasive diagnostics confirm the diagnosis of internal jugular phlebectasia.

The diagnosis of cystic neck swelling is challenging, and the differential diagnosis in pediatric patients is broad, and in addition to phlebectasia, it includes: laryngocele, external laryngeal diverticulum, brachial cyst, cystic hygroma, cavernous hemangioma, tumors and cysts of the upper mediastinum, inflation of the pulmonary apical bulla, thyroglossal duct cyst, dermoid cyst, cervical adenopathy (23). The most common cause of a neck mass that increases with the Valsalva maneuver is laryngocele, but in children, phlebectasia of the internal jugular vein should also be considered (6).

Phlebectasia of the internal jugular vein increases in size in childhood until puberty, after which it spontaneously decreases. In asymptomatic and partially symptomatic phlebectasias, due to the benign, or self-limiting nature of the disease, the recommended treatment modality is conservative treatment with regular monitoring at home and periodic check-ups in a tertiary health care institution, most often lifelong (23).

Symptomatic phlebectasia of the internal jugular vein with complications such as thrombosis, compression of vascular structures, Horner's syndrome, or signs of rupture of the varicose vein are indications for urgent surgical intervention (24). Surgical treatment includes ligation of the varicose vein, resection of part of the phlebectatic venous wall, longitudinal venous constriction suture, coating and fixation of the varicose vein with the omohyoid muscle or an 8mm polytetrafluoroethylene tube - PTFE. (25). Cases of right-sided internal jugular phlebectasia that were treated surgically have been published, the treatment modalities are shown in the table (Table 1).

Table 1: Review of world literature - right-sided phlebectasia of the internal jugular vein.

Serial number	Author	Title of the work and year of publication	Number of patients	sex		Treatment	
1.	P.Sirivastava , V. Upadhyaya, A. Gangopadhyay, S. Sharma, R. Jaiman.	Internal Jugular Phlebectasia in Children: a Diagnostic Dilemma.The Internet Journal of Surgery. 2008	1	m	/	conservatively	/
2.	Basbug HS, Kizilgoz V.	A rare childhood entity: Massive internal jugular vein phlebectasia. Arch Basic Clin Res. 2021	1	m	/	conservatively	/
3.	Alessandro Raffaele, Marta Gazzaneo, Piero Romano, Maria Sole Prevedoni Gorone	Congenital Internal Jugular Phlebectasia: An Anomaly Still Poorly Recognized. European J Pediatr Surg 2023	1	m	/	conservatively	/
4.	Shah K. Chavan P.	Profiling of rigt Internal jugular vein phlebectasia: a rare case study. Int J Otorhinolaryngol Head Neck Surg 2024	1	m	/	conservatively	/
	Miljenko Raos, Jelica Marković	Flebektazija unutarnje jugularne vene: prikaz slučaja. 2010	1	m	/	conservatively	/
6.	Bindal SK, Vasisth GO, Chibber P.	Phlebectasia of Internal Jugular Vein. J Surg Tech Case Report 2012	1	m	/	/	Surgical (vein ligation)
7.	Dr. Pedro S. Jimenez Urueta et al.	Flebectasia de la vena jugular interna en ninos. Acta					

		pediatrica de Mexico. 2005	4	m	/	/	Surgical (PTFE)
8.	Sultan Alrabea, Anoof Eshky, Thamer Albilasi, Mazyad Alenzi and Samir Bawazir.	Internal jugular phlebectasia in pediatric patients: a report of two Saudi cases. 2021	2	m	/	conservatively	/
9.	Kandiah R. Mohamed I	The louder the bigger: A case of jugular phlebectasia in a child. Malays Fam Physician. 2019	1	m	/	conservatively	/
10.	VishnuKanth, R. Manju, Jineesh Joseph, Balla Nagamali Kumar, Abhisekh Chauhan	Jugular vein ectasia presenting with hoarseness of voise: A rare association. 2017	1	/	f	conservatively	/
11.	Karthik N. Rao, Shrinivas S. Chavan et al.	IJV Phlebectasia: an approach algorithm.2017	1	m	/	conservatively	/
12.	Ayse Enise Goker, Ziya Salturk, Perihan Taskale,Enes Atac,Yavuz Uyar	Congenital jugular phlebectasia : analysis of two cases. 2015	2	m	f	conservatively	/
13.	Amber Kesarwani, Amit Goyal, Amit Kumar	Phlebectasia of Internal Jugular Vein- a Rare Differential Case of Neck Swelling With Review of Literature.Iran J. Otorhinolaryngol.2019	1	/	f	conservatively	/
14.	Deepanjan Bhattacharya, Mounika Endrakanti,Rakech Kuhar	Right Internal Jugular Vein Phlebectasia: A Rare Cause of Neck Swelling . Case reports in Pediatrics 2017	1	m	/	conservatively	/
15.	M. Afal, A Mohamed, Y Volkin	Jugular Vein Phlebectasia in a Pediatric Patient With Tracheomalacia. 2023	1	m	/	conservatively	/
16.	Neha D. Shetty et al.	A Case of Phlebectasia in a Child Presenting With Neck Mass 2023	1	m	/	conservatively	/
17.	Dr. Mehmet Demiracan et al.	Jugular Phlebectasia in Children: A Case Report.1997	1	m	/	/	Surgical (PTFE)
18.	Y. Gao et al	Diagnosis and Treatment of Internal Jugular Phlebectasia-three cases report. 1999	3	m	/	/	Surgical (excision vein)
19.	Ksim S. Kasim et al.	Internal Jugular Vein Phlebectasia in a Child : A Case Report . 2018	1	m	/	conservatively	/
20.	Alexandra Zimm	Internal Jugular Phlebectasia. 2010	1	/	f	conservatively	/
21.	V. Malk, Virender, Kumari et al.	Phlebectasia of internal jugular vein with intracranial extension. 2015	1	m	/	conservatively	/
22.	M. Safi et al.	A rare presentation of Horner syndrome due to internal jugular phlebectasia . 2021	1	m	/	conservatively	/

23.	Yoko Omata, Yochiko Takahashi,Tomo ko Nakazawa, Taku Omata	Paediatric primary internal jugular poucough headache with phlebectasia. 2021	1	m	/	conservatively	/
24.	Tamami AIN, Al Macki K.	Internal Jugular Phlebectasia: A Case Report and Literature Review. J Otolaryngol ENT Res. 2015	1	m	/	conservatively	/
25.	Jayakumar V, Arora PK	Right internal jugular vein phlebectasia-a rare cause of neck swelling in paediatric population. Int J Otorhinolaryngol Head Neck Surg. 2022	1	m	/	conservatively	/

* polytetrafluoroethylene tube- PTFE

Conclusion

Phlebectasia of the internal jugular vein should be included in the differential diagnosis of atypical neck masses in children. It can be easily diagnosed with a detailed history and physical examination. The diagnostic modality of first choice is ultrasound examination of the soft tissues of the neck at rest, and during the Valsalva maneuver, because it can be easily and effectively used for monitoring, so that the extent of the swelling can be documented. Magnetic resonance imaging with contrast angiography and venography of the main blood vessels of the neck is reserved for the definitive diagnosis of phlebectasia, especially in pediatric patients. After diagnosis, the patient should be followed up regularly. Inform the patient and his parents about the risk of possible complications. Most importantly, the patient and his parents should be reassured that this is most often a benign condition, and that it will not affect the normal life regimen. The presented patients correspond to the largest number of patients presented in the world literature in terms of clinical characteristics, diagnostic method and proposed treatment modalities..

Literature:

1. Harris RL. Congenital venous cyst of mediastinum. Ann Surg 1928;88:953-6.
2. Zukschwerdt L. Seltene localisation einer venectasie. Ditsch Z Chir 1929;216:283-285.
3. Gerwing WH Jr. Internal jugular phlebectasia.Ann Surg 1952;135:130-133.
4. Sander S, Elicevik M, Unual M, et al. Jugular phlebectasia in children: is it rare or ignored? J Pediatr Surg 1999;34:1829-1832 .
5. Dhillon MK, Leong YP. Jugular venous aneurysm – a rare caue of neck swelling. Singapur Med J. 1991;32(2):177-178.
6. Jianhong L, Huewu J, Tingze H. Surgical treatment of jugular vein phlebectasia in children. Am J Surg 2006;192:286-90.
7. Miljenko Raos, Jelica Marković. Flebektazija unutarnje jugularne vene: prikaz slučaja. Med Jad 2010;40(3-4):103-106.
8. Kuo WR, Chien CC, Choi CY et al. Internal jugular phlebectasia. 1992;8:503-9.
9. Figueroa Sanchez J. A. et al. Internal jugular phlebectasia a systematic rewiev. Surg Neural Int. 2019;10:106.
10. Indudharm R, Quah BS, Swaib IL. Internal jugular phlebectasia-an unusual case of neck swelling.Annuals of Tropical Pediatrics 1999;19(1)105-8.
11. Kim SW, Shay JW, Lee S. Unusal presentation of a cervical mass revealed as extended jugular venous aneurysm. Vasc Specialist Int. 2016;32:205-7.
12. Stivens KE, Price JE, Marko J, Kalor SG. Neck masses due to jugular venous ectasia. Child's Neur Syst. 1995;11(9):533-535.
13. PaleriV, GopalakrishnanS. Jugular phlebectasia: theory of pathogenesis and rewiev of literature. J Int Pediatr Othorynolaringol 2001;57:155-9.
14. La Monte et al. Internal jugular phlebectasia. A clinicoroentgenographic diagnosis. Arch Otolaryngol. 1976;102:706-8.
15. Yokomori K et al. Internal Jugular phlebectasia in two siblings.Manometric and histopathological studies of the pathogenesis. J Pediatr Surg.1990;25:762-5.
16. Kwok LL, Lam HS, Ho DKK. Unilateral right-sided internal jugular phlebectasia in ashmatic children. J Pediatr Child Health. 2000;36:517-519.
17. Leighton JE. Jugular phlebectasia . Postgraduate Medline Journal. 1962;470-73.
18. Eksioglu AS, Senel S, Cinar G, Karacan CG. Sonographic measurment criteria for the diagnosis of internal jugular phlebectasia in children. J Clin Ultrasound. 2013;41:486-492.
19. Hsou Chin C et al. Ultrasonographic diagnosis and color flow doppler sonography of Internal jugular venous ectasia in children. J Ultrasound Med 1999;18:411-416.
20. Rosi A, Tortori- Donati P. Internal jugular vein phlebectasia and duplicationa case report with magnetic resonance angyography features. Pediatr. Radiol 2001;31(2):134.
21. Rajandran UR, Vasu CK, Regi G, Anja MA, Anoop P. Unilateral internal Jugular phlebectasia. Indian J Pediatr 2004;71:751-753.
22. Bowdler DA, Singh SD. Internal Jugular phlebectasia. Int J Pediatr Otorinolaryngol 1986;12:165-71.
23. Blindal Sk et al . Phlebectasia of internal jugular vein. J Surg Tech Case Rep 2012;4(2):103-05.
24. M. Safi et al. A rare presentation of Horner's syndroms duo to internal jugular phlebectasia. JAAPOS (2022)
25. Hung T, Campbell A. Surgical repair of left internal jugular phlebectasia. J Vasc Surg 2008;47:1337-8.

Vol. 51 (2026) No. 1 TIMOK MEDICAL GAZETTE Case report

MYOTONIC DYSTROPHY TYPE I; WITH A SPECIAL FOCUS ON CLINICAL SIGNIFICANCE IN PREGNANCY

Vesna Martić-Popović, Marina Nikolić

CLINIC FOR NEUROLOGY- MILITARY MEDICAL ACADEMY

Abstract: Myotonic dystrophy type I (MD1) is a complex, slowly progressive multisystem disorder affecting not only muscles but also the eyes, heart, endocrine, reproductive, and central nervous systems. The disease is inherited in an autosomal dominant manner and is characterized by the phenomenon of genetic anticipation. A 34-year-old female patient was hospitalized for evaluation of progressive muscle weakness and hypotrophy. Neurological examination and electrodiagnostic testing revealed typical signs of MD1, confirmed by DNA analysis. The patient has a history of spontaneous miscarriages and prenatal complications, likely resulting from undiagnosed MD1. MD1 during pregnancy can lead to serious complications. Genetic counseling and assisted reproduction options are key to minimizing the risk of disease transmission..

Keywords: Myotonic dystrophy type I; *DMPK* gene; muscle weakness; myotonia; multisystem complications; reproductive health and pregnancy; genetic counseling; preimplantation genetic diagnosis

INTRODUCTION

Myotonic dystrophy type I is a slowly progressive multisystem disorder that, in addition to skeletal muscles, most commonly affects the eyes, heart, endocrine system, and central nervous system. The disease has an incidence of 5 to 20 affected individuals per 100,000 population [1]. It is inherited in an autosomal dominant manner and is caused by an expansion of CTG trinucleotide repeats in the gene encoding serine-threonine protein kinase on chromosome 19. The number of CTG repeats correlates with the clinical severity. These repeats tend to increase in successive generations, leading to more severe clinical manifestations and an earlier onset of symptoms—a phenomenon known as genetic anticipation.

Due to the increased number of CTG repeats in the DMPK gene, transcription results in mutant toxic RNA that accumulates in the nucleus and interferes with the processing of various primary RNA transcripts, which is considered the key pathogenic mechanism of the disease. This leads to disrupted pre-mRNA splicing of multiple genes encoding chloride channels, insulin receptor, tau protein, beta-amyloid, NMDA receptor, ryanodine receptor, amphiphysin, as well as skeletal and cardiac troponins [2,3].

Based on the age of symptom onset, MD1 can be divided into at least four subtypes: congenital, juvenile, adult-onset, and late-onset MD1 [2]. Childhood- and adolescent-onset forms are often underdiagnosed due to minimal muscular symptoms [4], and patients frequently develop significant muscle weakness only later in life [5].

The clinical presentation of MD1 typically includes distal muscle weakness and atrophy, active and percussion myotonia, ptosis, dysarthria (rhinolalia), and a characteristic myopathic facial appearance. MD1 can be suspected based on the clinical picture, the presence of a myotonic pattern on electromyoneurography (EMNG), ECG abnormalities (e.g., AV block), elevated creatine kinase levels, hypogammaglobulinemia, and early-onset cataracts [6]. The diagnosis is confirmed by DNA analysis [1].

Pregnancy in women with MD1 requires special medical supervision due to an increased risk of complications, including cardiac arrhythmias, respiratory impairment, worsening muscle weakness, and obstetric complications during delivery. The literature reports an increased risk

of spontaneous abortion, preterm birth, and higher maternal and neonatal morbidity and mortality, emphasizing the need for careful planned medical management and multidisciplinary follow-up to ensure optimal outcomes for both mother and child [7–9].

Currently, there is no disease-modifying therapy, and treatment remains strictly symptomatic [6]. Nevertheless, establishing the diagnosis—even later in life—is important for planning physical therapy, preventing and managing complications, and enabling genetic counseling and prenatal diagnosis in families planning offspring [10].

CASE REPORT

Patient V.D., a 34-year-old woman, was hospitalized for the first time at the Neurology Clinic after being evaluated in the emergency department due to a sensation of "stiffness and weakness" in the left leg, accompanied by pain radiating along the same limb.

The patient reports that since the age of 14–15 she has noticed muscle wasting and weakness of the left calf, without gait or running difficulties. She occasionally experiences muscle twitching in the same region. Since childhood, she has had speech abnormalities. Prior to hospitalization, lumbar spine MRI was performed, showing bulging and partial rupture of the annulus fibrosus of the intervertebral disc at L4–L5 on the left, with mild compression of the left L5 nerve root.

Her personal medical history is otherwise unremarkable. She had two pregnancies: the first ended in spontaneous abortion in the fourth month of gestation, and the second resulted in preterm delivery in the seventh month with stillbirth.

Family history reveals that the father was treated for colorectal carcinoma and has type 2 diabetes mellitus. The mother is on regular treatment for hypertension and hypothyroidism and underwent cataract surgery at the age of 61. Her brother was diagnosed with diabetes mellitus at the age of 31 and has been on insulin therapy since.

Neurological examination revealed hypomimic facies with weakness of the frontal and orbicularis oculi muscles. Speech was nasal without clear fatigability on counting test. The tongue was midline without atrophy or fasciculations, with mild percussion myotonia of the tongue present. Mild weakness of neck flexion was noted. There was atrophy of the sternocleidomastoid muscle, giving a "swan-neck" appearance.

The upper extremities showed normal muscle bulk and preserved strength in both proximal and distal muscle groups, except for mild weakness of finger abduction and palmar flexion. Percussion myotonia was present in the thenar region. Upper limb reflexes were absent, except for the right triceps reflex.

In the lower extremities, there was marked atrophy of the entire left calf and the distal third of the left thigh. Mild weakness of left thigh flexion, left leg extension, and left foot dorsiflexion was observed. The right patellar reflex was decreased, while the left was present. Plantar responses were absent bilaterally.

Electromyography (EMG) revealed abundant myotonic discharges in both lower limb muscles and in the left upper limb, involving both proximal and distal muscle groups. The findings were typical for a myotonic disorder [11,12]. Motor unit potentials were predominantly myopathic, moderately to severely reduced in pattern.

Nerve conduction studies (NCS) showed prolonged duration of M responses in both peroneal nerves, with reduced amplitude on the right side. Other motor nerves were within normal limits. A mild, non-significant reduction in motor conduction velocity was observed in most motor nerves. F-wave responses were difficult to obtain in the left peroneal nerve. Sensory nerve conduction was normal in the lower limbs. Overall findings were consistent with a myotonic myopathy.

Laboratory findings showed elevated creatine kinase (CK) levels (311 U/L). Anti-acetylcholine receptor antibodies were within normal limits. Endocrinology consultation was obtained. Hormonal analysis was within reference ranges, except for slightly decreased TSH (0.275 mIU/L) and dehydroepiandrosterone (DHEA) (1.02 μmol/L). Thyroid and abdominal ultrasound examinations were unremarkable. Gynecological examination revealed no pathological findings.

Ophthalmologic evaluation revealed reduced distance vision. Optical coherence tomography (OCT) demonstrated an epiretinal membrane in the left eye.

Cardiological evaluation revealed no anginal symptoms or syncopal episodes. ECG showed no rhythm disturbances or ST/T changes; QTc was 442 ms (borderline value) [13].

After discharge, the patient was referred for genetic testing for myotonic dystrophy types I and II. Genetic analysis confirmed the diagnosis of myotonic dystrophy type I.

DISCUSSION

The patient first noticed symptoms in childhood, in the form of mild weakness and hypotrophy of the left calf. Since there were no gait disturbances, she did not seek neurological evaluation. Only at the age of 34, after the appearance of more pronounced symptoms including pain and altered sensation in the left leg, she consulted a physician.

Before specialist evaluation, MRI of the lumbar spine showed mild compression of the L5 nerve root. Due to unclear correlation between MRI findings and the clinical picture, the patient was referred by a neurosurgeon to a neurologist, who recommended hospitalization and further evaluation.

Suspicion of myotonic dystrophy was already raised after neurological examination. The patient presented a typical myopathic facial appearance, “swan neck,” distal weakness and atrophy, along with subtle myotonic phenomena.

Myotonia refers to delayed and prolonged relaxation of a previously contracted muscle and can be observed clinically as active or percussion myotonia. In this patient, a mild myotonic response was recorded after percussion of the thenar muscles, which fatigued quickly.

The presence of myotonia significantly narrows the differential diagnosis to a limited group of disorders. Besides myotonic dystrophy type I and II, myotonia may also occur in nondystrophic myotonias, including myotonia congenita, paramyotonia congenita, sodium channel myotonia, periodic paralyses (hypokalemic and hyperkalemic), Andersen–Tawil syndrome, as well as rare disorders such as Schwartz–Jampel syndrome and Brody disease.

No clear hereditary pattern was identified in the family history. However, there is a history of endocrine disorders: maternal hypothyroidism, brother with diabetes mellitus, and early cataract surgery in the mother at age 61. Heterozygous carriers with a small number of expansions (50–100 CTG repeats) may be asymptomatic or have mild clinical manifestations, which explains why family history is often unclear despite autosomal dominant inheritance of DM1.

EMG findings and the presence of myotonic discharges are key in establishing the diagnosis of myotonic disorders [11,12]. Myotonic discharges are spontaneous potentials with waxing and waning amplitude and frequency, easily identified on EMG. In DM1, they are most commonly recorded in distal muscles. Sensory responses are typically normal, while motor amplitudes are often reduced, likely due to muscle degeneration and axonal involvement. The patient’s findings are fully consistent with this clinical and electrophysiological pattern.

The clinical presentation of DM1 is highly variable, ranging from asymptomatic forms (myotonia only on EMG) to severe weakness and disability, including multisystem involvement. DM1 is frequently associated with cardiac rhythm disturbances, infertility, cataracts, and insulin resistance.

During hospitalization, specialists from multiple fields were consulted to assess systemic involvement.

A wide range of ophthalmological abnormalities may occur in DM1. In addition to early cataract, patients may develop ptosis, lagophthalmos, recurrent conjunctivitis, epiretinal membrane, and rarely blepharospasm. The patient reported long-standing reduced distance vision and did not use corrective lenses. Visual acuity testing revealed astigmatism. OCT showed an epiretinal membrane in the left eye, and follow-up OCT was recommended in 6 months. In a study of 30 DM1 patients, 56.7% had an epiretinal membrane in at least one eye. Epiretinal membrane is surgically

treatable, but routine OCT monitoring is recommended in DM1 patients with visual complaints.

Cardiology consultation was also performed despite the absence of syncope, palpitations, chest pressure, or pain—symptoms commonly associated with DM1. The most frequent ECG abnormalities in DM1 include sinus bradycardia, low P-wave amplitude, first-degree AV block, and prolonged QTc interval. Echocardiographic abnormalities are present in about 14% of mildly affected patients, with dilated and hypertrophic cardiomyopathy being the two main forms. The patient's ECG showed no rhythm or ST/T abnormalities; QTc was 442 ms, considered borderline by some authors. Cardiology recommended further follow-up and echocardiographic evaluation.

The most common endocrine disorders in DM1 include insulin resistance and gonadal dysfunction, with additional involvement of the thyroid, parathyroid glands, pituitary, and adrenal glands described in the literature. The patient's hormonal status was within reference ranges, with slightly reduced TSH and DHEA. Thyroid and abdominal ultrasound findings were normal. Endocrinology consultation did not indicate further diagnostic work-up.

REPRODUCTIVE HEALTH AND PREGNANCY

The clinical significance of DM1 in reproductive health is substantial due to frequent pregnancy complications and the risk of transmission to offspring. In this patient, V.D., who had two pregnancies—one ending in spontaneous miscarriage at four months and the second in preterm delivery at seven months with stillbirth—there is a clear history of reproductive complications that may be related to previously undiagnosed DM1.

Women with DM1 are at increased risk of complications during pregnancy, including ectopic pregnancy, polyhydramnios, placenta previa, spontaneous miscarriage, and preterm delivery.

DM1 is inherited in an autosomal dominant manner—both men and women can transmit the disease to offspring. Heterozygotes may be asymptomatic or mildly affected but still have a significant risk of transmission. In men with DM1, progressive testicular atrophy, oligospermia, or azoospermia may occur, while in women hormonal dysfunction and infertility have been reported in 15–20% of patients.

Women with DM1 are exposed to multiple pregnancy risks, including increased rates of spontaneous abortion, preterm birth, ectopic pregnancy, and high neonatal morbidity and mortality. Additional complications include polyhydramnios, abnormal placental positioning, and the need for cesarean section in about 10% of cases. These complications are often associated with pathological changes in muscle and cardiovascular function, requiring continuous multidisciplinary monitoring.

In this patient, who already has a complicated reproductive history, these findings are particularly important and indicate an increased risk of further complications should she become pregnant again..

GENETIC COUNSELING AND ASSISTED REPRODUCTION OPTIONS

For patients with myotonic dystrophy type I (MD1), various options are available for pregnancy planning and reducing the risk of disease transmission to offspring. Genetic counseling is of crucial importance to help the patient understand the mechanism of inheritance and available reproductive options.

The most effective method for preventing transmission of MD1 to offspring is in vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD). This method allows analysis of CTG repeat expansion in embryos, and only genetically unaffected embryos are transferred into the uterus [17,19]. In cases of high risk or failure of attempts, the use of donor oocytes may be considered to avoid transmission of MD1. After conception, prenatal procedures such as chorionic villus sampling (CVS) or amniocentesis enable direct detection of CTG expansions in the fetal genome [17].

THERAPEUTIC OPTIONS AND FOLLOW-UP

Currently, there is no cure that modifies the course of the disease; treatment remains

symptomatic and supportive [6]. Continuous monitoring of cardiovascular and endocrine status during pregnancy and outside of it is essential [8,20]. Preimplantation genetic diagnosis and prenatal testing are available options for reducing the risk of disease transmission [17].

CONCLUSION

The clinical significance of DM1 is particularly pronounced during the reproductive period and pregnancy due to the risk of complications and disease transmission to offspring. Family planning in individuals with DM1 requires comprehensive genetic counseling and a multidisciplinary approach, including prenatal diagnostics and assisted reproduction options. Continuous medical monitoring during pregnancy, with special emphasis on cardiology and endocrinology follow-up, is essential to reduce risks and ensure the safety of both mother and child.

As previously noted, there is currently no therapy capable of altering the course of the disease [6], and treatment remains exclusively symptomatic. Research into gene therapy and molecular interventions represents an important direction for the future. Numerous studies on potential causal treatments for DM1 are ongoing. Gene therapy approaches using CRISPRi methods and antisense oligonucleotide (ASO) therapy represent promising novel therapeutic strategies for the treatment of DM type I [15,21]..

Literature:

1. Nicholas E Johnson, Russell J Butterfield, Katie Mayne, Tara Newcomb, Carina Imburgia, Diane Dunn, Brett Duval, Marcia L Feldkamp, Robert B Weiss. Population-Based Prevalence of Myotonic Dystrophy Type 1 Using Genetic Analysis of Statewide Blood Screening Program. Neurology. 2021 Feb 16;96(7):e1045–e1053.
2. Turner C, Hilton-Jones D. The myotonic dystrophies: diagnosis and management. J Neurol Neurosurg Psychiatry. 2010;81:358–367.
3. Fernando Morales, Michael Pusch. An Up-to-Date Overview of the Complexity of Genotype-Phenotype Relationships in Myotonic Channelopathies. Front Neurol. 2020 Jan 17;10:1404.
4. Ho G, Cardamone M, Farrar M. Congenital and childhood myotonic dystrophy: current aspects of disease and future directions. World J Clin Pediatr. 2015;4:66–80.
5. Daigo Hayashi, Minoru Saito. Myotonic dystrophy type 1 presenting with grip myotonia and functional improvement after rehabilitation. BMJ Case Rep. 2021 Apr 13;14(4):e241552.
6. Romeo V. Myotonic Dystrophy Type 1 or Steinert's Disease. In: Ahmad SI (ed). Neurodegenerative Diseases. Advances in Experimental Medicine and Biology, vol 724. 2012.
7. Hahn C, Salajegheh MK. Myotonic disorders: A review article. Iran J Neurol. 2016;15(1):46–53.
8. Michael K Hehir, Eric L Logigian. Electrodiagnosis of myotonic disorders. Phys Med Rehabil Clin N Am. 2013 Feb;24(1):209–220.
9. Ahmet Z Burakgazi. Electrodiagnostic findings in myotonic dystrophy: A study on 12 patients. Neurol Int. 2019 Dec 2;11(4):8205.
10. J N Johnson, M J Ackerman. QTc: how long is too long? Br J Sports Med. 2009 Sep;43(9):657–662.
11. Stojan Z. Perić. Ispitivanje funkcionalnih i morfoloških poremećaja centralnog nervnog sistema kod bolesnika sa miotoničnom distrofijom tip 1. Univerzitet u Beogradu; 2014.
12. Hannah M Kersten, Richard H Roxburgh, Nicholas Child, Philip J Polkinghorne, Chris Frampton, Helen V Danesh-Meyer. Epiretinal membrane: a treatable cause of visual disability in myotonic dystrophy type 1. J Neurol. 2014 Jan;261(1):37–44.
13. Vidosava Rakočević-Stojanović. Miotonična distrofija i srčani poremećaji. Zadužbina Andrejević; 1997.
14. Yu-Xi Jia, Chun-Ling Dong, Jia-Wei Xue, Xiao-Qin Duan, Ming-Yu Xu, Xiao-Min Su, Ping Li. Myotonic dystrophy type 1 presenting with dyspnea: A case report. World J Clin Cases. 2022 Jul 16;10(20):7060–7067.
15. Florent Porquet, Lin Weidong, Kévin Jehasse, Hélène Gazon, Maria Kondili, Silvia Blacher, Laurent Massotte, Emmanuel Di Valentin, Denis Furling, Nicolas Albert Gillet, Arnaud François Klein, Vincent Seutin, Luc Willems. DMPK-promoter targeting by CRISPRi reverses myotonic dystrophy type 1-associated defects in patient muscle cells. Mol Ther Nucleic Acids. 2023 May 13;32:857–871.
16. De Souza RF, et al. Pregnancy outcomes in women with myotonic dystrophy type 1: a systematic review and meta-analysis. Orphanet J Rare Dis. 2020. (open access)
17. Bainbridge M, et al. Reproductive options for myotonic dystrophy: preimplantation genetic diagnosis and prenatal testing. Front Genet. 2021. (open access)
18. Meola G, Cardani R. Clinical aspects and management of myotonic dystrophy type 1. Curr Opin Neurol. 2015. (open access review)
19. Turner C, et al. Management of pregnancy in women with neuromuscular disorders. BMC Pregnancy Childbirth. 2019. (open access)
20. Di Stefano V, et al. Cardiac involvement in pregnant women with myotonic dystrophy type 1: implications for monitoring. Eur J Obstet Gynecol Reprod Biol. 2020. (open access)
21. Harper PS, et al. Ethical and practical considerations of genetic testing in reproductive decision-making for myotonic dystrophy. J Community Genet. 2022. (open access)

THE IMPORTANCE OF PANENDOSCOPY IN DETECTING AN UNKNOWN PRIMARY HEAD AND NECK CARCINOMA – A CASE REPORT

Silvana Babić (1), Aleksa Korugić (1), Maša Petrović (2), Svetozar Memarović (1), Tamara Nedeljković (1)

(1) CLINIC FOR OTORHINOLARYNGOLOGY AND MAXILLOFACIAL SURGERY, UNIVERSITY CLINICAL CENTER OF SERBIA, 11000 BELGRADE, SERBIA; (2) INSTITUTE FOR CARDIOVASCULAR DISEASES "DEDINJE", 11000 BELGRADE, SERBIA

ABSTRACT: Introduction: Cystic neck masses in adult patients represent a significant diagnostic challenge, as they may conceal metastatic disease. Although cystic cervical metastases are most commonly associated with HPV-positive oropharyngeal squamous cell carcinomas, a cystic presentation does not exclude an HPV-negative etiology. The aim of this study is to highlight the importance of a systematic diagnostic approach, including panendoscopy with bilateral tonsillectomy, in the evaluation of cervical metastases of unknown primary origin. Case Report: We present a 47-year-old female patient with a painless cystic lesion in the left parotid region, initially interpreted radiologically as a benign lesion. Histopathological analysis following surgical excision revealed a cystic metastasis of squamous cell carcinoma with extracapsular extension and p16 negativity. Further diagnostic workup, including panendoscopy and bilateral tonsillectomy, identified synchronous bilateral HPV-negative tonsillar squamous cell carcinoma. Following bilateral selective neck dissection, adjuvant radiotherapy with concomitant chemotherapy was administered. At follow-up, there were no signs of disease recurrence. Conclusion: A cystic neck mass in adults should be considered malignant until proven otherwise. A negative radiological finding does not exclude the presence of a primary tumor in the oropharynx. This case highlights the diagnostic value of panendoscopy with bilateral tonsillectomy in identifying occult primary tumors, particularly in the context of HPV-negative disease.
Keywords: cystic neck mass; cervical metastasis; panendoscopy; tonsillar squamous cell carcinoma; HPV-negative

INTRODUCTION

Neck masses in adult patients represent a common clinical problem and a significant diagnostic challenge in everyday otorhinolaryngology practice. Unlike the pediatric population, in which cystic neck lesions are most often congenital and benign, in adults any newly developed mass requires thorough and systematic diagnostic evaluation due to the real possibility of malignancy [1]. In this population, an initially benign interpretation of a lesion may lead to delayed diagnosis and postponement of appropriate oncological treatment.

Cystic lesions of the neck pose a particular diagnostic dilemma, as in the absence of local symptoms, inflammation, or infiltrative growth, they are often perceived as benign. However, in adult patients, a cystic morphology does not exclude malignancy; on the contrary, it may represent a manifestation of metastatic disease.

Cystic cervical metastases are most commonly associated with HPV-positive oropharyngeal squamous cell carcinomas, particularly those of the tonsils and the base of the tongue [2]. This association has led in recent years to a widespread clinical assumption that a cystic metastatic structure implies HPV-positive etiology and potentially more favorable tumor biology. However, HPV-negative oropharyngeal carcinomas represent a biologically and clinically distinct entity, characterized by different risk factors, a more aggressive disease course, and a poorer prognosis [3]. Reports of cystic metastases originating from HPV-negative tumors are rare and largely derive from older literature, which continues to make them a diagnostic pitfall in contemporary clinical practice.

The aim of this paper is to highlight, through a case report, the importance of panendoscopy in the diagnosis of cervical metastases of unknown primary origin, as well as to emphasize the need for a structured and systematic approach to cystic neck lesions in adult patients.

CASE REPORT

A 47-year-old female patient presented for an otorhinolaryngology examination due to a painless mass in the left parotid region, which she had noticed several months earlier and which had gradually increased in size, without signs of inflammation or other local symptoms. She denied any ENT-related complaints. She had been an active smoker for more than 20 years, while she did not consume alcohol. Her past medical history was notable for depression, for which she was receiving antidepressant therapy. There was no history of prior malignancy. Family history revealed oropharyngeal carcinoma in the patient's sister.

Clinical examination revealed a well-defined, elastic, mobile, and painless tumor mass measuring approximately 3 cm in diameter in the left parotid region. The overlying skin appeared normal. The remainder of the otorhinolaryngological examination was unremarkable.

Ultrasound examination of the neck demonstrated an oval, well-circumscribed cystic lesion without suspicious vascularization on color Doppler imaging. Contrast-enhanced MSCT of the neck and all three levels of the pharynx showed a cystic lesion located below the lower pole of the left parotid gland, without signs of infiltration into surrounding structures and without enlarged cervical lymph nodes. Based on radiological findings, the lesion was initially interpreted as benign.

Given the unclear etiology and location of the lesion, a maxillofacial surgeon indicated surgical excision. Histopathological analysis revealed a lymph node with cystic metastasis of squamous cell carcinoma. Immunohistochemical findings showed positivity for CK and p40, with negative p16 and CK7, as well as a negative EBER-ISH result. Extracapsular extension of the metastasis was observed.

Following histopathological diagnosis, further diagnostic workup was performed to identify the primary tumor. Panendoscopy of the upper aerodigestive tract with targeted biopsies was carried out, along with bilateral tonsillectomy. Histopathological analysis of both tonsillar specimens confirmed infiltrative squamous cell carcinoma, HPV-negative (p16–), with lymphovascular invasion and no evidence of perineural invasion.

In the subsequent course of treatment, the patient underwent bilateral selective neck dissection, with no residual neoplastic proliferation identified in the removed lymph nodes. The case was presented at a multidisciplinary tumor board for head and neck cancers, after which postoperative radiotherapy with concurrent chemotherapy was indicated. Radiotherapy was administered to a total dose of 64 Gy in 32 fractions, along with two cycles of cisplatin (CDDP) at a dose of 100 mg/m^2.

At follow-up after completion of treatment, local and regional findings showed no evidence of disease recurrence. As a treatment-related complication, the patient developed grade II post-therapeutic xerostomia. Intensive oncological follow-up at shorter intervals was recommended..

DISCUSSION

The presented case illustrates a typical scenario in which cystic morphology and the absence of symptoms lead to an initial benign interpretation. It is well established that cystic neck masses in adults represent a diagnostic pitfall. Contemporary guidelines emphasize that any persistent cervical mass in an adult should be considered malignant until proven otherwise, and that the diagnostic algorithm must be systematic and clearly sequenced, with fine-needle aspiration biopsy as the preferred initial method, while avoiding primary open lymph node biopsy [1]. Although in our patient an open biopsy was the first diagnostic step, further evaluation was conducted in accordance with current recommendations.

In the context of squamous cell carcinoma of unknown primary origin, the oropharynx—particularly the palatine tonsils—represents the most common site of occult primary tumors.

Contemporary series show that the primary lesion is identified in the tonsil in approximately one quarter of patients following diagnostic tonsillectomy. Additionally, systematic analyses indicate that the prevalence of synchronous bilateral or contralateral tonsillar carcinoma may reach around 10% in patients with head and neck carcinoma of unknown primary origin, further justifying routine bilateral tonsillectomy within the diagnostic algorithm [4].

It is important to emphasize that unilateral tonsillectomy may result in missing a contralateral or synchronous tumor. The literature reports that in a subset of patients with squamous cell carcinoma of unknown primary origin, the primary tumor is identified exclusively after bilateral tonsillectomy. Although bilateral tonsillar carcinoma is rare, it represents a clinically significant entity. In our case, a systematic approach including bilateral tonsillectomy enabled the detection of synchronous bilateral HPV-negative tonsillar carcinoma, confirming the diagnostic value of such an approach. These findings have direct clinical implications and further support routine bilateral tonsillectomy as part of panendoscopic evaluation, even when imaging studies do not indicate a clearly suspicious lesion [4,5].

Although contrast-enhanced MSCT of the neck is a standard initial diagnostic modality in the evaluation of cervical metastases, its sensitivity for detecting small, submucosal, or cryptic HPV-related oropharyngeal tumors remains limited. Moderate sensitivity (approximately 60–70%) with relatively high specificity (80–90%) indicates that a negative radiological finding does not exclude the presence of a primary tumor in the oropharynx [6]. Therefore, modern diagnostic algorithms recommend a multimodal approach, including a combination of imaging techniques, endoscopic examination under general anesthesia, and selective surgical procedures such as bilateral tonsillectomy and, when indicated, lingual tonsillectomy.

HPV-negative oropharyngeal carcinomas represent a biologically distinct entity compared to HPV-positive tumors. They are more frequently associated with traditional risk factors, particularly long-term tobacco and alcohol exposure, exhibit more pronounced keratinization, greater genetic instability, and generally a more aggressive clinical course. Unlike HPV-positive tumors, in which p16 immunohistochemistry has significant prognostic and therapeutic value, HPV-negative carcinomas are associated with poorer overall and disease-specific survival. In this context, the presented case gains additional clinical importance, as it demonstrates that a cystic metastasis may represent the first and only manifestation of a biologically more aggressive, p16-negative tumor [7].

The presence of extracapsular extension in a metastatic lymph node is an unfavorable prognostic factor and a strong indication for a more aggressive therapeutic approach. Therefore, timely identification of the primary tumor is crucial, as it allows for appropriate planning of multimodal therapy and precise delineation of radiation fields [6].

An interesting finding in this case is the fact that the patient's sister had the same type of tumor, which may suggest a potential genetic predisposition. Although familial occurrence of oropharyngeal carcinoma is rarely described in the literature, epidemiological data indicate an increased risk among individuals with a positive family history. In a multicenter study by Garavello et al., a family history of oral or pharyngeal carcinoma in first-degree relatives was associated with approximately a 2.6-fold increased risk of developing these tumors (OR 2.6; 95% CI 1.5–4.5) [8].

After completion of treatment, patients with oropharyngeal carcinoma require intensive follow-up, particularly during the first years when the risk of recurrence is highest. In clinical practice in our setting, follow-up examinations are performed every 1–2 months during the first year, every 2–3 months during the second year, then every 4–6 months up to the fifth year, and annually thereafter. This follow-up regimen allows for timely detection of local or regional recurrence, as well as late complications of treatment [9].

In this context, the presented case integrates several diagnostic challenges—cystic presentation, HPV-negative biology, and bilateral primary tumors—thereby further emphasizing the need for a structured and systematic diagnostic approach..

CONCLUSION

A cystic neck mass in an adult should be considered malignant until proven otherwise. A negative radiological finding does not exclude the presence of a primary tumor in the oropharynx, particularly in the tonsil.

The presented case confirms that a cystic cervical metastasis may be the first manifestation of an HPV-negative squamous cell carcinoma, including a synchronous bilateral tonsillar tumor.

Panendoscopy with bilateral tonsillectomy represents a key diagnostic step in the systematic evaluation of metastatic squamous cell carcinoma of the neck with an unknown primary origin.

PATIENT CONSENT

Written informed consent was obtained from the patient for publication of this case report..

LITERATURE

1. Pynnonen MA, Gillespie MB, Roman B, Rosenfeld RM, Tunkel DE, Bontempo L, et al. Clinical Practice Guideline: Evaluation of the Neck Mass in Adults. Otolaryngol Head Neck Surg 2017;157:S1–30. https://doi.org/10.1177/0194599817722550.
2. Huang Y-H, Yeh C-H, Cheng N-M, Lin C-Y, Wang H-M, Ko S-F, et al. Cystic nodal metastasis in patients with oropharyngeal squamous cell carcinoma receiving chemoradiotherapy: Relationship with human papillomavirus status and failure patterns. PLoS One 2017;12:e0180779. https://doi.org/10.1371/journal.pone.0180779.
3. Mehanna H, Beech T, Nicholson T, El-Hariry I, McConkey C, Paleri V, et al. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer--systematic review and meta-analysis of trends by time and region. Head Neck 2013;35:747–55. https://doi.org/10.1002/hed.22015.
4. Charlton A, Mughal Z, Sharin F, Sahota RB, Mansuri MS, Mair M. Prevalence of synchronous bilateral/contralateral tonsil carcinoma: A systematic review and meta-analysis. Oral Oncol 2025;162:107180. https://doi.org/10.1016/j.oraloncology.2025.107180.
5. Theodoraki M-N, Veit JA, Hoffmann TK, Greve J. Synchronous bilateral tonsil carcinoma: case presentation and review of the literature. Infect Agent Cancer 2017;12:38. https://doi.org/10.1186/s13027-017-0146-5.
6. Manoharan M, Kalman NS, Rabinowits G. Head and Neck Squamous Cell Carcinoma of Unknown Primary: A Diagnostic Work-Up. Oncologist 2024;29:192–9. https://doi.org/10.1093/oncolo/oyad311.
7. Lewis JS. p16 Immunohistochemistry as a standalone test for risk stratification in oropharyngeal squamous cell carcinoma. Head Neck Pathol 2012;6 Suppl1:S75-82. https://doi.org/10.1007/s12105-012-0369-0.
8. Garavello W, Foschi R, Talamini R, La Vecchia C, Rossi M, Dal Maso L, et al. Family history and the risk of oral and pharyngeal cancer. Int J Cancer 2008;122:1827–31. https://doi.org/10.1002/ijc.23199.
9. Pfister DG, Spencer S, Adelstein D, Adkins D, Anzai Y, Brizel DM, et al. Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl ComprCancNetw2020;18:873–98. https://doi.org/10.6004/jnccn.2020.0031.

SUCCESSFUL TREATMENT OF AN APPARENTLY TERMINAL STAGE OF HEART FAILURE WITH ANASARCA RESULTING IN ACHIEVED CARDIAC COMPENSATION – A CASE REPORT

Pavle Nešović (1), Silvana Babić (2), Mila Bastać (3), Zoran Joksimović (1), Dušan Bastać (1)

(1) INTERNAL MEDICINE PRACTICE "DR BASTAĆ", ZAJEČAR; (2) CLINIC FOR OTORHINOLARYNGOLOGY, UNIVERSITY CLINICAL CENTER OF SERBIA, BELGRADE; (3) MEDSCAN TADIĆ DIAGNOSTICS, ZAJEČAR

Abstract: Introduction: Chronic heart failure (CHF) represents the end stage of various cardiovascular diseases and is one of the leading causes of hospitalization and mortality in the elderly population. Decompensated chronic heart failure (DCHF), with or without acute exacerbation, often leads to circulatory congestion and fluid accumulation, with anasarca (generalized edema) being one of the most severe manifestations, along with cardiac cachexia. In addition to the four "pillars" of CHF treatment across different severity stages according to the New York Heart Association (NYHA) classification, diuretic therapy remains the cornerstone of treatment in the terminal stage with severe systemic congestion, such as anasarca. Diagnostic and therapeutic challenges are frequently present due to comorbidities such as chronic kidney disease and anemia. Case report: An 88-year-old male patient with a history of chronic heart failure with reduced left ventricular ejection fraction (HFrEF), permanent atrial fibrillation, and significant comorbidities: stage 3b chronic kidney disease and severe iron-deficiency anemia. On admission, the patient presented with dyspnea at rest, tachypnea, bilateral hydrothorax, severe edema of the lower legs and forearms (anasarca), and marked general weakness. Laboratory findings showed elevated NT-proBNP levels, markedly reduced hemoglobin (68 g/L), aggravated by hemodilution, and impaired renal function (glomerular filtration rate, GFR = 44 mL/min/1.73 m^2). Echocardiography revealed left ventricular dilation (end-diastolic diameter, EDD = 59 mm) and left atrial enlargement (left atrial volume index, LAVI = 45 mL/m^2), an inferior wall scar with an aneurysm of the basal inferior segment, and anteroseptal-apical dyskinesia. The left ventricular ejection fraction was significantly reduced (EF = 37%). The right ventricular systolic pressure (RVSP) was 64 mmHg, global longitudinal strain (GLS) was 11.6%, and there were signs of grade II diastolic dysfunction (E/e' = 15.0).
The therapeutic approach included urgent parenteral administration of high-dose furosemide over three days in a day-hospital setting (the patient refused hospitalization and blood transfusion). Optimization of chronic therapy was performed, including the introduction of sacubitril/valsartan (ARNI) and sodium-glucose co-transporter 2 (SGLT2) inhibitors, along with restriction of salt and fluid intake and more intensive correction of iron-deficiency anemia. During outpatient follow-up, significant improvement was achieved: marked diuresis, body weight reduction of 14 kg, excellent regression of edema, normalization of lung findings with a significant reduction in hydrothorax, improvement in EF to 47%, improvement in diastolic function (E/e' = 13.6), and reduction of RVSP to 25 mmHg. Renal function normalized (GFR = 64 mL/min/1.73 m^2), and hemoglobin increased to 128 g/L. Conclusion: This case report highlights the importance of individualized intravenous diuretic therapy in combination with contemporary pharmacological strategies in patients with the most severe form of decompensated chronic heart failure (NYHA class IV) with anasarca. Timely initiation of parenteral diuretics, optimization of baseline therapy, and correction of associated disorders led to significant clinical, echocardiographic, and laboratory improvement. This report emphasizes the importance of continuous monitoring of critically ill patients using ECG monitoring and other vital parameters, as well as therapy adjustment according to diuresis, body weight, blood pressure, heart rate, and echocardiographic parameters, to achieve optimal outcomes alongside the management of comorbidities in consultation with other specialties.
Keywords: terminal chronic heart failure with reduced ejection fraction (HFrEF), decompensated congestive heart failure, anasarca (generalized edema), chronic kidney disease, chronic iron-deficiency anemia, pharmacotherapy, furosemide, sacubitril/valsartan, dapagliflozin, bisoprolol, rivaroxaban, spironolactone, digoxin..

INTRODUCTION

Chronic heart failure is a progressive and complex syndrome representing the end stage of various cardiovascular diseases and is one of the leading causes of morbidity and mortality worldwide. Acute heart failure is the most severe clinical form, characterized by cardiogenic pulmonary edema and cardiogenic shock, with the highest mortality, requiring urgent hospital treatment, although it is fortunately much less common than chronic heart failure. The prevalence in the general population is estimated at 1–2%, while in individuals older than 75 years it reaches up to 10% [1,2]. Globally, more than 64 million people live with this condition, and a further increase is expected due to population aging [3].

Decompensated chronic heart failure is characterized by congestion in the pulmonary and/or systemic circulation and fluid accumulation in the body. The most severe form of this process is anasarca, a diffuse generalized edema that may include ascites, pleural effusions, and pericardial effusion [4]. In addition to heart failure, anasarca also occurs in other conditions (nephrotic syndrome, liver cirrhosis, severe hypoalbuminemia), but in the context of heart failure it indicates a terminal stage, exhaustion of compensatory mechanisms, and poor prognosis [5].

The diagnosis and management of patients with anasarca are challenging, as a combination of cardiac, renal, and hepatic dysfunction is often present. Treatment is based on aggressive and individualized intravenous diuretic therapy, correction of electrolyte imbalances, optimization of hemodynamics, and a multidisciplinary approach involving consultants [6].

This case report is particularly significant as it demonstrates that a severe form of heart failure, seemingly refractory terminal-stage decompensated chronic heart failure, can be successfully treated with intensive therapy dominated by high-dose intravenous furosemide, in addition to the standard pillars of heart failure management in patients with anasarca.

The contemporary approach to chronic heart failure treatment is based on the so-called “four pillars of therapy” (ARNI/ACE inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and SGLT2 inhibitors), which significantly reduce mortality and hospitalizations [6–9]. Equally important in the setting of anasarca is the “fifth pillar” — diuretic therapy with intravenous loop diuretics.

CASE REPORT

Basic patient data: Male patient, K.A., 88 years old; anthropometric parameters: body weight 78 kg, height 167 cm, body mass index (BMI) 29.4 kg/m^2, body surface area (BSA) 1.9 m^2, waist circumference 92 cm, and oxygen saturation (SpO_2) 96%.

The patient was admitted on June 6, 2025, in a state of severe decompensated chronic heart failure with marked congestion and anasarca, representing a clinical indicator of advanced disease [5].

Medical history: The patient presented with progressive dyspnea, swelling of the lower legs and forearms, marked weakness, fatigue, and shortness of breath on minimal exertion and at rest following exertion. Symptoms had been present for the past 14 days, with rapid progression. Increased fatigue had been noted over the previous two weeks (he was unable to climb to the first floor), accompanied by rapid and irregular heart rhythm and significant swelling of the lower legs, followed by the forearms.

He was examined by an internist in the hospital one week earlier, when low-dose therapy was initiated: furosemide 40 mg once daily orally, spironolactone 25 mg once daily, and rivaroxaban 15 mg once daily. The patient denied chest pain. Blood pressure at home was generally low. He reported a history of treated hypertension over the past four years, without prior use of cardiac medications.

Previous long-term therapy: bisoprolol 5 mg (1 + 0 + ½), rivaroxaban 15 mg once daily, ramipril/hydrochlorothiazide 5/25 mg once daily in the morning, ramipril 5 mg once daily in the evening, allopurinol 100 mg once daily, furosemide 40 mg once daily, spironolactone 25 mg once daily, and iron supplementation 30 mg once daily.

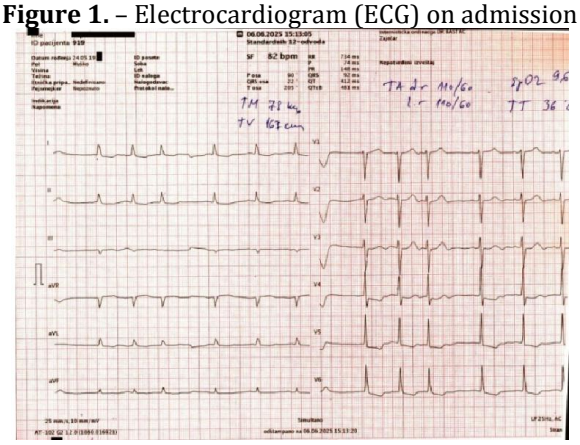
Physical examination on admission:

General condition: Pale and dyspneic, acyanotic, afebrile. Vital parameters: blood pressure 110/60 mmHg, heart rate approximately 82/min, irregular rhythm. Oxygen saturation (SpO_2) 95%. Skin and mucous membranes pale.

Lungs (auscultation): Breath sounds diminished, bilaterally absent at the bases; percussion note dull at the lung bases on both sides.

Heart: Displaced apical impulse on palpation. Heart rate 82/min, heart sounds attenuated, rhythm irregular consistent with atrial fibrillation. A holosystolic regurgitant murmur grade 2–3/6 was heard over the apex, without radiation.
Abdomen: The liver was palpable 4 cm below the right costal margin in the midclavicular line, with soft consistency; the spleen was not palpable. No signs of ascites.
Extremities: Massive, pitting, cold edema of the lower legs (right side: subpatellar circumference 41 cm, mid-tibial 36 cm, supramalleolar 25 cm; left side respectively 35 cm, 34 cm, 27 cm); mild edema of the hands and forearms.
Laboratory findings:
NT-proBNP: 1314 pg/mL (<526 for patient's age)
D-dimer: 0.46 μg/mL (<0.4)
Urea: 17 mmol/L
Creatinine: 133 μmol/L
GFR: 44 mL/min/1.73 m^2
Liver enzymes: AST 96 U/L, ALT 165 U/L
Hemoglobin: 68 g/L, RBC 3.65 × 10^{12}/L, MCV 67.7 fL
Laboratory findings indicated chronic heart failure with cardiorenal syndrome and severe anemia, which are common comorbidities and further worsen prognosis [10–12].
Electrocardiogram (ECG):
Atrial fibrillation with absolute ventricular arrhythmia, heart rate 82/min, intermediate electrical axis, normal QRS duration, occasional ventricular extrasystoles (PVCs), ST depression up to 2 mm with negative T waves in leads V4–V6, and ST depression up to 0.5 mm with negative T waves in leads I, II, and aVL (Figure 1).).

Figure 1. – Electrocardiogram (ECG) on admission



ECHOCARDIOGRAPHY:

The findings are dominated by left ventricular dilation, with normal left ventricular wall thickness, no myocardial hypertrophy, and reduced global systolic function: the left ventricular ejection fraction (EF) was 39% by M-mode (Teichholz method) (Figure 2), and 35% and 39% by Simpson's method, with a biplane EF of 37% (Figures 3, 4)..

Figure 2. – M-mode echocardiogram: ejection fraction (EF) = 39% according to Teichholz

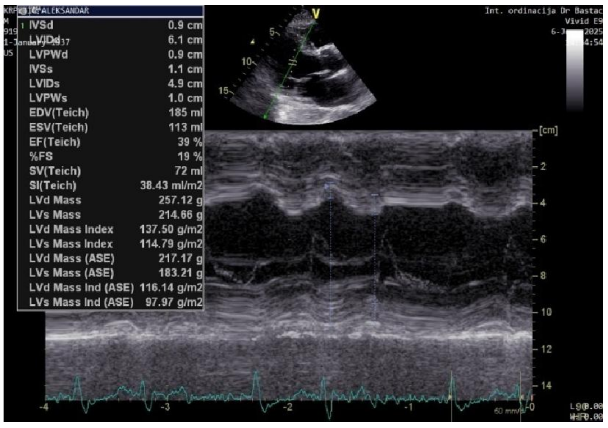


Figure 3. – B-mode echocardiogram: automatic endocardial border detection – ejection fraction (EF) = 35% by Simpson's method (2-chamber view)

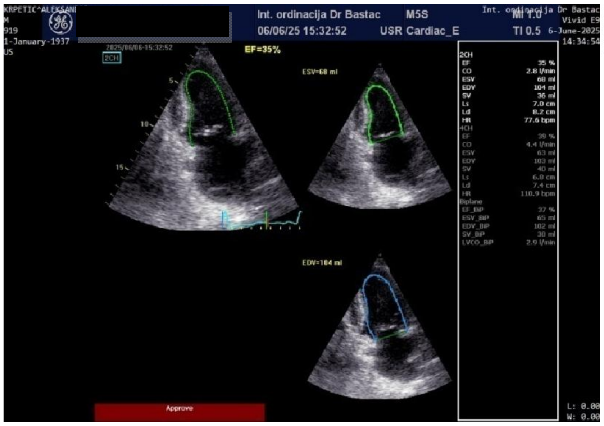
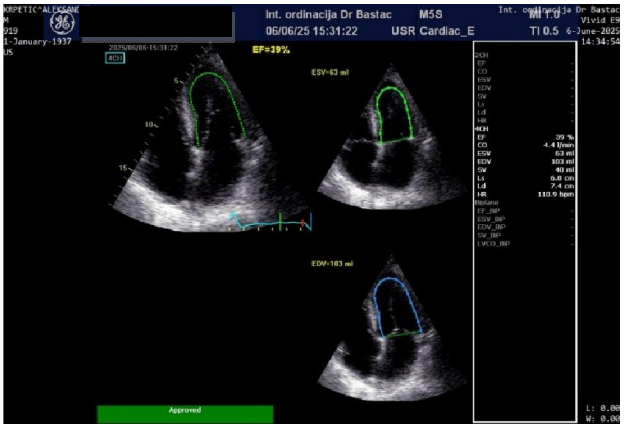


Figure 4. – B-mode echocardiogram: automatic endocardial border detection – ejection fraction (EF) = 39% by Simpson's method (4-chamber view)



A small aneurysm of the basal segment was observed on the inferior wall, with a suspected organized thrombus. Anteroapical and anteroseptoapical dyskinesia were present. The most representative parameter of diastolic function, the E/e′ ratio, was markedly elevated at 15.0 (normal <8.0; E/e′ represents the ratio of early transmitral inflow velocity (E) to the average mitral annular velocity on tissue Doppler imaging (e′)).

The left atrium was dilated, with a left atrial volume index (LAVI) of 45 mL/m² (normal <34 mL/m²) (Figure 5). The maximum velocity (Vmax) of tricuspid regurgitation was measured at 3.3 m/s (tricuspid gradient 44 mmHg), and the right ventricular systolic pressure was 64 mmHg.

Lung ultrasound: Hydrothorax was present, with an anteroposterior (AP), basal pleural, hypoechoic "dense" effusion: on the left side measuring 9.9 × 9.4 cm (Figures 6, 7), with an AP diameter of 6.5 × 4.6 cm at the level of the scapular angle; on the right side, 3 cm below the scapular angle (AP), measuring 7.0 × 7.0 cm, and laterally 7.0 × 10.0 cm.

Figure 5. – Left atrial volume index (LAVI)

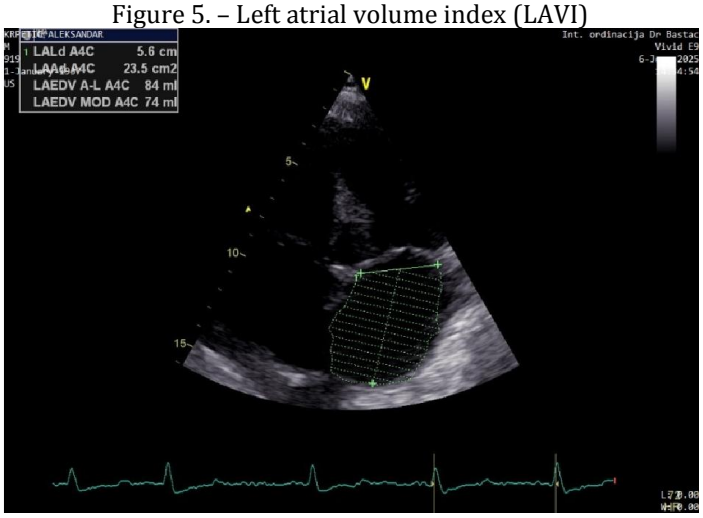


Figure 6. – B-mode echocardiogram: hypoechoic "dense" pleural effusion, AP diameter 9.4 cm with fibrin strands

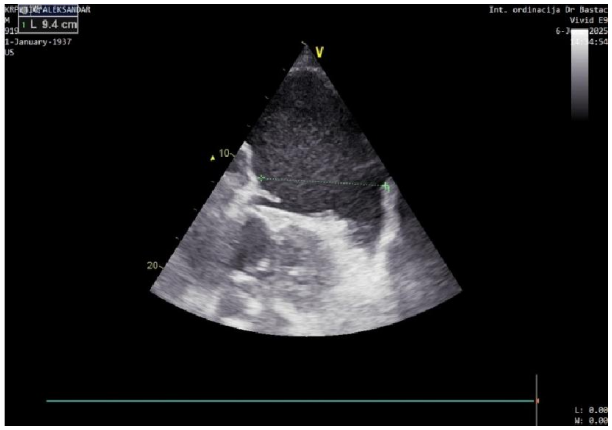
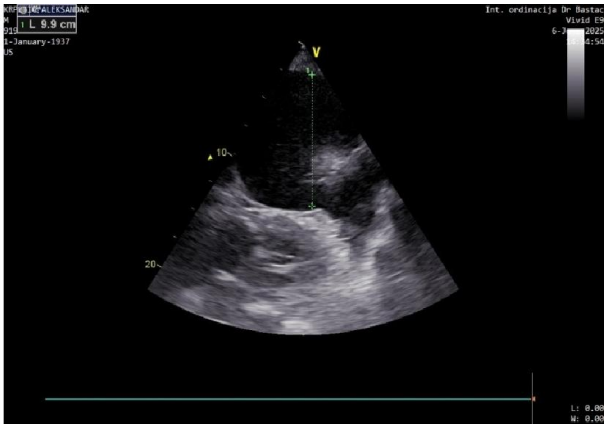


Figure 7. – B-mode echocardiogram: pleural effusion, cranio-caudal (CC) diameter 9.9 cm



Working diagnoses:

Congestive heart failure (ICD-10: I50), with echocardiographically reduced left ventricular ejection fraction (HFrEF ≈ 35%), accompanied by the following cardiac conditions: permanent atrial fibrillation (fibrillatio atriorum permanens), post-infarction myocardial scar of the inferior wall (cicatrix myocardii post infarctum parietis inferioris), functional left ventricular aneurysm of the inferior wall (aneurysma functionalis ventriculi sinistri cordis parietis inferioris), bilateral hydrothorax, mitral valve insufficiency and aortic semilunar valve insufficiency, and pulmonary arterial hypertension.

Comorbidities: Chronic kidney disease stage 3b (morbus renalis gradus 3b) and severe chronic microcytic iron-deficiency anemia (anemia microcytica sideropenica chronica, gradus gravis)..

COURSE OF DISEASE (DECURSUS MORBI)

The patient refused the proposed hospitalization at the Department of Internal Medicine, ZC Zaječar, despite being informed about the life-threatening condition requiring intensive care management. He was followed in a day-hospital setting at our outpatient facility with continuous ECG monitoring, blood pressure and urine output measurements, oxygen saturation monitoring, and other vital parameters. Due to severe anemia, blood transfusion of packed red blood cells was indicated; however, the patient did not present to the Blood Transfusion Service. The patient was immediately started on intensified parenteral diuretic therapy: on the day of examination, furosemide ampoules 20 mg, total No VIII (160 mg), administered in two intravenous boluses, in accordance with recommendations for the treatment of acute decompensation [6,13,14]. Early and aggressive diuretic therapy resulted in significant reduction of volume overload, which represents a key therapeutic goal [13–15]. A prompt and excellent diuresis was achieved.

On the following day, intravenous furosemide was continued at 20 mg ampoules No IV (80 mg). Previous outpatient therapy was adjusted: bisoprolol 5 mg tablets ½ tablet twice daily; rivaroxaban 15 mg once daily; spironolactone 25 mg once daily; and iron supplementation. Ramipril/hydrochlorothiazide 5/25 mg once daily in the morning, ramipril 5 mg once daily in the evening, and allopurinol 100 mg once daily were discontinued.

Guideline-directed medical therapy was introduced with ARNI: sacubitril/valsartan 26/24 mg, ½ tablet twice daily, and dapagliflozin 10 mg once daily, in accordance with current recommendations [7,8,16–18]. For improved correction of anemia, the iron therapy was intensified to a maximum dose of iron preparation (300 mg/day) instead of the previous supplementation regimen.

Correction of anemia was initiated due to its negative impact on functional status and clinical outcome, as it further aggravates tissue hypoxia [12,19]. Non-pharmacological measures included strict fluid and salt restriction and prohibition of physical activity. Under this therapeutic approach, a progressive increase in diuresis and significant reduction of edema were observed..

At the first control visit on the third day of treatment (June 7, 2025), an excellent response in fluid removal was observed: the patient had a weight reduction of 7 kg, with complete resolution of dyspnea on minimal exertion and a significant reduction of lower limb edema (circumference measurements: right leg 40 cm, 35 cm, 24 cm; left leg 36 cm, 34 cm, 24 cm). Hemoglobin increased to 72 g/L. At this point, from day 4, oral therapy was introduced with furosemide forte ½ tablet of 500 mg, and digoxin 0.25 mg ½ tablet every second day due to atrial fibrillation and hypotension. The patient was referred for multidetector computed tomography (MDCT) of the chest, which was not performed later in the course.

At the second control visit on the fifth day of treatment (June 11, 2025), the patient had a total weight loss of 12 kg and minimal residual edema (leg circumference: right 33 cm, 33 cm, 24 cm; left 34 cm, 33 cm, 24 cm). Lung examination showed normal breath sounds with mildly reduced basal ventilation, no prolonged expiration, and dullness to percussion at the bases below the 10th rib.

Echocardiographic evaluation demonstrated improvement in left ventricular ejection fraction and improved diastolic function (left ventricular compliance), with an E/e′ ratio of 7.5. Laboratory results showed serum iron <1 μ mol/L (normal 11 – 31) and ferritin 19.2 ng/mL (normal 20–250 ng/mL).

At the follow-up after two weeks (June 19, 2025), the patient maintained excellent clinical improvement, with an additional 2 kg weight loss (total 14 kg reduction from baseline), representing a very good therapeutic response. He reported dizziness and instability, attributed to hypotension (BP 90/55 mmHg and 80/50 mmHg), leading to dose reduction of hypotensive medications: furosemide 500 mg ½ tablet every second day and sacubitril/valsartan 26/24 mg ¼ tablet twice daily. Due to lower leg pain, diosmin + hesperidin 1000 mg once daily was added for venous symptoms.

New laboratory findings included: hemoglobin 88 g/L, erythrocyte sedimentation rate (ESR) 55 mm/h, urea 15.4 mmol/L, creatinine 131 μmol/L, GFR 44.8 mL/min/1.73 m^2, and potassium 4.4 mmol/L.

ECG: Atrial fibrillation with absolute arrhythmia, heart rate 65/min, ST depression up to 2 mm with negative T waves in V4–V6, and ST depression up to 0.5 mm with negative T waves in leads I, II, and aVL (Figure 8).

At routine follow-up after two months (August 25, 2025), the patient was asymptomatic, with a further 2 kg weight reduction, no leg edema, and no longer hypotensive. A marked increase in hemoglobin to 128 g/L was observed, attributed to iron therapy and correction of hemodilution. Renal function normalized (GFR = 64 mL/min/1.73 m^2).

Echocardiography (Figures 9, 10, and 11) showed a significant improvement in left ventricular systolic function, with M-mode EF of 47% and biplane Simpson EF of 46%, along with a reduction in left ventricular dilation (LVEDD = 50 mm, LVESD = 40 mm) and resolution of pulmonary hypertension (RVSP = 25 mmHg).

Further optimization of maintenance therapy was performed, including reduction of furosemide dose to 500 mg ¼ tablet every second or third day..

Figure 8. – ECG at 2-week follow-up

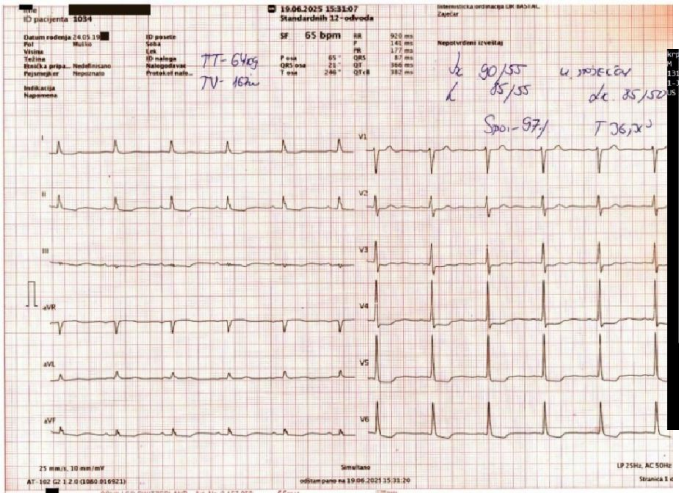


Figure 9. – M-mode echocardiogram: follow-up ejection fraction (EF) = 47% according to Teichholz method

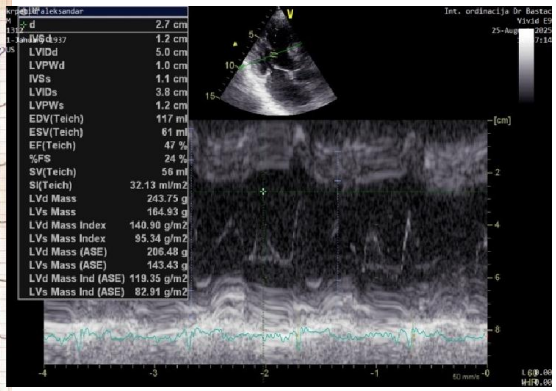


Figure 10. – B-mode echocardiogram: left ventricular ejection fraction (EF) = 52% (monoplane, Simpson's method, 4-chamber view)

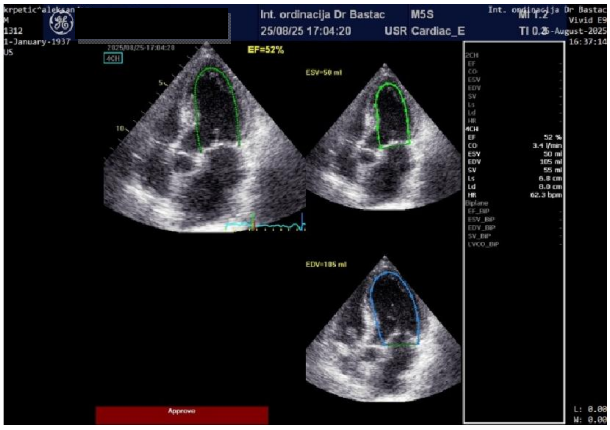
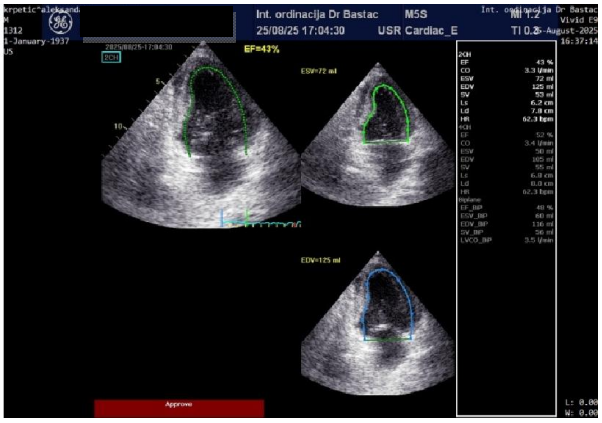


Figure 11. – B-mode echocardiogram: left ventricular ejection fraction (EF) = 43% (monoplane, Simpson's method, 4-chamber view)



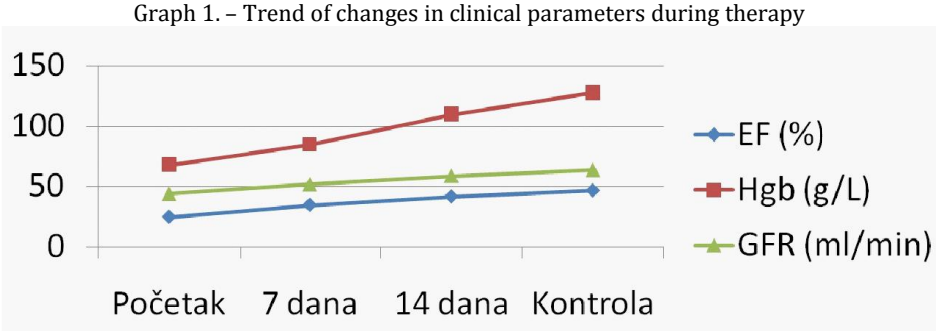
CLINICAL OUTCOME:

Following intensive intravenous diuretic therapy and three days of day-hospital management with ECG monitoring and continuous assessment of vital parameters, a significant clinical improvement was achieved. The patient was subsequently transitioned to oral therapy.

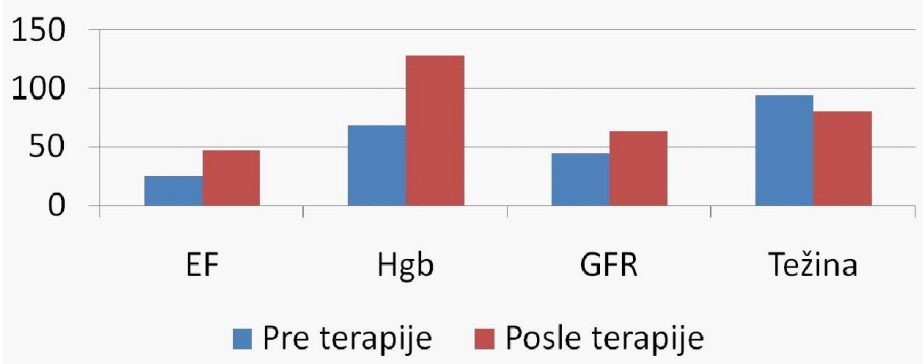
A total weight loss of 14 kg was recorded over a two-week period, accompanied by complete resolution of peripheral edema and normalization of lung auscultation findings. Pleural effusions regressed to minimal levels. Left ventricular systolic function remained preserved at approximately 46–47% ejection fraction, with improvement in diastolic function on echocardiography.

Laboratory parameters demonstrated progressive recovery of renal function (GFR improved from 44 to 64 mL/min/1.73 m^2) and a significant increase in hemoglobin levels following iron supplementation (Graph 1 and 2)

Graph 1. – Trend of changes in clinical parameters during therapy



Graph 2. – Comparative presentation of pre- and post-therapy effects



DISCUSSION

Anasarca represents an extreme form of fluid retention and a marker of advanced heart failure with a poor prognosis [5].

Diuretics remain the cornerstone of congestion therapy, with intravenous administration enabling faster and more effective decongestion [6,13,14]. However, their use requires careful monitoring due to the potential deterioration of renal function [10,20], hypokalemia, and, less frequently, hypovolemia and dehydration.

In this case, the improvement in renal function following therapy suggests reversibility of cardiorenal syndrome after congestion relief, as previously described in the literature [10,11]. Contemporary studies indicate that early initiation of SGLT2 inhibitors provides rapid clinical benefit and reduces hospitalization rates [17,21–23]. ARNI therapy further contributes to improved myocardial remodeling and reduced mortality [16]. Current guidelines emphasize the simultaneous or early sequential implementation of the five foundational therapeutic pillars, which is associated with the best clinical outcomes [7–9,24].

Congestion management remains the key therapeutic target, and individualized intravenous diuretic therapy with careful monitoring of body weight, urine output, and renal function is essential for successful treatment [14,15]. Anemia is a common comorbidity in heart failure, and its correction—particularly with intravenous iron preparations—improves symptoms and quality of life [12,19].

This case highlights the importance of timely initiation of intensive diuretic therapy, continuous monitoring of diuresis and laboratory parameters, and an individualized approach depending on comorbidities. It also demonstrates that an outpatient approach, under adequate supervision, may be feasible in selected patients with severe decompensated chronic heart failure that appears terminal and refractory to treatment, although such patients are most commonly managed in hospital settings [25].

CONCLUSION

Decompensated heart failure with anasarca represents a severe and life-threatening condition requiring an aggressive yet carefully titrated individualized therapeutic approach. Diuretic therapy remains the cornerstone in controlling volume overload. This case report highlights the importance of individualized diuretic therapy combined with contemporary pharmacological strategies in patients with the most severe forms of decompensated heart failure and anasarca. Timely initiation of high-dose parenteral diuretics, optimization of baseline therapy, and correction of associated disorders led to significant clinical and laboratory improvement in this patient.

This case also emphasizes the importance of intravenous therapy administration under continuous ECG monitoring, along with close observation and adjustment of treatment according to urine output, blood pressure, heart rate, serum potassium and nitrogenous waste levels, blood pressure, and oxygen saturation, in order to achieve optimal outcomes. Particular importance is given to individualized therapy and early recognition of refractoriness to standard oral treatment strategies in chronic heart failure management.

The combination of intensive diuretic therapy and modern pharmacological strategies can lead to substantial clinical improvement even in patients with advanced disease, as demonstrated in this case, which was successfully stabilized in an outpatient day-hospital setting.

LITERATURE:

1. Savarese G, Lund LH. **Global public health burden of heart failure.** Card Fail Rev. 2017;3(1):7–11.
2. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. **Heart disease and stroke statistics—2021 update: a report from the American Heart Association.** Circulation. 2021;143(8):e254–e743.
3. GBD 2022 Heart Failure Collaborators. **Global, regional, and national burden of heart failure, 1990–2022: a systematic analysis for the Global Burden of Disease Study 2022.** Lancet. 2022;400(10363):121–144.
4. Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J. **Harrison's Principles of Internal Medicine.** 19th ed. New York: McGraw-Hill Education; 2015.
5. Eapen ZJ, Tang WHW, Felker GM, Hernandez AF. **Defining true clinical equipoise: cardiac cachexia versus anasarca in advanced heart failure.** Eur J Heart Fail. 2012;14(5):495–500.
6. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. **2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.** Eur Heart J. 2021;42(36):3599–3726.
7. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. **2023 ACC Expert Consensus**

Decision Pathway on Management of Heart Failure with Reduced Ejection Fraction. J Am Coll Cardiol. 2023;81(18):1835–1878.
8. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. **2023 Focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.** Eur Heart J. 2023;44(37):3627–3739.
9. Greene SJ, Butler J, Fonarow GC. **Simultaneous or rapid sequence initiation of guideline-directed medical therapy for heart failure.** J Am Coll Cardiol. 2023;81(2):185–197
10. Damman K, Valente MAE, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. **Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis.** Eur Heart J. 2014;35(7):455–469.
11. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. **Cardiorenal syndrome.** J Am Coll Cardiol. 2008;52(19):1527–1539.
12. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, et al. **Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency.** Eur Heart J. 2015;36(11):657–668.
13. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. **Diuretic strategies in patients with acute decompensated heart failure.** N Engl J Med. 2011;364(9):797–805.
14. Verbrugge FH, Mullens W, Tang WHW. **Management of congestion in heart failure: state-of-the-art review.** Eur Heart J. 2023;44(24):2187–2200.
15. Damman K, Beusekamp JC, Boorsma EM, Swart HP, Smilde TDJ, Elvan A, et al. **Randomized, double-blind trial comparing high versus low dose loop diuretics in acute heart failure.** Eur J Heart Fail. 2023;25(3):456–466.
16. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. **Angiotensin–neprilysin inhibition versus enalapril in heart failure.** N Engl J Med. 2014;371(11):993–1004.
17. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. **Dapagliflozin in patients with heart failure and reduced ejection fraction.** N Engl J Med. 2019;381(21):1995–2008.
18. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. **Cardiovascular and renal outcomes with empagliflozin in heart failure.** N Engl J Med. 2020;383(15):1413–1424.
19. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al. **Ferric carboxymaltose in patients with heart failure and iron deficiency.** N Engl J Med. 2009;361(25):2436–2448.
20. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, et al. **The use of diuretics in heart failure with congestion – a position statement from the Heart Failure Association of the European Society of Cardiology.** Eur J Heart Fail. 2019;21(2):137–155.
21. Butler J, Anker SD, Filippatos G, Khan MS, Ferreira JP, Pocock SJ, et al. **Empagliflozin and outcomes in patients with heart failure with preserved, mildly reduced, and reduced ejection fraction: pooled analysis of EMPEROR trials.** Eur Heart J. 2023;44(5):449–460.
22. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Ferreira JP, Zannad F, et al. **Time to clinical benefit of dapagliflozin in patients with heart failure with reduced ejection fraction: insights from the DAPA-HF trial.** Circulation. 2023;147(5):375–385.
23. Docherty KF, Jhund PS, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. **Effects of dapagliflozin across the spectrum of ejection fraction in heart failure.** Nat Med. 2024;30(1):123–131.
24. Maddox TM, Januzzi JL Jr, Allen LA, Breathett K, Butler J, Davis LL, et al. **2024 ACC Expert Consensus Decision Pathway for optimization of heart failure treatment.** J Am Coll Cardiol. 2024;83(9):1056–1098.
25. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, et al. **The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries.** J Am Coll Cardiol. 2014;63(12):1123–1133.
26. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. **SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials.** Lancet. 2020;396(10244):819–829.
27. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. **Semaglutide in patients with heart failure with preserved ejection fraction and obesity (STEP-HFpEF trial).** N Engl J Med. 2023;389(12):1069–1084.

INSTRUCTIONS TO ASSOCIATES OR AUTHORS

Timok medical GAZZETTE publishes previously unpublished scientific and professional papers bilingually, in Serbian and English language from all fields of medicine and related branches. Original papers, patient case reports, review articles, medical and health history articles, book and journal reviews, editorial letters and other medical information are received for publication. The authors propose a category of their work and the Editorial Board reserves the right to change the category with the consent of the author.

Manuscripts should be prepared in accordance with the Vancouver Recommendations: UNIFORM REQUIREMENTS FOR MANUSCRIPTS SUBMITTED TO BIOMEDICAL JOURNALS, recommended by ICMJE (International Committee of Medical Journal Editors - Ann Intern Med. 1997; 126: 36-47), or in accordance with the Serbian languageversion JEDNOBRAZNI ZAHTEVI ZA RUKOPISE KOJI SE PODNOSE BIOMEDICINSKIM ČASOPISIMA, Serbian Archives of Medicine, 2002; 130 (7–8): 293. The digital version is freely available on the ICMJE website, www.icmje.org, as well as at www. tmg.org.rs/saradn.htm

When writing atext in English, one should adhere to the American English language standard and use short and clear sentences. Manuscripts received by the editorial staff are not expected to contain results already published by authors in another journal or similar publication. The original manuscript must be accompanied by the certificate of authorship (you can download the form at: www.tmg.org.rs), scanned signatures of all authors of the article.

The editorial board sends all the papers for peer review - usually two reviewers. Proceedings in supplements are not peer reviewed.

In works where the described patient may be identified, the utmost care should be taken to avoid any details that can identify him/her or obtain written consent for publication from the patient himself or his immediate family. When consent exists, it should be stated in the article.

If the paper receives positive anonymous reviews (2 reviewers) it will be accepted for publication. After receiving a positive review, in order for the paper to be published in electronic version on the website www.tmg.org.rs and printed, it is necessary to pay a fee for the cost of editing the article, proofreading and printing costs for the Timok medical journal **only for the first author**, which amounts to six thousand dinars (6000 RSD) paid to the current account.

Current Account: 205-167929-22
Serbian Medical Association-Zajecar Branch;
purpose: material processing for TMG.

TECHNICAL REQUIREMENTS

The manuscripts are to be submitted exclusively in electronic form, bilingually (starting with volume 45), in Serbian (preferably Cyrillic) and in English. Papers submitted only in Serbian or English only will not be considered. Send the manuscripts in electronic form to: tmglasnik@gmail.com

The electronic format of the manuscript should be in Microsoft Office Word (with a .doc or .docx extension) and should include a final version of the manuscript. All text, references, tables and titles of tables and images and legends of images should be in one document. It is best to form the filename by the first author's last name, one keyword and type of work (for example: paunkovic_tiroidea_originalni.doc).

Use the Times New Roman font, 12p size. Write the paragraph so that only the left alignment is straight. Do not divide words into syllables at the end of the line. Insert only one blank space after the punctuation mark. Allow the titles and subheadings to be aligned with the left edge. Use bold, italic, sub, and superscript and underlined letters only where necessary. **Tables, images and charts should be inserted in the text where they should appear in the paper**. Acceptable formats for tables, charts, illustrations, and photos are doc, xls, jpeg, gif, and npg.

TYPES AND SCOPE OF MANUSCRIPTS

The title of all types of articles is followed by Summary (up to 300 words) and keywords (3 to 8).

The Original Paper (work) is a systematically published research of a problem according to scientific criteria and a clear aim of the research. **The integral parts of the paper are: a) introduction**- (the aim of the paper as the last paragraph of the introduction); **b) material and methods**; **c) results; d) discussion; e) conclusion; f) literature**. The length of the text is limited to 3500 words, with a maximum of 5 tables, charts, or pictures (up to 12 pages of text).

A Review Article covers a systematically addressed specific medical problem, in which the author made some contribution, visible on the basis of self-citations. **Integral parts of the paper are: a) introduction**- (the aim of the review paper as the last paragraph of the introduction); **b) the text of the review of literatureonthe problem , with subtitles**; **c) conclusion; d) literature**. The review article is usually commissioned by the Editorial Board, but non-commissioned manuscripts are also considered. Contact the Editorial Board before writing a review article. Text length can be up to 5000 words (18 pages).

A Case Report (patient presentation**)** sheds light on individual cases ofmedical practice. It usually describes one to three patients, or one family. The integral parts of the paper are: **a) introduction**- (the aim of the paper as the last paragraph of the introduction); **b) presentation of the patient; c) discussion and d) conclusion**. Unlike the original research, omit the section on methodology and results. The text is limited to 2500 words, max 4 tables, or 4 pictures and up to 25 references (up to 6 pages of text in total). Patient names, initials, or medical history numbers should not be used, especially in the illustrations. Casereportsmust not have more than 5 authors

Articles in the history of medicine and health culture shed light on certain aspects of medical practice in the past. Text length can be up to 2500 words (6 pages). These and the articles statedbelow do not have a prescribed structure, such as original papers, case reports, and review articles. Short contributions from the field of medical practice (diagnostics, therapy, remarks, suggestions and opinions on methodological problems, etc.) are published, too, as well as presentations from various medical meetings, symposia and congresses in the country and abroad, book reviews and articles from foreign journals up to 1000 words, 1-2 tables or images, up to 5 references (up to 3 pages of text). Editorial letters have up to 400 words, or 250 words if they contain comments on published articles. By order of the editorial board, or in agreement with the editorial board, works of didactic character are published.

If the work is part of a master's thesis, or a doctoral dissertation, or is done in the framework of a scientific project, this should be **clearlyindicated in the note after the abstract and before the text**. Also, if the work has been previously announced at a professional meeting, state the official name of the meeting, the venue and time of the event, whether the work has been published and how it has been published (eg the same or a different title or abstract).

ETHICAL CONSENT. Manuscripts on human research should include a statement in the form of a written consent of the persons interviewed in accordance with the WMADeclaration of Helsinki and the approval of the responsible ethics committee that the research can be carried out and is in accordance with legal standards. Experimental research on human material and animal testing should include a statement from the ethics committee of the institution and be in accordance with legal standards. Information on this must be provided in the section

AUTHORSHIP. All persons listed as authors of the work should qualify for authorship. Each author should have participated sufficiently in the work on the manuscript to be able to take responsibility for the entire text and the results presented in the work. Authorship is based solely on: making a significant contribution to the concept of the work, obtaining results or analyzing and interpreting the results; the planning of the manuscript or its critical revision of considerable intellectual importance; the final refinement of the print version of the manuscript. Authors should attach a description of the contributions individually for each co-author within the Submission Letter form. Financing, collecting data or generally overseeing a research team cannot by itself justify authorship. All other contributors who are not the authors of the manuscript should be listed onthe

acknowledgementpage, with a description of their contribution to the work, with written consent, of course.

STATEMENT OF CONFLICT OF INTEREST. The manuscript is accompanied by a signed statement in the form of a Submission Letter stating the authors of each possible conflict of interest or lack thereof. For more information on the different types of conflicts of interest, visit the World Association of Medical Editors' Association (WAME; http://www.wame.org), entitled "Conflict of Interest Statement Policy".At the end of the paper, below the Remarks section, in a separate section Conflict of Interest,each possible conflict of interest or its absence should be declaredfor each author individually (full name of the author or initials) For example Zoran Petrovic: Krka (lecturer) Ljiljana Aleksic: none. Mila Bastac: Pfizer, Sanofi, Bristol-Meyers Squibb (lecturer, honorary consultant, researcher on ascientific project).

PLAGIARISM. As of January 1st, 2019, all manuscripts are subjected to plagiarism / autoplagiarism through the SCIndeks Assistant-Cross Check (iThenticate). Papers containing plagiarism or self-plagiarism will be rejected and the authors sanctioned.

ABBREVIATIONS. Use only when necessary, for very long names of chemical compounds, that is, abbreviations that are already recognizable (standard abbreviations, such as DNA, AIDS, HIV, ATP). For each abbreviation, the full term should be stated when first quoted, unless it is a standard unit of measure. Do not use abbreviations in the title. Avoid using abbreviations in the abstract, but if necessary, explain each abbreviation when first referenced in the text.

ACKNOWLEDGEMENTS. List all contributors who contributed to the creation of the work but did not meet the criteria for authorship, such as those providing technical assistance, writing assistance, or managing a department that provides general support. Financial and material assistance, in the form of sponsorships, scholarships, gifts, equipment, medicines and more, should also be listed

MANUSCRIPT PREPARATION

The text of the paper contains first and foremost the title of the paper, in the following lines: full names of the authors and all co-authors; the name, place and address of the institutions from which the author and co-authors come (in parentheses, associate the names of the authors); possibleacknowledgementfor help with elaborationofthe paper;

It is obligatory to submit:

-proposal of the manuscript category (original work, review article, case report, etc.);

-**first and last name, year of birth of the author and all co-authors**;

-**full address, telephone and fax numbers, as well as the author's e-mail for correspondence**.

The following is a SUMMARY (Abstract), up to 300 words is best. A summary cannot have footnotes, tables, images, or references. A summary of **the original papers** should include: Introduction (state the objective in the last sentence), **Material and methods, Results and Conclusions**. Write each of the segments listed at the beginning of the sentence in bold. Provide the most important results (numerical values) of the statistical analysis and the levelofsignificance. The conclusion must not be general, but must be directly linked to the results of the work. **For case reports, the summary** should have the following parts: **Introduction** (state the objective in the last sentence), **Case report, Conclusion**. For other types of papers the summary has no specific structure.

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

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

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

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

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

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

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

REFERENCES

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

Journal articles

Standard journal article:

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

Organization as author:

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

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

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

Books and other monographs

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

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

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

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

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

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

Electronic material

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

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

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

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

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

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

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

For any additional information, please contact the address and email below.

EDITORIAL ADDRESS

Timočki Medicinski Glasnik
(Timok Medical Journal)
Zdravstveni centar Zaječar
(Zaječar Health Center)
Pedijatrijska služba Pediatric Service
Rasadnička bb, 19000 Zaječar,
Serbia (Republic of Serbia-RS)

Ordinacija "Dr Bastać",
Kosančićev venac 16 19000 Zaječar
Serbia (Republic of Serbia-RS)
063402396, 019432333
dusanbastac@gmail.com

Email: tmglasnik@gmail.com
Website: http://www.tmg.org.rs/

TIMOČKI MEDICINSKI GLASNIK

TIMOK MEDICAL GAZETTE