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HEALTH RISK ASSESSMENT OF THE POPULATION OF THE CITY OF BOR (SERBIA) DUE TO THE INCREASE IN COPPER SMELTER CAPACITY

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Abstract: This study presents the results of research on the increased risk of non-carcinogenic health threats to children and adults, as well as the carcinogenic risk to the citizens of the city of Bor (Serbia), due to the 2.5-fold increase in the capacity of the copper smelter in Bor in mid-2023 and the exploitation of the "Čukaru Peki" mine with an increased arsenic (As) content multiple times above the limited values. After the stabilization of conditions in the new smelter, an analysis of the ambient air quality in the urban part of the city of Bor for the year 2024 was performed, as well as its impact on the risk of non-carcinogenic and carcinogenic effects on human health. The obtained results for the Hazard Quotient (HQ) < 1 indicate that the non-carcinogenic risk is acceptable. The results for carcinogenic risk (CR) = $5.58 \text{ E-}4$ for the measured maximum values of pollutant content in ambient air for 2024 indicate a highly unacceptable carcinogenic risk. For the average air quality values for 2024, CR = $1.24 \text{ E-}4$, which gives an assessment of a slightly unacceptable risk. The obtained results indicate that As and cadmium (Cd) have a predominant influence on CR values, while nickel (Ni) has a negligible influence. The influence of lead (Pb) requires a separate analysis using the Integrated Exposure Uptake Biokinetic Model (IEUBK) methodology.

Keywords: air pollution, PM₁₀, Pb, Cd, Ni, As, risk assessment,

Introduction

Ambient air pollution in industrially developed regions worldwide poses serious risks to human health [1], which is also the case in Serbia, especially in mining regions [2]. Many studies indicate that the concentration of particulate matter (PM) plays a major role in air pollution, primarily due to their chemical composition, which under aerodynamic conditions varies within diameters of 2.5 and 10 μm . PM particles have been identified as having an impact on human health during long-term exposure to high concentrations, which the World Health Organization (WHO) limited to 20 $\mu\text{g}/\text{m}^3$ in 2019 [3]. The air quality standard in the European Union (EU), defined by the European Environment Agency (EEA), sets annual limit values for PM₁₀ at 40 $\mu\text{g}/\text{m}^3$ as well as the content of heavy metals in them: Pb (0.5 $\mu\text{g}/\text{m}^3$), As (6 ng/m^3), Cd (5 ng/m^3), and Ni (20 ng/m^3) [4]. The legal regulations in Serbia are the same as in the EU [5]. It is necessary to point out the fact that the European Environment Agency (EEA) in 2024 adopted new limit values until 2030 as well as target values until 2050, where the value for PM₁₀ is reduced by 50%, while the values for Pb, Cd, Ni, and As remain at the same limit values [6,7].

According to the report of the International Agency for Research on Cancer (IARC), Cd seriously affects the health of children and adults, belonging to Group 1 of carcinogenic metals. Cd causes lung and kidney cancer since it enters the bloodstream. In children, it increases respiratory infections, reduces cognitive abilities, while in adults it causes hypertension, chronic kidney failure, and lung cancer [8]. Lead (Pb), which is also found in PM₁₀ particles, accumulates cumulatively in the bloodstream and is difficult to excrete from the body. In children, it causes learning and memory disorders, causes permanent brain damage, and reduces intelligence quotient (IQ). In adults, it causes cardiovascular problems, kidney failure, and osteoporosis [9]. Nickel (Ni) accumulates in the lungs and bloodstream. IARC classifies Ni and its compounds into Group 1 of carcinogenic elements. Ni is associated with cancer of the lungs, larynx, and nasal cavity, as well as DNA damage [10]. Arsenic (As) is also classified by IARC into Group 1 of carcinogenic substances, and WHO emphasizes that there is no safe level of As in ambient air [39]. In children, it causes bronchitis and respiratory tract infections, and in combination with Ni, it negatively affects the development of the nervous system and cognitive abilities, as well as cancer in

adulthood. In adults, it negatively affects the cardiovascular system, most often causing lung, bladder, and liver cancer [11,12].

SIGNIFICANCE AND AIM OF THE STUDY

The study is conducted to provide an answer about the level of risk from inhaling polluted air, after the 2.5-fold increase in the capacity of the copper smelter in Bor (Serbia) in mid-2023 [5], from the standpoint of exposure to PM10 particles containing heavy metals (Pb, Cd, Ni, and As).

Information from the Institute for Mining and Metallurgy in Bor (Serbia), available on the website of the City of Bor administration, was used [13].

In this study, PM10 particles were chosen instead of PM2.5 for the following reasons [12]:

- a) PM10 particles are a verified pollutant harmful to human health. The new WHO air quality guidelines from 2021 provide recommendations for six pollutants, one of which is PM10, which significantly affects human health independently of PM2.5 [39],
- b) Although PM2.5 penetrates the lungs more easily than PM10, the impact of particle exposure on human health depends on their chemical composition, not just their size.
- c) It should also be noted that PM10 particles correspond to particles with a smaller aerodynamic diameter than 10 μm , which also includes PM2.5 [14, 15].

The main aim of this study is the analysis of spatial and temporal variation of heavy metals (As, Cd, Pb, and Ni) and the assessment of the Hazard Quotient (HQ) and Cancer Risk (CR) in children and adults using different routes of pollutant intake into the body: inhalation, ingestion, and dermal absorption [1].

For the analysis of the set goals, available data from measuring stations that were operational in the territory of the urban part of the city of Bor (Serbia) in the period after the 2.5-fold increase in the capacity of the copper smelter in Bor were used [5]. Annual results for 2024, when production in the copper smelter stabilized, were analyzed, indicating that the same ambient air quality can be expected in the coming period. The exceedances of heavy metal concentrations in the considered year 2024 in PM10 particles indicate an increased risk of cancer in both children and adults [1,16,17],

which indicates the justification of the research whose results are presented in this paper.

The problems of ambient air pollution in Bor, especially after the 2.5-fold increase in smelter capacity, do not pose a risk to human health only in the area of this agglomeration, but can have potential cross-border consequences, considering that the air distance to the border with Bulgaria is about 20 km, and to Romania, an EU member state, about 80 km. These circumstances indicate the need for enhanced monitoring of ambient air quality and consistent tracking of compliance with European Union standards in this area, which further confirms the relevance of the conducted study.

MATERIAL AND METHODS OF RESEARCH

The ambient air quality in the Bor agglomeration was problematic primarily due to the copper smelter that began operation at the beginning of the 20th century. Episodes of extremely high concentrations of sulfur dioxide SO₂ were problematic [18] until the construction of the new smelter in 2015, when the SO₂ concentration was reduced to acceptable limits [5]. In addition to the SO₂ content in ambient air, the concentration of PM10 particles with increased heavy metal content, primarily Pb, Cd, Ni, and As [19], in the air but also in the soil in the wider surroundings of the smelter [20], has always been problematic. Air contamination with heavy metals contained in PM10: As, Cd, Pb, Ni, which is continuously measured, still represents a problem for the citizens of Bor [16], especially after 2023 [5]. In mid-2023, the foreign owner of the copper smelter in Bor reconstructed it and increased the smelter's capacity by 2.5 times compared to the previous state, which represents a great challenge for the ambient air quality in Bor. The reconstructed smelter uses Flash Smelting and Converting Furnaces technology [21], achieving temperatures up to 1300 °C. Undesirable heavy metals under such conditions—Pb, Cd, Ni, and As—melt at 327 °C, 321 °C, 1455 °C, and 614 °C, respectively, with As sublimating at that temperature. Cd, Pb, and Ni boil at the following temperatures: 767 °C, 1749 °C, and 2913 °C, respectively, indicating that As and Cd are converted to a gaseous state during the process, and during cooling, they transform into fine particles that are found in ambient air in the form of oxides [21], while the content of Pb and

Ni partly comes from dust from copper concentrate and mining production.

The problem of ambient air quality and negative impacts on human health is increased by the opening of the new copper mine "Čukaru Peki" with a copper content in the ore of 2.71% Cu and 1.75 g/t Au, with full ownership by a foreign company and a mining royalty of only 3%, which is extremely attractive for accelerated exploitation. In the obtained copper concentrate from processing this ore, the Cu content ranges from 20–30% Cu (which is optimal for the technological smelting process) and copper utilization ranges from 88–95%. A major problem arises from the fact that As concentrations in the copper concentrate range from 0.52–2.5% [22]. Copper concentrate with such a high As content, according to the laws of the EU and Serbia, should not be smelted in copper smelters [5, 23]. According to the law of the Republic of Serbia, the upper limit of As content in copper concentrate that can be treated in a copper smelter is 0.2% As, which in real conditions in the Bor copper smelter is more than ten times higher. However, the copper smelter and the mine are owned by a foreign company that does not respect the laws of Serbia. In addition to copper concentrate produced in Serbia, this company imports concentrates from abroad, and their chemical composition is not available to the public. Also, copper concentrate from Bor is exported through the port of Bar (Montenegro), where the concentrate is transshipped from trucks to ships. Recently, an increased Pb content in the blood of these workers was determined. The allowed limit of Pb in human blood is 2.8 µg/dL. Much higher values were found in 58 out of 63 tested workers who experienced visible health problems. The Pb content in the blood ranged from 8.0–15.9 µg/dL, and in one worker, a content of 25.1 µg/dL was determined. At the same time, an increase in Pb content in the blood was registered in workers at the copper smelter in Bor who sought medical help [24]. EU directives have lowered the limit values for Pb content in the blood of workers in plants with increased Pb concentration from 40–70 µg/dL to 15 µg/dL, which indicates that after the increase in the capacity of the copper smelter in Bor, monitoring of air quality in the smelter as well as in the ambient air in the city of Bor must be increased.

The problem of PM10 concentration in the ambient air in Bor, as well as in the working environment of the copper smelter, greatly increases concern. By measuring the concentration of these particles in a closed classroom at the Technical Faculty in Bor in the period March 5–19, 2018 (winter period when the windows and doors of the classroom were closed), a concentration of PM10 particles inside the classroom of 28.2 µg/m³ was determined, while the concentration of these particles outside was 46.1 µg/m³. The concentration of carcinogenic metals in them was: As 17 ng/m³, Cd 1.4 ng/m³, and Pb 456.7 ng/m³. About 20 students stay in this classroom for 4–6 hours daily [25]. Also, in the period March 1 – April 1, 2025, measurements of PM10 and PM2.5 concentrations were carried out in 15 selected apartments where people live. The measurements determined the mean concentration in the apartment ambient of PM10 and PM2.5 at 31.3 µg/m³ and 17.6 µg/m³, respectively. The content of heavy metals was not determined, but the obtained results deserve special attention and justified concern [26].

In addition to the ambient air quality in the city of Bor, during more than a century-long tradition of copper production in the copper smelter, continuous contamination of the soil in the vicinity of this smelter is present. Research at 12 locations in the wider area around the copper smelter at about 20 km showed the following mean results of heavy metal content in the soil at a depth of about 30 cm: 913.33 µg/kg Cu, 86.67 µg/kg Pb, 2.92 µg/kg Cd, 36.83 µg/kg Ni, 1070 µg/kg Mn, and 59.08 µg/kg Hg, 0.133 µg/kg [20]. These results indicate the distribution of deposited heavy metals in the soil that can be further distributed through groundwater and surface water, and plants used by the population for food, which increases the risk to human health. These facts require a separate study, especially on the impact of Pb on human health using the Integrated Exposure Uptake Biokinetic Model (IEUBK), a methodology prescribed by the United States Environmental Protection Agency (US EPA) as early as 2007 [27].

In the vicinity of the copper smelter in Bor, continuous measurement of the concentration of SO₂, PM10, and the content of As, Pb, Cd, and Ni in PM10 particles in ambient air is carried out, which is the predominant impact on human health. Measurements have

been carried out at eight measuring points since 2024, and monthly and annual reports of the Institute for Mining and Metallurgy in Bor are published on the website of the city of Bor [13].

RESULTS AND DISCUSSION

Health status of people in the city of Bor (Serbia)

The State Institute for Public Health of Serbia "Dr. Milan Jovanović Batut" in Belgrade publishes annual results on cancer incidence and mortality by region in Serbia. Table 1 shows the results for the period 2016-2022 for the Bor region, compared with the results in the region of Central Serbia and Serbia as a whole, from the aspect of new cases and the number of deaths from cancer [28].

Table 1. Number of newly diagnosed cases and number of deaths from cancer in the period 2016-2022 [28]

Year	Whole Serbia A		Whole Serbia B		Central Serbia A	
	A	B	A	B	A	B
2016	570	305	553	295	621	321
2017	587	306	570	300	657	324
2018	597	309	578	303	710	309
2019	609	307	585	300	739	295
2020	600	301	576	230	714	277
2021	611	292	595	285	730	264
2022	625	291	604	285	793	313

A: Number of new cancer cases per 100,000 inhabitants B: Number of deaths from cancer per 100,000 inhabitant

The results presented in Table 1 indicate a visibly higher rate of new cases and deaths from cancer per 100,000 inhabitants in the observed period in the Bor region compared to the region of Central Serbia as well as Serbia as a whole. With the 2.5-fold increase in the capacity of the copper smelter in Bor in mid-2023, as well as the increased content of carcinogenic metals in PM10, an increase in the number of new cases and deaths from cancer should be expected in the coming period.

Considering that the data given in Table 1 refer to the Bor District, which besides Bor

also includes the cities of Negotin, Kladovo, and Majdanpek, where exposure to polluted air is much lower, and that the city of Bor has about 35,000 inhabitants, a realistic estimate is that the number of new cases and deaths from cancer in the city of Bor is much higher than the figures stated in Table 1.

Due to increased mortality and migration trends, the population in Serbia is generally decreasing, but this decrease in Bor is about three times greater due to increased mortality in this city compared to the rest of Serbia, Table 2.

Table 2. Population decrease in Serbia in the period 2016 – 2022 [28]

Period	Whole Serbia		Whole Serbia		Central Serbia	
	Number	%	Number	%	Number	%
2016-2022	411319	5,83	270192	5,22	15502	13,30

A: Number of inhabitants that decreased B: Percentage (%) of decreased number of inhabitants

Health risk assessment from direct inhalation of heavy metals in PM10 has been applied in many studies [29, 12, 30, 31, 17].

For the assessment of health risk to human health in the city of Bor from direct inhalation of heavy metals in PM10 particles in ambient air from the aspect of non-carcinogenic and carcinogenic effects, the US EPA methodology [27] was used.

Non-carcinogenic effects

The Estimated Daily Intake (EDI) was performed according to the methodology [29]:

$$EDI = (C \times IR \times AF \times F \times ED) / (BW \times AT) \quad (1)$$

$$AT = ED \times 365$$

Meaning of individual symbols

Table 3. Symbols, names, and units of measure used in equations (1)-(5)

Symbol	English term	SERBIAN TERM	Translation
EDI	Estimated Daily Intake	procenjeni dnevni unos	estimated daily intake
C	Contaminant Concentration	koncentracija kontaminanta	contaminant concentration
IR	Intake Rate	stopa unosa/udisanja	intake/inhalation rate
AF	Bioavailability Factor	faktor bioraspoloživosti	bioavailability factor

F	Frequency of Exposure	učestalost izloženosti	frequency of exposure
ED	Exposure Duration	trajanje izloženosti	exposure duration
BW	Body Weight	telesna masa	body weight
AT	Averaging Time	vreme usrednjavanja	averaging time

The parameter for non-carcinogenic risk (HQ) represents the sum of all hazards for different substances [27], i.e., the HQ hazard quotient represents the ratio between the estimated exposure dose and the reference dose RfD.

That is:

$$HQ = EDI / RfD \dots\dots\dots (2)$$

where RfD represents the reference dose ($\mu\text{g}/\text{kg}$ body weight/day).

Values for reference doses RfD for different substances for non-carcinogenic risk assessment were used from reference databases [32,33]. If:

$HQ < 1$ risk acceptable.

$HQ > 1$ possible health problems.

The total non-carcinogenic risk HQ is determined by equation (3) ACCORDING to inhalation of a larger number of substances at the same time:

$$\Sigma HQ = HQ1 + HQ2 + \dots\dots + HQn \dots\dots\dots (3)$$

where 1–n represents the number of analyzed pollutants in the air..

Carcinogenic effects

Carcinogenic risk (CR) represents the lifetime risk of cancer. It is estimated that a person will develop cancer during their lifetime due to exposure to carcinogenic components [27, 32,33, 34]:

$$CR = EDI \times SF \dots\dots\dots (4)$$

where CR, EDI, and SF represent, respectively, carcinogenic risk (dimensionless quantity), estimated daily intake ($\mu\text{g}/\text{kg}$ body weight/day), and inhalation slope factor (SF) [$(\mu\text{g}/\text{kg}$ body weight/day) $^{-1}$].

Values of slope factors (SF) used for carcinogenic risk assessment for different substances were taken from relevant reference databases [35, 32, 33]. Total CR is used as a summary indicator for all carcinogenic substances, as the probability of cancer occurrence due to exposure:

$$\Sigma CR = CR1 + CR2 + \dots\dots + CRn \dots\dots\dots (5)$$

Acceptable risk limits are: CR: less than 10^{-6} - negligible risk; 10^{-6} - 10^{-4} - acceptable risk; $>10^{-4}$ - high risk.

For the impact of Pb from ambient air on general health and carcinogenic impact, a special procedure prescribed by IEUBK developed by US EPA 2021 is used [36]. This model includes the total intake of Pb into the body: from soil, water, house dust, food, and inhalation (which makes up about 10% of the total amount of Pb ingested), based on which the blood lead level (BLL) is calculated, which is not the subject of this study, considering the availability of only data on Pb content in ambient air [36,37].

The level of ambient air pollution in the urban part of Bor, measured at eight measuring stations by the concentration of PM10 particles, as well as the content of heavy metals in them, according to the US EPA standard [27]: Pb, Cd, Ni, and As. Table 4 shows the results of mean annual contents of the mentioned pollutants, maximum daily content, as well as the number of days during the calendar year when the upper limit values were exceeded, which served as starting values for health risk assessment in the Bor city agglomeration..

Table 4. Measured values of PM10, Pb, Cd, Ni, and As in ambient air in 2024 measured in the territory of the city of Bor

Measuring site		PM10 ($\mu\text{g}/\text{m}^3$)	Pb ($\mu\text{g}/\text{m}^3$)	Cd (ng/m^3)	Ni (ng/m^3)	As (ng/m^3)
Jugopetrol	X1	169,8	2,898	286	17,4	471
	X2	37	0,243	19,8	2,4	42
	X3	77	14	46	0	66
Oštrelj	X1	107,5	0,113	16,7	17,9	28,5
	X2	36,7	0,015	13,6	2	3,3
	X3	75	0	3	0	44
Brezonik	X1	139,5	0,390	28,3	12,6	88
	X2	30,6	0,029	2,65	2	5,6
	X3	86	0	53	0	75

Gradski park	X1	57,1	0,063	4,94	15,6	13,4
	X2	22,6	0,008	0,72	2	2,30
	X3	3	0	0	0	6
Ind. zona	X1	139,5	3,293	116,9	10,1	221,9
	X2	32,8	0,11	8,01	2	15,1
	X3	34	0	54	0	92
Krivelj	X1	85,3	0,121	26,8	17	35,8
	X2	26,8	0,070	0,68	2	14
	X3	16	0	5	0	9
Institut	X1	71,30	0,43	33,6	5,2	47,7
	X2	30,7	0,073	3,91	2	6,7
	X3	4	0	14	0	21
Metovnica	X1	57,1	0,063	4,94	15,6	13,4
	X2	22,6	0,08	0,72	2	2,3
	X3	3	0	0	0	8

X1 – Maximum measured mean daily value at the measuring site

X2 – Annual mean value at the measuring site

X3 – Number of days in which the allowed limit value was exceeded at the measuring site

Considering the fact that all eight measuring sites in the Bor city agglomeration are distributed at different locations in accordance with the existing wind rose, as well as the fact

that people move throughout the entire city area and are exposed to the effects of polluted air in the entire area where air monitoring was carried out. Therefore, the mean value of maximum concentrations measured at individual measuring sites (X1), the mean value of average values at all measuring sites (X2), and the mean value of the number of days when limit values were exceeded (X3) were calculated, and the obtained results are shown in Table 5.

Table 5. Annual mean values of pollutant concentrations at all measuring sites in the territory of the city of Bor in 2024.

Scenario	PM10 ($\mu\text{g}/\text{m}^3$)	Pb ($\mu\text{g}/\text{m}^3$)	Cd (ng/m^3)	Ni (ng/m^3)	As (ng/m^3)
X1	103,38	0,921	64,77	15,15	114,96
X2	29,97	0,0748	4,56	2,05	11,41
X3	37,25	1,78	21,87	0	40,19

X1- Arithmetic mean of measured maximum values in the territory of the city of Bor

X2- Arithmetic mean of mean annual values at all measuring sites in the territory of the city of Bor

X3- Arithmetic mean of the number of days when limit values of pollutants were exceeded in the territory of the city of Bor

Table 6 shows a comparative analysis of data by scenarios: X-1, X-2, and X-3 for mean values for all measuring sites in the Bor agglomeration for 2024 and 2025. In 2025, according to Scenario X-1, a decrease of $4.13 \mu\text{g}/\text{m}^3$ for PM10, a decrease of $0.431 \mu\text{g}/\text{m}^3$ for Pb, a decrease of $30.71 \text{ ng}/\text{m}^3$ for Cd, a decrease of $4.2 \text{ ng}/\text{m}^3$ for Ni, and an increase of $17.89 \text{ ng}/\text{m}^3$ for As were determined. According to Scenario X-2, an increase of $5.53 \mu\text{g}/\text{m}^3$ for PM10, an increase of $0.011 \mu\text{g}/\text{m}^3$ for Pb, a decrease of $2.4 \text{ ng}/\text{m}^3$ for Cd, a decrease of $0.04 \text{ ng}/\text{m}^3$ for Ni, and a decrease of $2.01 \text{ ng}/\text{m}^3$ for As were determined. According to Scenario X-3, the variation in the number of days of exceeding limit values for each pollutant individually is within the range of

(+/-) three days. The values for the first five months in 2026 are within the range of (+/-) 5% for all three scenarios. These facts indicate that the operation of the reconstructed copper smelter has stabilized, and that variations in the content of pollutants in the ambient air in the urban part of the city of Bor can affect the level of risk HQ and CR to human health, compared to the results obtained for 2024, with variations within limits below 5% in the coming period. The greatest danger arises from constant exposure of people to the stated concentrations of pollutants in ambient air over a longer period of time due to the cumulative effect that leads to a growing level of CR.

Table 6. Dependence of pollutant concentrations in ambient air of the city of Bor 2024/2025 according to scenario X-1 and X-2

Scenario	PM10 ($\mu\text{g}/\text{m}^3$) 2024/2025	Pb ($\mu\text{g}/\text{m}^3$) in PM10 2024/2025	Cd (ng/m^3) in PM10 2024/2025	Ni (ng/m^3) in PM10 2024/2025	As (ng/m^3) in PM10 2024/2025
X-1	103.38/99.25	0.921/0.496	64.77/34.06	15.15/10.95	114.96/132.85
X-2	29.97/35.5	0.078/0.089	4.56/2.15	2.05/2.01	11.41/9.40

For scenario X3, values vary within the range of (+/-) 3 days, indicating that the values from 2024 have not changed.

The results presented in Table 5 were used for health risk assessment for non-carcinogenic risks: Estimated Daily Intake (EDI) and HQ for children and adults, as well as for CR assessment for children and adults using equations (1) - (5). For calculating these values, the following parameters were used for children (7 years of age, 20 kg body weight, and inhalation rate of $10 \text{ m}^3/\text{day}$) and for adults (30 years of age, 70 kg body weight, and $20 \text{ m}^3/\text{day}$). For health risk assessment for metals in PM10 (Pb, Cd, Ni, and As), available data from the California Environmental Protection Agency (CalEPA 2016) and US EPA 2016 databases for RfD and slope factor (SF) were used, which enable the calculation of EDI, HQ, and CR for children and adults.

Health Risk Assessment

Assessment of non-carcinogenic risks

Assessment of non-carcinogenic risk by calculating the Estimated Daily Dose (EDD) was performed according to equation (1), and HQ assessment was performed using equation (2) with recommended values in databases [35,32] for children and adults.

a) Non-carcinogenic risk assessment for children
The calculated HQ1 values for children for individual toxic elements in PM10 for maximum pollutant content values in 2024 (Scenario X-1) are as follows: HQ1 - As = 0.18; HQ1 - Cd = 0.062; HQ1 - Ni = 0.00036. Total HQ1 = $0.24236 < 1$. The obtained results indicate that the non-carcinogenic risk for children is negligible based on maximum pollutant values in ambient air (Scenario X-1).

The values for mean annual concentrations of pollutants in ambient air of the city of Bor for 2024 (Scenario X-2) are as follows: HQ2-As = 0.018; HQ2-Cd = 0.0044; HQ2-Ni = 0.00005.

Total: HQ2 = $0.02245 < 1$.

The obtained results indicate that the non-carcinogenic risk for children is negligible based

on mean annual values of pollutants in ambient air in the city of Bor (Scenario X-2).

The values for HQ1 and HQ2 for children are < 1 , indicating that there is currently no acute non-carcinogenic risk. As shows the highest potential danger, which in long-term exposure to these concentrations of As and Cd pollutants can cumulatively be very dangerous for the health of the young population in this agglomeration.

b) Non-carcinogenic risk assessment for adults

For adults, HQ1 values based on maximum values for individual pollutants in ambient air in the city of Bor during 2024 (Scenario X-1) are:

HQ1-As = 0.11; HQ1-Cd = 0.036; HQ1-Ni = 0.00021. Total value: HQ1 = $0.14621 < 1$.

Non-carcinogenic risk assessment for adults based on mean annual values of pollutant content in ambient air of the city of Bor (Scenario X-2) was performed in the same way by assessing HQ2 values for each pollutant in ambient air:

HQ2-As = 0.010; HQ2-Cd = 0.0026; HQ2-Ni = 0.00003.

Total value: HQ2 = $0.01263 < 1$.

The obtained results indicate that the total non-carcinogenic risk HQ1 < 1 for adults based on maximum recorded values of pollutant concentrations in ambient air during 2024 (Scenario X-1) is negligible. Also, the total non-carcinogenic risk HQ2 < 1 for adults based on mean values of pollutant concentrations in ambient air during 2024 (Scenario X-2) is negligible.

In all cases, the non-carcinogenic risk for children and adults according to Scenario X-1 and Scenario X-2 has a decreasing trend in the series: HQAs $>$ HQcd $>$ HQNi. For Pb, the impact was not calculated because its impact requires a special IEUBK procedure, but considering its low content in ambient air, its impact could increase total HQ values by at most 10%, which would not affect the total HQ values.

Carcinogenic risk assessment

A) Carcinogenic risk assessment for the child population

CR calculation was performed using equation (4) and for the total annual risk equation (5). The obtained CR values for individual pollutants for

maximum values in 2024 for the child population are as follows (Scenario X-1):

CR1-As = $8.2\text{E-}5$; CR1-Cd = $4.7\text{E-}4$; CR1-Ni = $6.0\text{E-}6$. Total CR1 = $5.58\text{E-}4$.

For mean annual values for 2024, the following values were obtained (Scenario 2):

CR2-As = $8.1\text{E-}5$; CR2-Cd = $3.3\text{E-}5$; CR2-Ni = $5.0\text{E-}6$. Total CR2 = $1.24\text{E-}4$.

According to Scenario X-1, total CR = $5.58\text{E-}4$ is 5.6 times higher than the EPA value and represents an unacceptable risk in which Cd contributes 84.2%, As 14.7%, and Ni 1.1%. According to Scenario X-2, total CR = $1.24\text{E-}4$, which is about 24% above the EPA value and represents a slightly unacceptable risk in which As = 66.9%, Cd = 26.9%, and Ni = 6.5% participate.

B) Carcinogenic risk assessment for adults

Carcinogenic risk (CR) assessment for adults based on maximum pollutant values in PM10 during 2024 (Scenario X-1) shows the following values: CR1-As = $4.8\text{E-}4$; CR1-Cd = $2.7\text{E-}5$; CR1-Ni = $3.0\text{E-}6$. Total CR1 = $5.07\text{E-}4$.

The share of individual pollutants in total CR according to Scenario X-1 is as follows: As $\approx 94.7\%$, Cd $\approx 5.3\%$, and Ni $\approx 0.6\%$.

Carcinogenic risk assessment for mean annual values of pollutant concentrations in ambient air in the urban part of the city of Bor (Scenario X-2) shows the following values: CR2-As = $4.7\text{E-}5$; CR2-Cd = $2.0\text{E-}5$; CR2-Ni = $2.1\text{E-}6$. Total CR2 = $6.91\text{E-}5$.

The share of individual pollutants in total CR2 according to Scenario X-2 is as follows: As $\approx 68\%$, Cd $\approx 28.9\%$, and Ni $\approx 3\%$.

The value of total CR1 = $5.07\text{E-}4$ is multiple times higher than the limit value defined by the EEA of $1.0\text{E-}4$ and represents an unacceptable risk to the health of adults. For Scenario 2, CR2 = $6.91\text{E-}5$, which is within the limits between $1.0\text{E-}4$ and $1.0\text{E-}6$, so the risk is considered to be within acceptable limits. However, considering the fact that As has a predominant influence on CR and that its concentration during 2024 was above the allowed limit for a total of 40.19 days (Table 5), this indicates that the CR for ambient air in the studied region can be considered unacceptable..

Multivariate analysis

Based on bivariate analysis of annual concentrations of pollutants in ambient air in the urban zone in Bor, Pearson correlation coefficients were calculated in Table 7. Statistical analysis of data was performed using the SPSS statistical software package, with assessment of statistical significance of relationships between observed variables [38]. A positive correlation of 0.99 represents a high level of agreement ($p < 0.01$) between As concentration and Cd concentration. Also, a good positive correlation exists between As concentration and Ni of 0.93, as well as between Cd and Ni of 0.94. There is also a negative correlation between Pb concentrations and Cd: -0.96; Ni: -0.83; and As: -0.95, respectively. The obtained high positive correlation coefficients between As, Cd, and Ni indicate their relationship in the concentrates treated during 2024 in good correlation, while the negative correlation of Pb with As, Cd, and Ni indicates that the Pb content in the concentrate was variable..

Table 7. Pearson correlation coefficients between pollutants in PM10 particles

	Pb	Cd	Ni	As
Pb	1			
Cd	-0,96	1		
Ni	-0,83	0,94	1	
As	-0,95	0,99	0.93	1

Table 8 shows Pearson correlation coefficients between HQ and CR values for children and adults for both scenarios of pollutant concentrations in ambient air (Scenario X-1 and Scenario X-2). The obtained results show a high degree of positive correlation between values for child and adult populations for HQ within the range of 0.93 – 0.98, indicating a high correlation between non-carcinogenic health risk for child and adult populations according to

both scenarios X-1 and X-2, i.e., $(\text{HQ}_{1,2})\text{A} / (\text{HQ}_{1,2})\text{B} = 0.93\text{--}0.98$.

Positive correlation within the range of 0.96–0.99 between CR risk in child and adult populations according to Scenario X-1 and X-2, i.e., $(\text{CR}_{1,2})\text{A} / (\text{CR}_{1,2})\text{B} = 0.96\text{--}0.99$ indicates equal cancer risk for both populations. The lowest degree of positive correlation was found for the ratio of HQ and CR for Scenario X-1 and X-2, within the range of 0.78 – 0.83 for the adult population, and for the child population within

the range of 0.83-0.88. Taking into account that the HQ/CR correlation is positive for the child population relative to the same ratios for the adult population $(HQ_{1,2}/CR_{1,2})_A > (HQ_{1,2}/CR_{1,2})_B$, the probability that children

will be exposed to CR over time is higher. The correlation between $(CR_{1,2})_A / (CR_{1,2})_B = 0.96-0.99$ indicates that the probability of CR for both populations is in a high positive correlation..

Table 8. Pearson correlation coefficients between HQ and CR for children and adults according to scenario X-1 and X-2

	HQ ₁ -A	HQ ₂ -A	HQ ₁ -B	HQ ₂ -B	CR ₁ -A	CR ₂ -A	CR ₁ -B	CR ₂ -B
HQ ₁ -A	1							
HQ ₂ -A	0.98	1						
HQ ₁ -B	0.97	0.96	1					
HQ ₂ -B	0.95	0.94	0.93	1				
CR ₁ -A	0.88	0.85	0.84	0.82	1			
CR ₂ -A	0.86	0.83	0.82	0.80	0.99	1		
CR ₁ -B	0.87	0.84	0.83	0.81	0.98	0.98	1	
CR ₂ -B	0.84	0.81	0.80	0.78	0.97	0.96	0.98	1

(1) – Scenario X-1; (2) Scenario X-2; A- Child population; B- Adult population

CONCLUSION

The increase in the capacity of the copper smelter in Bor (Serbia) in the second half of 2023 by 2.5 times and the exploitation of the Čukaru Peki mine with increased As content in the ore, which in the copper concentrate has a content more than ten times above the allowed limit of 0.2% As, as well as the increase in Cd content in many ways, reduces the quality of ambient air in the urban area of the city of Bor. Also, the increased content of As and Cd in PM₁₀ particles in ambient air for years has led to increased illness and mortality from cancer in Bor, which is much higher than in the rest of Serbia. These facts justifiably lead to an increased risk to the health of people in the city of Bor after the increase in the capacity of the copper smelter, which is located in the immediate vicinity of the urban area of the city of Bor.

The results of the non-carcinogenic risk assessment for children and adults $(HQ_{1,2})_A < 1$ $(HQ_{1,2})_B < 1$ indicate that the non-carcinogenic risks according to both scenarios (1 and 2) for children (A) and adults (B) are currently at an acceptable level. However, long-term continuous increased content of As and Cd in PM₁₀ particles in ambient air in the urban environment of the city of Bor, due to their accumulation in the

human body, will over time increase the carcinogenic risk.

The carcinogenic risk assessment in the city of Bor according to the scenario of maximum values recorded during 2024 (Scenario X-1) is $CR_1 = 5.58E-4$ for children (A) and $CR_1 = 5.07E-4$ for adults (B), which are multiple times above the limit values (1.0 - 4) defined by EU standards, representing an unacceptable risk. According to the scenario of mean annual values (Scenario X-2), $CR_2 = 1.24E-4$ for children (A) and $CR_2 = 6.9E-5$ for adults (B), indicate a slightly unacceptable risk for the child population (A) and an acceptable risk for the adult population (B), which are within the limits (10^{-4} - 10^{-6}). The predominant influence on CR values is exerted by the concentrations of As and Cd in PM₁₀, whose concentrations in ambient air are in high mutual positive correlation of 0.99. Since these heavy metals accumulate in the human body, with long-term exposure to their contents in ambient air, the probability of increased CR increases. In conditions of increased capacity of the copper smelter, the risk to human health in the city of Bor increases, and due to the proximity of the border with Bulgaria and Romania, an EU member state..

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DRUG-INDUCED NEPHROTOXICITY: CURRENT CONCEPTS AND CLINICAL IMPLICATIONS

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Abstract: Drug-induced nephrotoxicity is a significant clinical problem and one of the leading causes of acute kidney injury, particularly among hospitalized patients, older adults, and individuals with chronic kidney disease. Due to the high blood flow through the kidneys, complex tubular functions, and active transport mechanisms, the kidneys are particularly susceptible to the harmful effects of drugs and their metabolites. It is estimated that drugs contribute to 20–25% of cases of acute kidney injury in adults, while the incidence is considerably higher among critically ill patients. The aim of this paper is to present current knowledge on the epidemiology, risk factors, classification, diagnosis, and clinical manifestations of drug-induced nephrotoxicity. Particular emphasis is placed to contemporary classification systems based on the site of injury, clinical phenotypes, and biomarkers of renal dysfunction and kidney injury. The most important mechanisms of kidney injury are presented, including hemodynamic disturbances, direct tubular toxicity, immune-mediated injury, crystal nephropathies, rhabdomyolysis, and thrombotic microangiopathy, with special emphasis on clinical presentation, preventive strategies, therapeutic options, and prognosis. In addition, the major groups of potentially nephrotoxic drugs encountered in everyday clinical practice are reviewed, including aminoglycosides, nonsteroidal anti-inflammatory drugs, renin-angiotensin-aldosterone system inhibitors, statins, and proton pump inhibitors. Timely recognition of risk factors, rational drug use, individualized dosing according to kidney function, and regular monitoring of renal parameters represent key measures for the prevention of nephrotoxicity. A better understanding of the pathophysiological mechanisms and clinical patterns of kidney injury enables earlier diagnosis, appropriate treatment, and reduction of the risk of permanent loss of kidney function.

Keywords: nephrotoxicity, acute kidney injury, drugs, acute interstitial nephritis, acute tubular necrosis, chronic kidney disease, prevention.

INTRODUCTION

The human kidneys are small paired organs that account for only 0.2–0.5% of total body mass, while receiving as much as 20–25% of the cardiac output. This intensive perfusion, together with the complex structure and function of the renal tubules, makes the kidneys particularly susceptible to the harmful effects of various drugs and chemicals. Most drugs and their metabolites are eliminated through glomerular filtration and/or tubular secretion. The elimination process is based on the capacity for drug metabolism through the oxidative-reductive phase of biotransformation, as well as on the conjugation of metabolites with specific carriers that facilitate their excretion into the urine [1–3].

Nephrotoxicity is defined as a rapid deterioration of kidney function caused by the toxic effects of substances, most commonly drugs, which may lead to acute kidney injury (AKI) and necessitate discontinuation of therapy

or even hemodialysis [4]. The proximal tubules are the nephron segment most susceptible to the nephrotoxic effects of drugs because of their intense metabolic activity, which, together with a high osmotic gradient and the presence of transport mechanisms, facilitates the accumulation of toxins and the development of injury [2].

Given the increasingly widespread use of drugs in modern therapy, understanding the mechanisms of nephrotoxicity and recognizing potentially harmful substances are of crucial importance for the prevention of kidney injury and the preservation of renal function.

EPIDEMIOLOGY

Drug-induced nephrotoxicity is currently considered to account for approximately 20% of all cases of nephrotoxicity, with hospitalized patients and those admitted to intensive care units being particularly vulnerable. Among older adults, the incidence reaches up to 66% owing to numerous comorbidities, polypharmacy, and

more frequent exposure to high-risk diagnostic and therapeutic procedures [5,2].

Nephrotoxicity may manifest as injury affecting different segments of the nephron and represents one of the etiopathogenetic factors of acute kidney injury (AKI) and chronic kidney disease (CKD). According to the results of prospective cohort studies, nephrotoxic drugs are responsible for AKI in 14–26% of adults,

whereas cross-sectional studies have reported rates of up to 37.5% [2,6]. Approximately 20% of all cases require kidney replacement therapy, with an associated mortality rate of 60%, even in developed countries [7].

Risk Factors

Risk factors for drug-induced nephrotoxicity include patient-related factors, kidney-related factors, and drug-related factors (Table 1).

Table 1. Risk factors for the development of drug-induced kidney disease²

Patient-related	Kidney-related	Drug-related
Older age (≥ 60 -65 years)	CKD with GFR <60 ml/min/1.73m ²	High doses of the drug or prolonged use
Female gender	Renal hypoperfusion	Direct nephrotoxic effects
Altered pharmacogenetics (genetic variations in hepatic CYP450 and kidney transporters)	Biotransformation of the drug into nephrotoxic metabolites and ROS	Exposure to multiple nephrotoxic agents
Comorbidities (cirrhosis, DM, HTN, HF, sepsis, active cancers)	High metabolic demand of proximal tubular cells despite relative hypoxia	Pharmacokinetic and/or pharmacodynamic drug interactions that increase the free fraction, interfere with biotransformation, or worsen drug/metabolite excretion
Metabolic perturbations (hypokalemia, hypercalcemia, hypomagnesemia acidosis)	Proximal tubular uptake of drugs: by the apical route or by the basolateral transporters	

Legend: CYP450, cytochrome P450; DM, diabetes mellitus; HTN, arterial hypertension; HF, heart failure; CKD, chronic kidney disease; GFR, glomerular filtration rate;

Patient-related risk factors may be non-modifiable (e.g., age, sex, and genetic variations) or at least partially modifiable, as in the case of chronic comorbidities and metabolic disorders. Both older age and female sex are associated with reduced lean body mass, lower total body water content, and decreased serum albumin concentrations, which may contribute to an increased free fraction of the drug. Furthermore, older individuals have been shown to have higher circulating levels of angiotensin II and endothelin, which contribute to vasoconstriction of the efferent arterioles, increased glomerular filtration, and a greater amount of drugs and metabolites reaching the renal tubules [3].

An increased risk of nephrotoxicity is undoubtedly associated with pre-existing CKD with a glomerular filtration rate (GFR) below 60 mL/min, as well as renal hypoperfusion, whether resulting from true or effective volume depletion. Additional contributing factors include intrarenal drug biotransformation, uptake of drugs by proximal tubular cells, and specific metabolic characteristics of tubular cells under hypoxic conditions.

One of the most important risk factors is the inherent nephrotoxicity of certain drugs. Some drugs, such as aminoglycosides, possess a high nephrotoxic potential and may cause kidney injury even in patients with minimal or no additional risk factors. In most cases, drug-induced nephrotoxicity is dose-dependent and/or associated with prolonged treatment duration. Such reactions are predictable because they are based on the known pharmacological properties of the drug and may be attenuated by dose reduction or drug discontinuation. Less frequently, nephrotoxicity develops as an unpredictable adverse reaction resulting from an immune-mediated response that is independent of dose and usually requires complete withdrawal of the offending drug for resolution of symptoms [3,5,8].

Exposure to multiple nephrotoxic agents and drug interactions affecting their pharmacokinetic and/or pharmacodynamic properties further increase the risk of nephrotoxicity.

CURRENT CLASSIFICATIONS OF DRUG-INDUCED NEPHROTOXICITY

Before 2002, the reported incidence of acute renal failure varied considerably due to the lack of a standardized definition. Since then, the RIFLE classification (Risk, Injury, Failure, Loss, End-stage Kidney Disease) has been developed and was first published in 2004 [9]. Soon thereafter, it became evident that even small increases in serum creatinine are clinically significant because they are associated with higher morbidity and mortality. Consequently, in 2007, the Acute Kidney Injury Network (AKIN) modified the RIFLE criteria (AKIN criteria) and introduced the term AKI instead of acute renal failure [10].

Classification of Drug-Induced AKI According to the Site of Injury

An important initial step in the evaluation of AKI is determining the primary site of injury. Accordingly, AKI can be classified as prerenal, renal (intrinsic), or postrenal (Table 2).

- Prerenal injury occurs primarily as a consequence of renal hypoperfusion. In the context of drug-induced nephrotoxicity, prerenal AKI may result from the use of nonsteroidal anti-inflammatory drugs (NSAIDs), calcineurin inhibitors (CNIs), and modulators of the renin-angiotensin-aldosterone system (RAAS).
- Renal or intrinsic injury may result from damage to any component of the kidney, including the renal tubules, glomeruli, vascular structures, interstitium, or tubular lumen. Acute tubular necrosis (ATN) and acute interstitial nephritis (AIN) are among the most common forms of intrinsic kidney injury, and anti-infective agents are the most frequent causative drugs.
- Postrenal injury resulting from obstruction leads to hydronephrosis and subsequent damage to the renal parenchyma. Drugs associated with tubular obstruction include acyclovir, methotrexate, and several antiretroviral agents [11].

Table 2. Potential causes of AKI and recovery expectations¹¹

Types of AKI	Nondrug-induced AKI	Drug-induced AKI	Recovery
Prerenal injury	Intravascular volume depletion, decreased CO, decreased SVR	<i>NSAIDs, ACEIs, ARBs, diuretics, calcineurin inhibitors</i>	Days to weeks
Renal injury			
ATN	Prolonged or severe prerenal states, toxin ingestion (ethylene glycol)	<i>Aminoglycosides, amphotericin B, rifampicin, cisplatin, cocaine, antiretrovirals</i>	Weeks to months; May require temporary RRT
AIN	Papillary necrosis, pyelonephritis, renal tuberculosis, fungal nephritis, FSGS, various viral infections	<i>Antimicrobials (betalactams, sulfonamides, quinolones, vancomycin), NSAIDs, allopurinol, diuretics</i>	Weeks to months; May require temporary RRT
Glomerulonephritis	Lupus	<i>Hydralazine, NSAIDs, ampicillin, lithium</i>	Weeks to months; May require temporary RRT
Postrenal injury	Tumor lysis syndrome, multiple myeloma, kidney stones, malignancy, BPH	<i>Acyclovir, methotrexate, sulfonamides, triamterene, some antiretrovirals, large doses of vitamin C</i>	Days to weeks; if reversal of obstruction is delayed, may not fully recover

Legend: AKI, acute kidney injury; ATN, acute tubular necrosis; AIN, acute interstitial nephritis; CO, cardiac output; SVR, systemic vascular resistance; FSGS, focal segmental glomerulosclerosis; BPH, benign prostatic hyperplasia; NSAIDs, non-steroidal anti-inflammatory drugs; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-II receptor blockers; RRT, renal replacement therapy);

Classification of Drug-Induced Nephrotoxicity According to Clinical Presentation (Four Phenotypes)

Despite the previously described classification systems, uniform standards for the identification of drug-induced nephrotoxicity were still lacking, and kidney injury often remained unrecognized. Therefore, in 2015, Mehta et al. proposed four phenotypes of drug-induced kidney disease according to the underlying mechanism of injury: acute kidney injury (AKI), glomerular disorder, tubular dysfunction, and nephrolithiasis.

The clinical presentation of each phenotype is based on changes in biomarkers and other evidence of kidney injury, including serum creatinine (AKI), proteinuria or hematuria (glomerular disorders), electrolyte

abnormalities (tubular dysfunction), and ultrasonographic findings (nephrolithiasis). In order to standardize the initial phenotypic classification, primary and secondary criteria were developed, with at least one primary criterion being required to verify drug-induced nephrotoxicity (Table 3).

Drugs differ in the time course of nephrotoxic manifestations. Some agents cause acute injury (e.g., aminoglycosides and cephalosporins), whereas others are associated with a slower and more insidious onset (e.g., lithium). Taking into account conceptual models of the temporal evolution of kidney injury, Mehta classified drug-induced kidney disease into three categories: acute (1–7 days), subacute (8–90 days), and chronic (>90 days) [12].

Table 3. Primary and secondary criteria for the four main phenotypes¹²

Phenotype	Clinical features	Criteria	
		Primary	Secondary
Acute kidney injury	AIN ATN Osmotic nephrosis	Rise in sCr presents as or progresses to stage 2 AOB (KDIGO) 2.0–2.9 x reference sCr or higher OR Decline by at least 50% from peak Scr over 7 days in relationship to change in drug dosing adjustment or discontinuation within 2 weeks	Oliguric <500 ml/day or <0.5 ml/kg/hr for 12 hrs (KDIGO stage 2) Non-oliguric >500 ml per day Urinalysis findings: cylindruria consistent with ATN, eosinophils, proteinuria FeNa >1% Negative ultrasound findings Positive Gallium scan for AIN Clinical symptoms for AIN: fever, rash and joint pain
Glomerular disorder	Hematuria Proteinuria	Biopsy proven drug induced glomerular disease (within 4 weeks of stopping drug), AND Proteinuria: > 1 g/24h; UPC or UACR > 0.8; Urinalysis 2+ protein 100–300 mg/dL albumin Hematuria: >50 rbc/HPF	URINE: sterile pyuria, >50 wbc/HPF, casts, RBC; granular. Absence of secondary disorder that can cause GN: DM, lupus, infectious, hepatitis, etc Microangiopathic changes in the blood smear, LDH; haptoglobin Nephritic, nephrotic, mixed sy
Tubular dysfunction	RTA Fanconi syndrome Phosphaturia Diabetes insipidus SIADH	Hypophosphatemia OR Glucosuria: by urine analysis 3+ glucose without diabetes OR Hyperchloremic metabolic acidosis AND Hypokalemia or hyperkalemia Diabetes insipidus: Na>155 mEq/l; polyuria >3 l/day	Phosphaturia: FePO4 >5%; PO4 excretion >100 mg/24h Hypomagnesemia: serum Mg <1.2 mg/dl Hypouricemia: Serum Ac uricum <2 mg/dl Tubular proteinuria: Urinalysis <2+, UPC <0.8; <1 g /24h; DI: serum osmolality >300 mOsm/kg, urine osmolality <100 mOsm/kg, urine Na <10 mEq/l
Nephrolithiasis	Crystalluria Nephrolithiasis Ultrasound findings of stone with or without obstruction	New onset after drug exposure with no previous history No evidence of congenital etiology for nephrolithiasis If obstructive, rise in Scr that presents as or progresses to stage 2 AOB (KDIGO) or higher; Without obstruction: Urinalysis with crystals Ultrasound with stone	Urine electrolytes Stone work up

Legend: AIN, acute interstitial nephritis; ATN, acute tubular necrosis; DM, diabetes mellitus; FeNa, fractional excretion of sodium; FePO4, fractional phosphorus excretion, GN, glomerulonephritis; HPF, high powered field; LDH, lactate dehydrogenase; SIADH, syndrome of inadequate antidiuretic hormone secretion; UPC, urinary protein/creatinine ratio; UACR, urinary albumin/creatinine ratio;

Biomarker-Based Classification of Nephrotoxicity

The following conceptual classification was proposed in 2019 by an international expert panel composed of nephrologists and pharmacists. This classification integrates both functional biomarkers and biomarkers of kidney damage, together with the predominant mechanisms of nephrotoxicity, and categorizes drugs into four groups: dysfunction without damage, damage without dysfunction, both dysfunction and damage, and neither dysfunction nor damage. Examples of drugs belonging to each category are provided to further illustrate this classification system, while possible transitions between categories are shown by arrows (Figure 1).

1. Neither dysfunction nor damage

This category includes drugs that cause an increase in serum creatinine without inducing kidney dysfunction or structural damage. For example, some drugs may reduce tubular creatinine secretion or increase creatinine production without affecting kidney function. These drugs are not truly nephrotoxic, and this clinical situation is referred to as pseudo-AKI.

2. Dysfunction without damage

This category includes drugs that impair kidney function by affecting systemic or intraglomerular

hemodynamics. By reducing renal perfusion, they decrease intraglomerular pressure, filtration fraction, and GFR, resulting in an increase in serum creatinine concentration. In some cases, this alteration in glomerular hemodynamics represents an adverse effect, whereas in others it reflects the intended therapeutic action of the drug. The most common examples are RAAS modulators and vasoactive agents.

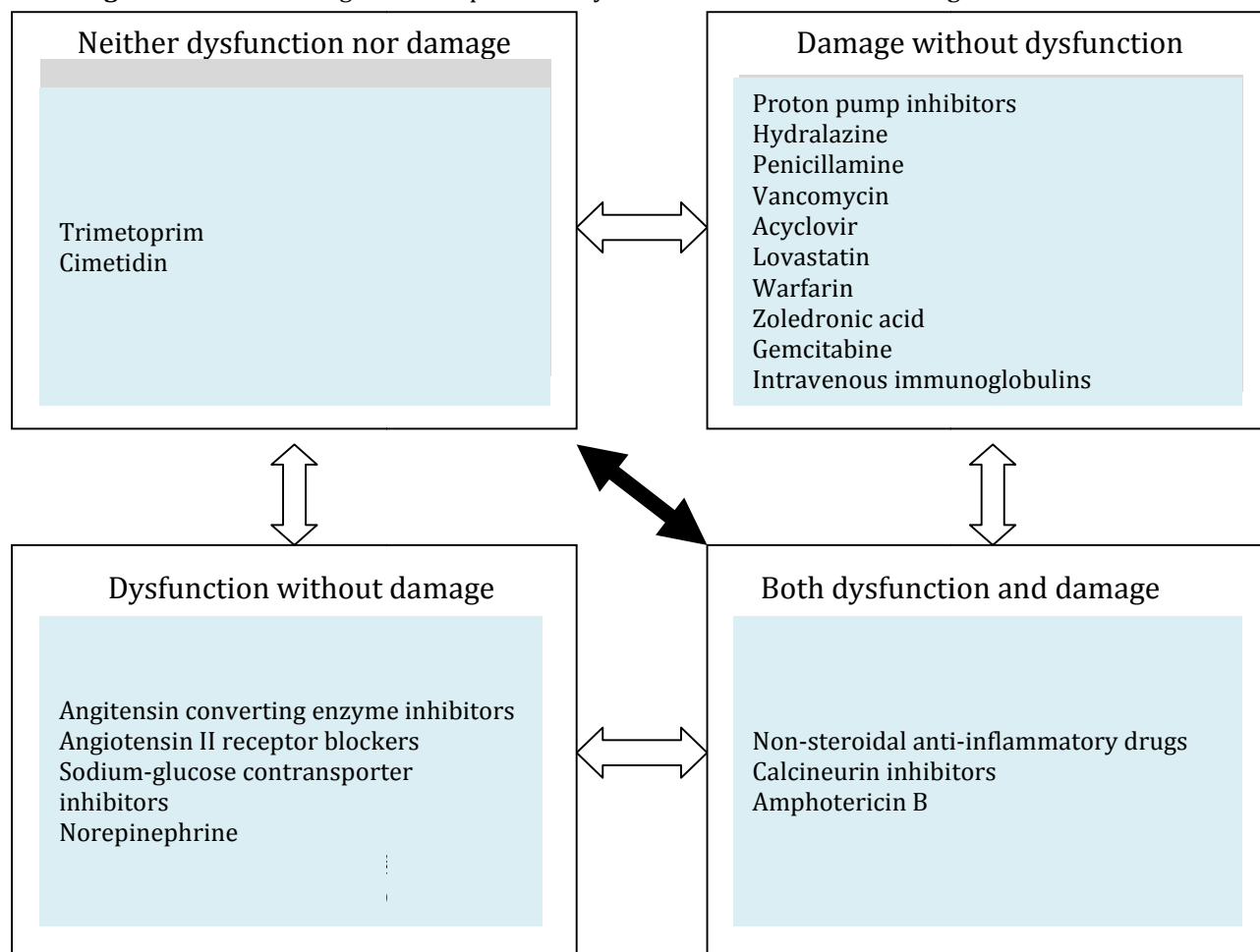
3. Damage without dysfunction

Kidney damage within this category may involve the glomeruli, tubules, or interstitium. Drugs may induce direct or indirect tubular damage/injury through crystal and cast formation, oxidative stress, inflammation, mitochondrial dysfunction, and immune-mediated reactions.

4. Both dysfunction and damage

This category includes drugs associated with both hemodynamic and non-hemodynamic mechanisms of AKI development. Non-hemodynamic features of AKI include glomerular, tubular, and interstitial injury occurring either alone or in combination. A given drug may induce functional changes through one mechanism and tissue damage through another, or both may result from the same pathogenic pathway. Typical examples are NSAIDs and CNIs [13].

Algorithm 1. Four categories of nephrotoxicity based on functional and damage biomarkers¹³



Drug-induced nephrotoxicity, similarly to other kidney diseases, can be diagnosed using simple blood and/or urine tests, including the measurement of serum creatinine and blood urea levels, as well as assessment of GFR using creatinine clearance. However, these tests are known to be imperfect markers of kidney function, as they are influenced by numerous renal and extrarenal factors.

Owing to continuous research efforts, novel biomarkers have been identified that are more sensitive and capable of detecting kidney injury at an earlier stage. Functional biomarkers include cystatin C, proenkephalin A (PENK), beta-trace protein (BTP), and neutrophil gelatinase-associated lipocalin (NGAL), which are measured in plasma. In addition, urinary biomarkers have been identified that may indicate injury to specific nephron segments. However, further studies are required before their routine clinical application can be recommended. Such studies should address several issues of crucial importance: when these biomarkers should be measured, whether they should be used to guide clinical decision-making, and what actions should be taken when their levels are elevated [14].

DRUG-INDUCED KIDNEY DISEASES

Acute Tubular Necrosis

ATN is a common cause of AKI in critically ill patients and is most often a consequence of

prolonged prerenal insults or exposure to nephrotoxins. Histological changes demonstrate necrosis of the renal tubular epithelium, with necrotic cells being shed into the tubular lumen, where they may cause extensive tubular injury. Regeneration is possible if the tubular basement membrane remains intact. The injury is usually reversible, although it may persist for days or weeks, and temporary renal replacement therapy (RRT) may be required. If ischemia is severe and prolonged, the injury may become irreversible [15,11].

Direct tubular injury may be caused by various classes of drugs, including antimicrobial agents, chemotherapeutic drugs, calcineurin inhibitors, bisphosphonates, and contrast media. Preventive strategies for many of these agents include volume expansion to correct hypovolemia and increase tubular flow, adjustment of drug dosage according to baseline GFR, and the use of alternative agents (e.g., mTOR inhibitors instead of calcineurin inhibitors or denosumab instead of bisphosphonates). For certain drugs, such as vancomycin and CNIs, therapeutic drug monitoring is required. Specific measures for vancomycin include avoidance of concomitant administration with piperacillin–tazobactam, whereas the nephrotoxicity of amphotericin B is significantly reduced when lipid-based or liposomal formulations are used (Table 4) [6].

Table 4. Drugs associated with acute tubular injury and preventative strategies⁶

Drug class	Medications	Preventative strategies
Antibiotics	Aminoglycosides	Once daily dosing, adjust dose for underlying GFR, administration of tobramycin over gentamicin if possible
	Vancomycin	Adjust dose for underlying GFR, therapeutic drug monitoring, avoiding combinations with piperacillin–tazobactam, use alternative agents
	Colistin	Adjust dose for underlying GFR, avoid prolonged administration, use alternative agents
Antifungals	Amphotericin B	Use lipid or liposomal form, IV isotonic crystalloids hydration
Antiviral agents	Cidofovir, tenofovir, adefovir	Adjust dose for underlying GFR, screen for tubular toxicity to identify early injury, use alternative agents
Analgesics	NSAIDs (and COX-2i) ↑Acetaminophen	Use alternative agents, avoid use in high-risk patients, avoid excessive dosing especially in liver disease
Chemotherapeutic agents	Cisplatin	Adjust dose for underlying GFR, IV isotonic crystalloid-induced diuresis, use of lower-dose regimens, use of cisplatin analogs, consider Na thiosulfate in high-risk pts
	Ifosfamide	Adjust dose for underlying GFR, limit dose Mesna and N-acetyl cysteine of unproven efficacy
Calcineurin inhibitors	Cyclosporin,	Reduce dose and follow drug levels.

	tacrolimus	Consider alternative agents such as mTOR inhibitors
Bisphosphonates	Pamidronate	Duration of infusion > 2hr, use lower doses, use alternative agents such as denosumab
	Zoledronic acid	Use lower dose especially if GFR <60 ml/min/1.73m ² , contraindicated in AKI and GFR <30ml/min/1.73m ² , use alternative agents such as denosumab

Legend: IV, intravenous; NSAIDs nonsteroidal anti-inflammatory drugs; COX, cyclo-oxygenase; mTOR, mammalian target of rapamycin;

Acute Interstitial Nephritis

AIN is an immune-mediated form of kidney injury, with drugs being responsible for more than 70% of cases (drug-induced acute interstitial nephritis, DI-AIN) [17]. Kidney biopsies performed in the evaluation of AKI indicate that the incidence of DI-AIN is

approximately 15%. To date, more than 250 drugs have been reported to cause AIN, with antibiotics, NSAIDs, proton pump inhibitors (PPIs), and immune checkpoint inhibitors being the most commonly implicated agents (Table 5) [6,17,18].

Table 5. Drugs associated with acute interstitial nephritis

Drug class	Individual medications
Antibiotics	Beta-lactam antibiotics (penicillins, cephalosporins), sulfonamides, fluoroquinolones, macrolides, rifampicin
Analgesics	NSAIDs (including COX2 inhibitors)
Acid-suppressive therapy	Proton pump inhibitors, histamine H2 receptor antagonists
Immunotherapy	PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors
Diuretics	Loop diuretics (Furosemide, Bumetanide) Thiazide diuretics (hydrochlorothiazide)
Antiviral agents	Acyclovir, Abacavir, Indinavir, Atazanavir, Foscarnet
Anticonvulsants	Phenobarbitone, Phenytoin
Angiogenesis inhibitors	Bevacizumab, tyrosine kinase inhibitors (sorafenib, sunitinib)
Other agents	Ifosfamide, Pemetrexed, Lithium, Allopurinol, Mesalazine and other 5-aminosalicylates

Legend: NSAIDs nonsteroidal anti-inflammatory drugs; COX, cyclo-oxygenase; PD-1i, Programmed Death-1 inhibitors; PD-L1i, Programmed Death Ligand-1 inhibitors; CTLA-4i, Cytotoxic T-Lymphocyte Antigen-4 inhibitors;

DI-AIN presents either as AKI or as a subacute decline in kidney function, indicating that symptoms may develop within a few days or several weeks to months after exposure to the drug that triggered the inflammatory cascade. The classic hypersensitivity triad consisting of rash, fever, and eosinophilia is observed only rarely (<10%). More commonly, patients present with nonspecific symptoms such as fatigue, malaise, and nausea, occasionally accompanied by flank pain. Many patients develop hypertension due to increased angiotensin II activity and the resulting arterial vasoconstriction in the setting of interstitial inflammation. Patients are usually non-oliguric unless advanced AKI develops, and some may even be polyuric because of impaired urinary concentrating ability [18,19].

Nephrotic syndrome may occur in cases induced by NSAIDs, although proteinuria of up to 1 g/24 h, sterile pyuria with leukocyte casts, and microscopic hematuria are more common findings. Although

laboratory findings may support a high clinical suspicion of DI-AIN, these tests have limited sensitivity and specificity; therefore, the definitive diagnosis is established by kidney biopsy. Novel urinary biomarkers may provide a noninvasive diagnostic alternative in the future.

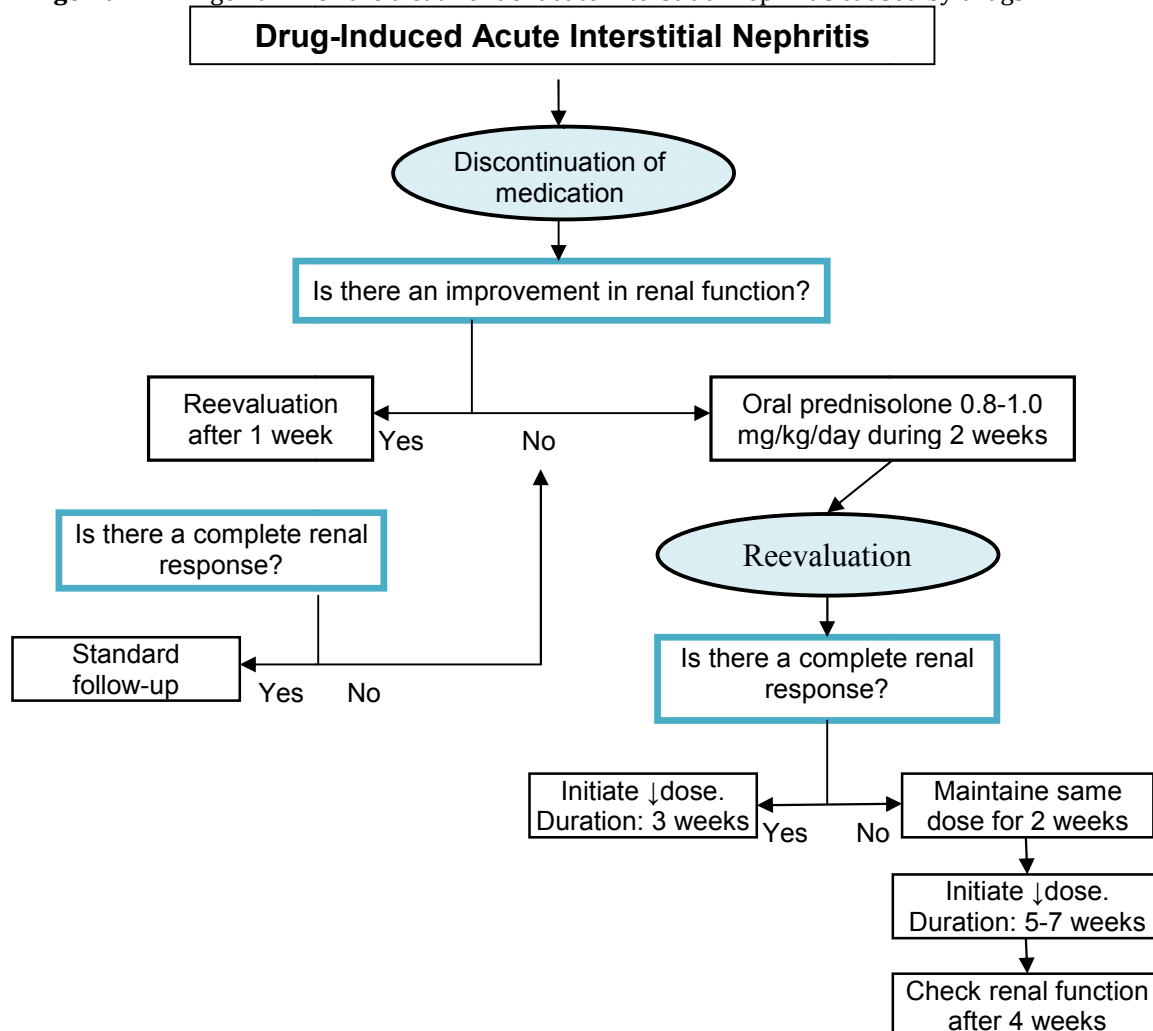
Histopathological findings indicate involvement of both the renal tubules and the interstitium. The characteristic feature is an extensive interstitial inflammatory infiltrate composed predominantly of lymphocytes and monocytes, although eosinophils, plasma cells, histiocytes, and polymorphonuclear leukocytes may also be present, and less commonly granulomas may be observed. Initially, the inflammatory infiltrate may be associated with interstitial edema; however, over time, interstitial fibrosis and tubular atrophy develop, findings that are characteristic of chronic interstitial nephritis [19,20]. Treatment and Prognosis of Drug-Induced Acute Interstitial Nephritis

Discontinuation of the suspected drug is generally considered the cornerstone of DI-AIN treatment, although identification of the offending agent may sometimes be challenging. Reassessment of serum creatinine is recommended one week after withdrawal of the suspected drug. In the absence of significant improvement, treatment with oral prednisolone at a dose of 0.8–1 mg/kg/day is recommended for 2 weeks. If a complete renal response is achieved, tapering of corticosteroid therapy should be initiated. In patients with an incomplete response, the same dose of prednisolone is recommended for an additional 2 weeks, followed by gradual dose reduction over a period of 5–7 weeks (Algorithm 1) [20].

Early reports of methicillin-associated AIN suggested that the disease was relatively benign and associated

with a favorable prognosis. However, this has proven to be far from reality, as incomplete recovery of kidney function is observed in approximately 40% of patients [21], and up to one-third of patients require dialysis treatment. Older adults are not only at a higher risk of developing the disease but also tend to have a poorer prognosis [20]. Prolonged impairment of kidney function is considered an unfavorable prognostic factor, whereas early diagnosis and timely initiation of treatment are associated with more favorable outcomes [22]. Histopathological findings undoubtedly have predictive value despite the inconsistencies reported in clinical studies: diffuse cellular infiltration, a greater degree of interstitial fibrosis and tubular atrophy, and the presence of granulomas have all been associated with a less favorable prognosis) [20].

Algorithm 1. Algorithm for the treatment of acute interstitial nephritis caused by drugs²⁰



Crystal Nephropathies Caused by Drugs

Crystal nephropathies are an important but often underrecognized cause of kidney disease and are characterized histologically by the presence of intrarenal crystal deposits that primarily affect the tubulointerstitial compartment. Clinically, patients present with urinary abnormalities such as crystalluria, proteinuria, and urinary casts, although tubulopathies, AKI, and CKD may also develop [23,24,25]. Microscopic identification of various pathological crystals and/or crystal-containing casts in the urine suggests the possibility of crystal nephropathy. Demonstration of crystals within the kidney by biopsy is crucial for establishing the diagnosis and requires evaluation of the underlying cause.

Drug-induced intrarenal crystal deposition occurs primarily as a consequence of renal excretion of the drug or its metabolites and drug supersaturation in urine. Conditions that favor

crystal formation include hypovolemia/dehydration (resulting in reduced urinary flow), drug overdose (leading to increased urinary drug concentrations), and urinary pH, the effect of which depends on the pKa of the respective drug (acidic urine for methotrexate and sulfadiazine, and alkaline urine for indinavir, atazanavir, and ciprofloxacin). The pathophysiological mechanisms involved in the development of drug-induced crystal nephropathy include substrate supersaturation, nucleation, aggregation, further crystal growth, cellular membrane injury, intratubular obstruction, direct and indirect cytotoxicity, inflammation, and necroinflammation [25]. The drugs most commonly associated with these processes are listed in Table 6, together with their clinical presentation and the basic preventive and therapeutic strategies.

Table 6. Drug-induced crystalline nephropathies²⁵

Medication	Renal syndromes	Preventive and therapeutic strategies
Methotrexate	Crystalluria, AKI and CKD	IV fluid before/during drug administration, alkalinize urine, adjust drug dose for kidney function, folic acid, glucarpidase if toxic level (<60h after drug)
Sulfo drugs (sulfadiazine, sulfamethoxazole)	Crystalluria, AKI, CKD and nephrolithiasis	Alkalinize urine, adjust drug dose for kidney function, assure euvoemia before drug exposure
Ciprofloxacin, levofloxacin	Crystalluria and AKI	Assure euvoemia during drug therapy and avoid alkaline urine (if possible)
Amoxicillin	Crystalluria and AKI	Assure euvoemia and adjust drug dose for kidney function
Acyclovir	Crystalluria, AKI and CKD	Avoid rapid IV bolus, adjust drug dose for kidney function, ensure euvoemia during drug therapy,
Indinavir, Atazanavir, Darunavir	Crystalluria, AKI, CKD and nephrolithiasis	Urine acidification does not play a role, assure euvoemia during drug therapy, switch to different medication
Foscarnet	AKI, hematuria, proteinuria and CKD	Assure euvoemia during drug therapy and adjust drug dose for kidney function
Triamterene	Crystalluria, AKI, CKD and nephrolithiasis	Alkalinize urine, assure euvoemia during drug therapy

Legend: AKI, acute kidney injury; CKD, chronic kidney disease; IV, intravenous;

Drug-Induced Rhabdomyolysis

Rhabdomyolysis is a clinical syndrome in which skeletal muscle injury leads to myocyte lysis and the release of intracellular contents into the systemic circulation, including electrolytes, purines, enzymes such as creatine kinase (CK),

and myoglobin [26]. Myoglobin is considered responsible for renal toxicity through three principal mechanisms: renal vasoconstriction, formation of intratubular casts, and direct toxicity to renal tubular cells [27]. The typical signs and symptoms of rhabdomyolysis are

known as the classic triad and include acute or subacute myalgia, muscle weakness predominantly affecting the proximal muscles of the lower extremities, and dark tea-colored urine. Clinical manifestations range from subclinical elevations of serum CK, lactate dehydrogenase (LDH), and aspartate aminotransferase (AST) to severe electrolyte disturbances, cardiac arrhythmias, AKI, and disseminated intravascular coagulation [28].

The most common causes of rhabdomyolysis in adults include strenuous physical activity, illicit drugs (heroin, cocaine, methadone, and methamphetamine), alcohol abuse, medications, muscle diseases, trauma, neuroleptic malignant syndrome, seizures, and prolonged immobilization [29]. Drugs most commonly implicated in the development of rhabdomyolysis include statins, fibrates, sedative-hypnotics, anesthetic agents associated with malignant hyperthermia, neuroleptics, anabolic steroids/corticosteroids, and newer-generation anticonvulsants [26,28]. Treatment consists of discontinuation of the offending drug and restoration of intravascular volume in order to achieve a urine output exceeding 2 L/24 h. At present, there is insufficient evidence to support the routine use of loop diuretics, mannitol, or bicarbonate in the treatment of rhabdomyolysis. In patients with severe AKI and other life-threatening complications, such as hyperkalemia, hypocalcemia, or volume overload, RRT should be considered [30].

Drug-Induced Thrombotic Microangiopathy

Drug-induced thrombotic microangiopathy (TMA) accounts for 10–13% of all cases of TMA and approximately 20–30% of secondary forms, which are considerably more common than primary forms (80–90%). The classic triad of microangiopathic hemolytic anemia, thrombocytopenia, and kidney injury is rarely observed in its entirety. More frequently, patients present with subacute forms characterized by mild thrombocytopenia and a gradual decline in kidney function, or even with kidney-limited TMA, which is associated with a more favorable prognosis [31]. The key pathological feature is endothelial injury caused by heterogeneous mechanisms, most commonly involving an idiosyncratic acute antibody-mediated immune response or a direct toxic effect of the drug related to dosage or duration of therapy [32,33]. The list of drugs potentially associated with TMA is rapidly expanding and

includes numerous antimicrobial agents, immunosuppressive drugs, chemotherapeutic agents, antiplatelet drugs, as well as various other medications and illicit substances [31,32,33].

The cornerstone of treatment is discontinuation of the suspected drug and supportive care. Plasma exchange and rituximab should be considered only in patients with suspected immune-mediated TMA, particularly in cases potentially associated with ticlopidine or in patients who fail to improve after withdrawal of the offending drug. In severe cases, complement blockade with the monoclonal antibody eculizumab may be used as rescue therapy. By inhibiting complement factor C5, eculizumab prevents the formation of the membrane attack complex and thereby inhibits cell lysis and death [31].

(POTENTIALLY) NEPHROTOXIC DRUGS IN CLINICAL PRACTICE

Aminoglycosides

The nephrotoxicity of aminoglycosides is well recognized (occurring in 10–25% of cases); however, these agents continue to be used in the treatment of severe Gram-negative infections and infective endocarditis. In recent years, their use has even increased because of the progressive resistance to other antimicrobial agents and the lack of new therapeutic alternatives [34]. The mechanisms underlying aminoglycoside-induced nephrotoxicity include interaction with proximal tubular cells leading to cellular apoptosis and necrosis, as well as a reduction in renal blood flow resulting in parenchymal ischemia and promoting the development of AKI. Nephrotoxicity most commonly manifests as non-oliguric AKI, usually occurring 5–7 days after the initial exposure to the drug, or as proximal tubular dysfunction known as Fanconi syndrome, which is characterized by metabolic acidosis, hypophosphatemia, glycosuria, and aminoaciduria [6,35].

Strategies for the safer use of aminoglycosides have been defined in clinical guidelines, which recommend that:

- aminoglycosides should not be used for the treatment of infections unless no suitable alternative is available;
- in otherwise healthy and clinically stable patients, aminoglycosides should be administered as a single daily dose rather than in multiple daily doses;

- aminoglycoside serum concentrations should be monitored when multiple daily dosing is continued for more than 24 hours or when once-daily dosing is continued for more than 48 hours;
- topical or local administration of aminoglycosides (e.g., respiratory aerosols or instilled antibiotic beads) should be preferred over intravenous administration whenever feasible and clinically appropriate [36].

Treatment of aminoglycoside-induced nephrotoxicity consists of supportive care and discontinuation of the offending drug. Following drug withdrawal, the prognosis is generally favorable, and recovery of kidney function usually occurs within several days to several weeks. However, pre-existing kidney disease, advanced age, and prolonged exposure to aminoglycosides are associated with a high risk of incomplete recovery and progression to CKD. On the other hand, aminoglycoside-induced AKI in critically ill patients is associated with increased morbidity and mortality, particularly when complicated by sepsis, hypotension, or multiple organ dysfunction [37].

Nonsteroidal Anti-inflammatory Drugs

NSAIDs exert their analgesic, anti-inflammatory, and antipyretic effects through inhibition of cyclooxygenase (COX), the enzyme responsible for converting arachidonic acid released from cell membranes into various eicosanoids, including thromboxane, prostaglandin E₂, and prostacyclin. Within the kidney, prostaglandins exert vasodilatory effects and influence the tubular transport of water and electrolytes by reducing sodium and water reabsorption and increasing potassium secretion [38]. Prostaglandin production is increased in CKD as a mechanism aimed at improving perfusion of

the remaining nephrons ("prostaglandin-dependent state"). Therefore, in these patients, both selective and non-selective COX inhibition are considered equally hazardous. Current clinical guidelines recommend avoiding prolonged NSAID use when the glomerular filtration rate is 30–60 mL/min/1.73 m² and complete avoidance when the glomerular filtration rate is below 30 mL/min/1.73 m² [39]. The nephrotoxic effects of NSAIDs may manifest clinically in several ways:

- AKI, predominantly mediated by hemodynamic mechanisms, leading either to a reversible decline in GFR or to ischemic tubular injury;
- Fluid and electrolyte disorders, including hyperkalemia, occasionally metabolic acidosis, hyponatremia, and sodium and water retention, resulting in edema, worsening of congestive heart failure, and hypertension;
- AIN (NSAIDs account for 10–15% of cases);
- Proteinuria and nephrotic syndrome resulting from membranous nephropathy or minimal change disease as less common complications;
- Risk of CKD progression associated with cumulative drug exposure [38].

The use of NSAIDs is generally not considered excessively harmful in young individuals without kidney disease or significant comorbidities. However, because their nephrotoxic effects are dose-dependent, particular attention should be paid to chronic use, which increases the risk of nephrotoxicity. In CKD, NSAIDs directly affect kidney function through inhibition of prostaglandin synthesis; therefore, the indications for their use should be carefully evaluated, taking into account existing risk factors and the expected clinical benefit [40]. Risk factors for NSAID-induced nephrotoxicity are presented in Table 7 [38].

Table 7. Risk factors for NSAID-induced nephrotoxicity³⁸:

Acute kidney injury
True vascular volume depletion • exercise-induced, diarrhea, vomiting
Effective vascular volume depletion • nephrotic syndrome, liver cirrhosis, congestive heart failure
Exposure to high cumulative doses
Concurrent calcineurin inhibitors and other vasoconstrictors
Concurrent therapy with RAAS inhibitors and/or diuretics
Hyperkalemia
Concurrent use of drugs that promote hyperkalemia • RAAS inhibitors, trimethoprim, heparin, other drugs
Exposure to radiocontrasts with concomitant RAAS inhibitors
Age over 65 years,
Hyporeninemic hypoaldosteronism,
RTA type 4
Hyponatremia

Vascular volume depletion (true or effective) Conditions associated with SIADH Increased free water intake ± increased sodium losses Use of thiazides in the elderly
Worsening of hypertension
Underlying HTN, including on effective treatment Hyporeninemic status (in the elderly and DM)
Hypervolemia
Underlying comorbid conditions that promote sodium avidity (congestive heart failure, liver cirrhosis, nephrotic syndrome)
Progression of CKD
Age >65 year, high cumulative doses, coronary artery disease

Legend: RAAS, renin-angiotensin-aldosterone system; RTA, renal tubular acidosis; SIADH, syndrome of inadequate antidiuretic hormone secretion; HTN, arterial hypertension; DM, diabetes mellitus;

Renin-Angiotensin-Aldosterone System Inhibitors

The nephroprotective effects of RAAS inhibitors are well established, particularly in patients with kidney disease and diabetes mellitus. These effects are mediated through blood pressure reduction, slowing of GFR decline, reduction of proteinuria, and delay of progression to advanced stages of CKD [2,41]. Initial decline in eGFR after RAAS inhibitor initiation should not automatically be interpreted as nephrotoxicity. These drugs are rarely truly nephrotoxic, but their effects on intrarenal hemodynamics may result in a reversible decline in GFR and consequently AKI [2].

Such adverse renal effects may occur in patients with pre-existing impairment of glomerular autoregulation, which depends on prostaglandin-mediated vasodilation of the afferent arteriole and angiotensin II-mediated vasoconstriction of the efferent arteriole [42]. Nephrotoxicity may result from hypoperfusion associated with low mean arterial pressure (reduced cardiac output or low systemic vascular resistance), volume depletion (e.g., due to diuretic therapy), or pre-existing renovascular disease, such as bilateral renal artery stenosis or severe intrarenal arteriosclerosis [43]. The nephrotoxic potential of RAAS inhibitors may also become apparent as a result of drug interactions. A typical example is the concomitant chronic use of NSAIDs and RAAS inhibitors, particularly in older adults, with an additional increase in risk when a diuretic is also prescribed. This phenomenon is commonly referred to as the “triple whammy” interaction [44].

Management of patients with hemodynamic instability and AKI requires correction of hypovolemia and hypotension; therefore, temporary discontinuation of all

antihypertensive agents, including RAAS inhibitors, is a logical approach. However, after restoration of an adequate circulating volume, normalization of blood pressure, and recovery of GFR, these agents should be reintroduced according to the original indication for their use [41]. In patients with CKD, treatment with RAAS inhibitors should be continued unless serum creatinine increases by more than 30% within four weeks after initiation of therapy or dose escalation. Dose reduction or discontinuation of RAAS inhibitors should be considered in the presence of symptomatic hypotension or uncontrolled hyperkalemia despite medical treatment, or in order to reduce uremic symptoms during the management of kidney failure (estimated GFR <15 mL/min/1.73 m²) [45].

Statins

Statins (HMG-CoA reductase inhibitors) play an undisputed role in the primary and secondary prevention of cardiovascular disease, including among patients with predialysis CKD [45]. However, they may also exert nephrotoxic effects, making careful monitoring of kidney function during the first months of treatment advisable. Statin-induced nephrotoxicity has been directly associated with high drug doses and indirectly with interactions involving other agents that may increase serum statin concentrations [46]. Potential mechanisms of toxicity include alterations in cell membrane permeability, reduced ubiquinone levels, and depletion of isoprenoids resulting from inhibition of cholesterol synthesis [46]. Identified risk factors include advanced age, female sex, liver dysfunction, and diabetes mellitus. The clinical presentation of statin-induced nephrotoxicity includes rhabdomyolysis, ranging from mild elevations in serum creatine kinase levels and myalgia to severe muscle weakness, muscle cramps,

myositis, and rhabdomyolysis. In addition, statins may cause acute or subacute interstitial nephritis through immune-mediated mechanisms, which generally resolves following drug withdrawal and corticosteroid therapy [47].

Recent epidemiological studies have indicated a significantly increased risk of AKI, particularly among patients initiating treatment with high-potency statins [48]. However, these cases are often underreported, which may be explained by the characteristics of the population receiving these drugs. Patients treated with statins are generally older and frequently have comorbidities such as diabetes mellitus, hypertension, and atherosclerotic renovascular disease. In addition, they often receive concomitant medications, including RAAS inhibitors and diuretics, all of which may contribute to renal dysfunction. Furthermore, many patients are treated with antiplatelet agents, making kidney biopsy more difficult in the setting of AKI. Finally, statin-induced acute or subacute tubulointerstitial nephritis may develop insidiously and remain subclinical, thereby going unrecognized if kidney function is not routinely monitored [47,49].

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are among the most commonly used drugs worldwide, with an estimated 53–69% of prescriptions lacking an appropriate medical indication [50]. Although PPIs were considered safe for many years, evidence from observational studies suggests an association between PPI use and a variety of adverse effects, particularly adverse renal outcomes, including AKI, AIN, and CKD [50,51]. AIN may develop within hours to several months after initiation of therapy and rarely presents with the classic triad of fever, rash, and eosinophilia. However, sterile pyuria, hematuria, and eosinophiluria may be detected on urinalysis. A rapid decline in kidney function may precipitate AKI, or AIN may be complicated by the development of interstitial fibrosis and

tubular atrophy, resulting in chronic interstitial nephritis that gradually progresses to CKD. According to available studies, more than half of patients fail to achieve complete recovery of kidney function following AIN. Hypomagnesemia has also been reported as an adverse effect. Although the underlying mechanisms remain insufficiently understood, available evidence suggests an association with CKD [50,52].

Preventive measures include limiting excessive PPI use to appropriate medical indications, with careful attention to both dose and duration of therapy. Particular caution is warranted in patients with CKD or those at increased risk of developing CKD, and alternative therapeutic options should be considered whenever appropriate. When treatment with PPIs is clearly indicated, monitoring of GFR and serum magnesium levels is recommended, especially in patients receiving concomitant diuretic therapy [50].

CONCLUSION

Drug-induced nephrotoxicity is a significant cause of both acute and chronic kidney injury and represents an important contributor to morbidity and mortality in contemporary clinical practice. The risk of kidney injury is particularly pronounced in older adults, patients with pre-existing CKD, multiple comorbidities, and polypharmacy. Timely identification of risk factors, rational use of potentially nephrotoxic drugs, individualized dosing, and regular monitoring of kidney function constitute the cornerstone of prevention. Advances in the understanding of pathophysiological mechanisms and the development of novel biomarkers provide opportunities for earlier detection of kidney injury and more precise patient monitoring. Given that a substantial proportion of drug-induced kidney injuries are potentially preventable, physician education aimed at the early recognition of nephrotoxicity remains a key element in preserving kidney function and improving treatment outcomes.

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PSYCHOSOCIAL ADAPTATION IN PATIENTS WITH COLOSTOMY: A LITERATURE REVIEW

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Summary: Colostomy, a surgical procedure most commonly performed due to colorectal cancer, inflammatory bowel disease or trauma, causes significant changes in patients' physical, emotional and social functioning. The aim of this review was to synthesize the existing literature on psychosocial adaptation after colostomy creation, identify key influencing factors, challenges and possible interventions. A search was conducted in PubMed, Scopus, Google Scholar and PMC using keywords related to psychosocial adaptation and quality of life in stoma patients (1995–2025). The literature indicates a high prevalence of anxiety and depression (30–50%) in the first months after surgery, as well as issues with body image, social isolation and sexual dysfunction. Key factors for successful adaptation include social and family support, disability acceptance, time since surgery and early education. A multidisciplinary approach involving support groups and psychological counseling significantly improves outcomes. The lack of local studies in Serbia highlights the need for further research in our context.

Keywords: colostomy, ostomy, psychosocial adaptation, quality of life, social support.

Introduction

Colostomy represents a surgical intervention in which an artificial opening is created on the abdominal wall for the elimination of digestive waste products. It most commonly results from the treatment of colorectal cancer, inflammatory bowel diseases (Crohn's disease or ulcerative colitis), or trauma [1]. The procedure for creating a colostomy can be temporary or permanent. It is estimated that more than 100,000 colostomies are performed annually in Europe and North America, with a growing number of patients surviving the underlying disease owing to advances in oncology and surgery [1]. Although colostomy, as part of emergency or elective surgical procedures, saves lives, it leads to significant changes in patients' daily functioning, which can substantially affect their physical, emotional, and social well-being [2].

Psychosocial adaptation of patients after colostomy creation is a complex process of adjustment to numerous changes. This process encompasses emotional reactions, social interactions, alterations in body image perception, and sexual function [2, 3]. The literature indicates that 30–50% of patients experience significant psychological difficulties

in the first months following surgery, including feelings of stigma, loss of control, and diminished quality of life [1]. Factors such as gender, time elapsed since surgery, and the level of social support play a crucial role in this process. For instance, acceptance of disability and participation in support groups facilitate better adaptation [3].

Despite the clear medical benefits, psychosocial challenges remain insufficiently recognized in clinical practice. This creates a need for a holistic, patient-centered approach that integrates psychological support and education [2]. However, in Serbia, there is a notable lack of local empirical studies on the psychosocial adaptation of patients with colostomy. The majority of available data originate from Asian and Western European countries, which limits the direct applicability of these findings to our specific cultural, social, and healthcare context — particularly in rural areas with limited access to multidisciplinary care.

The aim of this literature review is to synthesize the existing body of literature on psychosocial adaptation in patients with colostomy, to identify key influencing factors, challenges, and potential interventions, with a special emphasis on the implications for

biopsychosocial care in modern medicine and the urgent need to conduct similar research in Serbia..

Methods

For this literature review, a comprehensive search of the available literature was conducted to identify relevant sources on the psychosocial adaptation of patients following colostomy creation. The following databases were searched: PubMed, Scopus, Google Scholar, and PubMed Central (PMC). These databases were selected because they provide extensive coverage of both medical and psychosocial literature and offer substantial open-access resources.

The search keywords included: “stoma adaptation”, “psychological effects ostomy”, “psychosocial adaptation stoma”, and “quality of life colostomy patients”. The search covered articles published between 1995 and 2025 in order to include both recent findings and earlier seminal works relevant to the core concepts. Only articles written in English and Serbian language were included. No relevant results were identified in the Serbian language.

Inclusion criteria encompassed review articles, empirical studies, case studies, and meta-analyses that addressed the psychosocial aspects of colostomy. Articles were excluded if they focused exclusively on the surgical technique of stoma creation without addressing psychosocial issues, or if they had significant methodological limitations (e.g., sample size smaller than 10 patients or lack of clearly described methodology).

Results

The literature review identified numerous studies addressing the psychosocial aspects of life in patients with colostomy. The findings were synthesized thematically into the following domains: psychological aspects, social aspects, sexual and intimacy-related issues, factors influencing adaptation, and implemented interventions.

Psychological aspects

Psychological problems are among the most common challenges faced by patients with colostomy, with the prevalence of anxiety and depression reaching 30–50% in the first months after surgery [1,7,8]. The literature highlights that patients frequently experience a sense of loss of control over their body, leading to changes in body image perception, decreased self-confidence, and possible body dysmorphia

[2,8,9]. For example, one review study noted that anxiety often arises from the fear of leakage or odor from the colostomy, which affects daily activities and contributes to social isolation [1]. Qualitative studies show that these symptoms tend to decrease over time but may persist in the absence of early intervention, particularly in patients with a permanent colostomy [4, 10]. Contradictions in the literature include cultural variations, where patients in Asian countries report higher levels of stigma compared to those in Western countries, which further exacerbates depression [3,11]. Additionally, older patients tend to demonstrate greater emotional resilience, whereas younger patients often experience a more intense sense of loss [5].

Social aspects

Social isolation is a frequent problem, as many patients avoid social contacts due to fear of stigmatization or practical difficulties related to the colostomy [8,9,10]. Studies emphasize the important role of family and social support in mitigating these effects. Patients with a strong support network show better adaptation and lower levels of loneliness [3,4,8]. Support groups, such as those in stoma clinics, contribute to the normalization of the experience through sharing personal stories, thereby reducing social anxiety and improving social integration [6,7,12]. However, some findings suggest that men more commonly experience social isolation due to cultural expectations of strength and independence, while women tend to make better use of social resources [5]. The literature also indicates that lack of family support leads to prolonged isolation, especially in rural areas with limited access to healthcare services [3,9].

Sexual and intimacy issues

Sexual dysfunction represents a significant aspect, with reports indicating that up to 40% of patients experience decreased libido or fear of intimacy due to changes in body image perception and physical limitations [1, 2]. The literature shows that these problems negatively affect partner relationships, as patients often avoid sexual activity out of fear of complications such as leakage from the stoma [8,9]. Women tend to report greater difficulties with the emotional aspects, while men more frequently report physical problems, such as erectile dysfunction, which can lead to increased marital tension [5,7,8]. Positive findings suggest that education and counseling can significantly improve sexual adaptation after 6–12 months,

provided that the problems are identified early [4,10]. Cultural differences are evident, with patients from more conservative societies reporting higher levels of sexual stigma [3,11].

Factors influencing adaptation

Several factors modulate the adaptation process, including time since surgery (better adaptation after 1–2 years), gender (women often adapt better socially, while men may adapt better psychologically), and the level of perceived stigma [3,5,10]. Acceptance of disability has emerged as a key predictor, with patients showing higher levels of acceptance demonstrating lower levels of depression and better quality of life [6,9,10].

Social factors such as family support and cultural context also play an important role. For example, patients of rural origin in Nepal experience greater difficulties due to a lack of resources, whereas patients in developed countries make better use of professional assistance [3,8,11]. Limitations of the literature include the scarcity of longitudinal studies, which hinders the tracking of long-term effects, as well as the frequent focus on specific populations, particularly oncology patients [2,9].

Additionally, factors such as education and employment status influence adaptation, with patients having higher education levels showing better adjustment [1,8].

Interventions

Interventions primarily focus on education, psychological counseling, and support groups. Studies demonstrate that support groups significantly improve adaptation by enabling the sharing of experiences and practical advice, reducing anxiety by 20–30% [4,7,12]. Nurses play a crucial role in early education on colostomy management, which decreases anxiety and enhances patient autonomy [5,6]. A multidisciplinary approach, including psychologists and social workers, is recommended for holistic care, with an emphasis on individualized programs [1,8,9]. The effectiveness of these interventions varies, with better outcomes observed in structured programs; however, there are conflicting findings regarding their long-term efficacy without continuous support [2,9]. The literature suggests that the integration of technology, such as online support groups, may improve access to support, particularly in rural areas [3,10,11].

Table 1: Comparison of key findings from selected

Study	Year	Type of Study	Main Focus	Key Findings	Main Limitations
Ayaz-Alkaya [1]	2019	Literature review	Psychosocial problems	High prevalence of anxiety and depression (30–50%)	Review article, no new empirical data
Bekkers et al. [2]	1995	Literature review	Adaptation to stoma	Emotional and social factors are important; interventions improve outcomes	Older study, limited contemporary context
Gautam & Poudel [3]	2016	Cross-sectional survey	Psychosocial adaptation	Family support is crucial; rural patients face greater difficulties	Small sample, limited to Nepal
Gautam & Poudel [5]	2016	Comparative study	Effect of gender	Gender differences in psychosocial adjustment	Limited to colorectal cancer patients
Xi et al. [10]	2022	Multicenter cross-sectional	Stigma and disability acceptance	Disability acceptance reduces depression and improves adaptation	Cross-sectional design, no longitudinal follow-up
Aker et al. [8]	2025	Correlational study	Social support and self-efficacy	Positive relationship between perceived social support and stoma self-efficacy	Correlational design, only permanent colostomies
Eraydın et al. [7]	2025	Descriptive cross-sectional	Adaptation and sleep quality	Poor sleep quality is associated with poorer adaptation and depression	Cross-sectional design, limited to Turkey
Kittscha et al. [4, 12]	2022/2024	Integrative review & qualitative	Adjustment to ostomy and peer support	Support groups significantly facilitate adaptation	Qualitative approach (for [12])
Repić [13]	2017	Prospective cohort study	Quality of life and depression in permanent colostomy	QoL lowest at 1 month; depression 57.1% → 32.1%; depression significantly worsens QoL	Older study (2017); limited to Vojvodina
Bogdanović et al. [14]	2023	Literature review	Factors affecting quality of life	Psychological aspects, body image and multidisciplinary support are crucial	Narrative review, no original data

Discussion

The synthesized findings from the literature confirm that psychosocial adaptation to colostomy is a complex, dynamic, and multidimensional process encompassing emotional, social, and sexual challenges. The early postoperative phase is also the most difficult, characterized by high levels of anxiety, depression, and body image disturbances, while patients' quality of life and autonomy gradually improve over time, particularly with adequate support [1,4,10].

These findings are largely consistent with the limited local research conducted in Serbia. Repić [13], in a prospective study, demonstrated that quality of life was poorest one month after permanent colostomy creation, with a high prevalence of depressive symptoms (57.1%) that significantly declined by the sixth month (32.1%). Similarly, Bogdanović et al. [14] emphasized the dominant influence of psychological factors, changes in body image perception, and the critical importance of early education and multidisciplinary support.

Key protective factors for successful adaptation include strong social and family support, acceptance of the new body image, and early education [3, 8, 10]. Although these findings are mostly consistent across the literature, some contradictions exist regarding the influence of gender and cultural context. The majority of studies were conducted in Asia (Nepal, Vietnam, China, Turkey) or Western Europe, whereas data from the Western Balkans, including Serbia, remain scarce [3, 8, 10, 11]. This constitutes a significant gap in the literature, given that cultural attitudes toward disability, body image, and sexuality vary considerably among populations.

The main limitations of the reviewed literature include the predominance of cross-sectional studies, small sample sizes, heterogeneity of populations (most studies focus on oncology patients) [2], and the lack of long-term longitudinal research. In the Serbian context, only two relevant publications are currently available — Repić's doctoral dissertation [13] and the review by Bogdanović et al. [14]. While these works provide valuable local insights, they are limited in scope and do not offer long-term follow-up beyond six months or representation of patients from all regions of the country.

Implications for Clinical Practice In Serbia, a holistic biopsychosocial approach is essential in the care of patients with colostomy. Early screening for anxiety and depression, regular education by trained stoma care nurses, establishment of support groups in hospitals, and inclusion of psychologists in the multidisciplinary team are strongly recommended [1, 4, 8]. Particular attention should be paid to patients from rural areas and younger individuals [7, 8, 12].

Recommendations for Future Research Longitudinal studies in Serbia are needed to follow patients during the first five years after surgery, examining factors such as cultural context and access to healthcare services. These studies should ideally employ mixed-methods designs to provide a deeper understanding of individual experiences, with special focus on subgroups such as younger patients or those with permanent colostomies [3]. Furthermore, research on the effectiveness of digital interventions (e.g., online support groups) would be particularly valuable in the contemporary setting [9].

Conclusion

Psychosocial adaptation in patients following colostomy creation is a complex and dynamic process that involves emotional, social, and sexual challenges. The early phase of adaptation is most often characterized by high levels of anxiety, depression, and alterations in body image perception. However, over time and with adequate support, patients' quality of life and autonomy significantly improve. The key factors for successful adaptation include strong social and family support, acceptance of the new condition, early education, and participation in support groups.

Early identification of problems and multidisciplinary support (involving physicians, nurses, and psychologists) can substantially reduce long-term negative consequences and help patients regain control over their lives.

Future research, particularly longitudinal studies conducted in the local Serbian context, would be of great value for a better understanding of the specific factors and needs of this population. Such studies would enable more effective and tailored care for patients with colostomy.

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CLINICAL APPROACH TO THE PATIENT WITH ABDOMINAL PAIN

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Abstract: Abdominal pain represents one of the most important diagnostic challenges for every physician, and its proper interpretation and treatment requires a systematic, often empirical clinical approach, and sometimes urgent action. The evaluation of a patient with abdominal pain requires the physician to have a comprehensive view, because this symptom, besides gastrointestinal causes, can be a consequence of diseases of other organ systems. For the evaluation and treatment of patients with abdominal pain, a thorough history and detailed clinical examination are crucial, guiding us in further procedures in the treatment of such a patient. The cause of abdominal pain is in most cases of a benign nature. Although it often remains undetermined in most such cases, the pain subsides spontaneously. When abdominal pain persists and despite extensive diagnostics and symptomatic treatment, we cannot identify an organic cause, we speak of functional abdominal pain syndrome. The paper defines types of pain according to pathophysiological basis, time course, and cause of occurrence. The procedure for the evaluation and treatment of patients with abdominal pain is described.

Keywords: abdominal pain; differential diagnosis; clinical examination; diagnostics; treatment

Introduction

Abdominal pain is one of the most common symptoms of various diseases of the abdominal cavity or diseases outside of it. It represents a great diagnostic challenge for both primary healthcare physicians and clinical specialists. The cause is very often completely benign, but it can also be a life-threatening condition that must be recognized early and appropriate measures taken. A precise history and detailed clinical examination are key and indispensable parts of the diagnostic process, as they determine the level of urgency and the scope of further consideration. We must be particularly cautious in the treatment of the elderly, women of reproductive age, and immunocompromised individuals, because the clinical picture of otherwise common diseases can be atypical, and at the same time we must also consider rarer and specific causes of abdominal pain. In these groups, abdominal pain can be acute, subacute, or chronic. The cause can be organic, but when the cause cannot be identified despite extensive diagnostics, we speak of functional abdominal pain syndrome. Depending on pathophysiological mechanisms, we distinguish visceral, somatic, and referred pain. Due to the specificity of treatment, a special entity is the so-called acute abdomen,

which is a life-threatening condition and requires urgent treatment.

Abdominal pain is classified as acute or chronic based on an arbitrary time frame of approximately 12 weeks. Establishing a differential diagnosis is very complex and requires a thorough history and comprehensive physical examination. However, the cause remains unknown in 30% of cases [1].

It is necessary to analyze abdominal pain with special emphasis on six characteristics: onset, progression, migration, character, intensity, and localization. The onset of pain

The onset of pain can be: sudden, rapid, and gradual. Sudden pain occurs in a second; typical for perforation of a peptic ulcer, rupture of an ectopic pregnancy, mesenteric infarction, aneurysm rupture. Rapid onset of pain – develops over several minutes; seen in cholecystitis, pancreatitis, obstruction, appendicitis, ureteral stone. Gradual onset is characterized by intensification of pain over hours or days; more common in tumors, chronic inflammation, and colon obstruction

Progression

It is important whether the pain intensifies, decreases, or transitions from intermittent to constant. For example, a perforated ulcer can give severe initial pain that

decreases if the perforation closes, while intermittent pain that becomes constant indicates obstruction with a risk of necrosis.

Migration of pain

Movement of pain from the site of origin is typical, for example, for acute appendicitis (from the epigastrium or periumbilical area, pain later moves to the right lower quadrant).

Character of pain

Abdominal pain can be characterized as crampy, dull, or sharp and as constant or intermittent. Crampy pain (colic) follows a pattern of waves that repeat at intervals — it suddenly intensifies to an unbearable peak, then subsides or completely disappears for a time. The most typical examples of colic in medical practice are renal colic and biliary colic. Colicky pain is also associated with mechanical obstruction of the small intestine and, when clearly present, is highly suggestive of that condition. Constant dull or sharp abdominal pain is usually caused by stretching or edema of the wall of a hollow organ. When a hollow organ, such as the gallbladder, becomes distended, which is most often the case due to obstruction of the cystic duct, constant, dull pain occurs. When the gallbladder contracts due to obstruction, the stretching of the gallbladder wall suddenly intensifies, creating crescendo pain (biliary colic), in addition to the already present constant dull pain.

Sharp (stabbing) pain is usually well localized (the patient can point with a finger where it hurts). It is usually sudden and very intense. It often indicates irritation of the peritoneum; it occurs in the late phase of appendicitis in the lower right part of the abdomen when every movement, cough, or pressure on that spot causes "stabbing." Sharp pain like a "knife stab" is also characteristic of ulcer perforation. Dull pain is more difficult to precisely locate. Patients describe it as a feeling of pressure, heaviness, or "squeezing" in the stomach. It usually comes from internal organs, most often as a result of irritation of the capsule of an enlarged liver or spleen, which patients describe as persistent, nagging, dull pain below the right or left rib arch.

Intensity of pain

The intensity of pain in an individual patient can often be assessed by the way the patient physically reacts to it. In somatic pain due to peritonitis, the patient is still, lies motionless with legs bent. In visceral pain, for example in

cholecystolithiasis or nephrolithiasis, the patient is restless, changes positions, tries to alleviate the symptoms himself.

Localization

Localization can indicate the origin and pathological basis of pain. Visceral pain is generally poorly localized, in the middle zones of the abdomen; often accompanied by nausea, vomiting, pallor, sweating. Somatic pain is well localized, intensifies with pressure, breathing, and movement; usually without vegetative symptoms [2].

Epidemiology

Abdominal pain is the cause of 5-10% of all visits to emergency medicine clinics.

From 50 to 75% of people older than 65 years with acute abdominal pain require hospitalization, and 1/3 of them require surgical intervention. In patients older than 65 years, compared to younger patients, mortality is 6 to 8 times higher. In 25% of patients who leave the emergency medicine clinic and even 35-41% of patients hospitalized due to abdominal pain, the cause remains undetermined. In 80% of patients with unexplained cause of abdominal pain, the pain usually subsides spontaneously within two weeks from the onset [3].

Pathophysiology

Based on origin, pain can be: nociceptive - tissue damage, neuropathic - nerve damage, and psychogenic - predominantly psychological. Given the multitude of diseases that can manifest with this symptom, accurate interpretation of abdominal pain represents a great challenge for the physician, requiring not only theoretical knowledge but also extensive practical experience. Depending on pathophysiological mechanisms, abdominal pain can be divided into visceral, somatic (parietal), and referred [4]. Sensory pain receptors or nociceptors are located in the mucosa, muscle layers of hollow organs of the gastrointestinal tract (GIT), and mesentery. Nociceptors are peripheral endings of myelinated A delta nerve fibers and unmyelinated C fibers.

Visceral pain arises from stimulation of free nerve endings in visceral organs and is transmitted by slow C fibers originating from the wall of hollow organs, mesentery, and capsule of solid organs. The fibers enter the spinal cord bilaterally and at several levels, so visceral pain is poorly circumscribed. The pain can be dull, sharp, or crampy in character. It does not depend on breathing or body position, but can

be characterized by radiation to adjacent parts of the body and the presence of other visceral symptoms such as nausea, vomiting, and loss of appetite. Visceral pain is caused by ischemia, inflammation, or stretching of hollow organs or the capsule of solid organs. The most characteristic visceral pain is colic, which arises from excessive contraction of the muscle of a hollow organ during obstruction (e.g., colic due to stone in the urinary or biliary tract). The moment when dull, diffuse pain transitions into clearly localized pain marks the spread of the pathological process from the visceral to the parietal peritoneum.

Somatic pain is transmitted by fast A fibers to the dorsal ganglia of the spinal cord on the side of the source of the painful stimulus and the corresponding dermatome, so this pain is well circumscribed. By nature, it is sharp and constant, depends on breathing and body position.

It is characteristic that muscle defense and skin hyperesthesia above the affected part of the peritoneum can occur. This is the result of direct irritation of the parietal peritoneum due to ischemia, inflammation, or stretching [5]. Table 1 shows the characteristics of visceral and somatic pain.

Table 1. Comparative characteristics of visceral and somatic pain

Characteristic	Visceral pain	Somatic (parietal) pain
Onset of pain	Gradual, often unclear onset	Sudden or clear moment of onset
Progression	Slow intensification, wave-like worsening	Quickly becomes intense and stable
Migration of pain	Frequent migration (e.g., periumbilical → right lower in appendicitis)	No true migration – remains fixed
Character of pain	Dull, pressure, burning, cramping (colic)	Sharp, "stabbing," "cutting," piercing
Intensity	Usually moderate to severe, but difficult to assess	Often very severe and precisely assessable
Localization	Poorly localized, diffuse	Precisely localized
Effect of movement	Movement does not significantly intensify pain	Movement, cough, and breathing worsen it
Muscle defense	Mostly absent	Present
Vegetative symptoms	Frequent: nausea, sweating, pallor	Rarer
Mechanism of occurrence	Irritation of internal organs (stretching, ischemia)	Irritation of parietal peritoneum, muscles, bones
Sensory innervation	Autonomic nervous system	Somatic nerves
Examples	Biliary colic, renal colic, early appendicitis	Peritonitis, late appendicitis, fracture

Referred pain is well-localized pain that is distant from the affected organ. It is felt in the skin dermatomes of somatic afferent nerves that enter the spinal cord at the same level as the visceral afferent fibers of the affected organ. It is pain felt at a site that is not the actual source of pain. It arises due to shared nerve innervation of the internal organ and the skin.

Practically, the brain "mislocalizes" the pain. Sometimes referred pain can be triggered or intensified by palpation of the affected organ. Pressure on the skin at the site where referred pain is felt usually does not change the intensity of pain [6]. The referral of pain from abdominal organs to other regions is so characteristic that from this referral one can conclude which organ is affected (Table 2).

Table 2. Correlation of localization of referred pain, potential source, and typical diseases

REGION WHERE PATIENT FEELS PAIN	MOST LIKELY ORGAN (SOURCE)	TYPICAL DISEASE
Right scapula	Gallbladder	Cholecystitis, gallstone
Right shoulder	Gallbladder, diaphragm	Cholecystitis, subphrenic abscess
Left scapula / left shoulder	Spleen	Splenic rupture (Kehr's sign)
Between shoulder blades	Esophagus, pancreas	Esophagitis, pancreatitis
Back in a "belt" (Th8-Th11)	Pancreas	Acute pancreatitis
Epigastrium	Stomach, duodenum, pancreas	Gastritis, ulcer, pancreatitis
Around umbilicus	Small intestine, early appendicitis	Enteritis, early appendicitis
Flank → groin → testis/labia	Ureter (left or right)	Ureteral calculosis
Sacrum / Perineum	Bladder, prostate, rectum	Cystitis, prostatitis, rectal tumor

Left side of chest	Spleen, stomach	Splenic rupture, ulcer
Right side of chest on breathing	Diaphragm - abdominal source	Subphrenic abscess
Suprapubic	Bladder	Cystitis, urinary retention
Lower abdomen + shoulder (women)	Fallopian tube	Ectopic pregnancy
Anterior thigh	Ureter	Ureterolithiasis
Testis without local finding	Kidney / ureter	Renal colic

DURATION OF PAIN

Depending on the time course, we distinguish acute, subacute, and chronic pain.

Acute abdominal pain can appear suddenly or develop over days or even weeks (subacute pain). It is usually constant, less often intermittent, with possible worsenings and improvements. It is one of the most common gastrointestinal symptoms and accounts for 5% of all emergency room visits. In 25-50% of patients, the cause of acute abdominal pain cannot be found. The most commonly identified causes are acute appendicitis, intestinal obstruction, diseases of the gallbladder and biliary tract, diseases of the urinary tract, intestinal diverticula, and acute pancreatitis. In women of reproductive age, we must always consider gynecological causes of abdominal pain [7].

We speak of chronic abdominal pain when it lasts at least 6 months. It can be constant or intermittent. Chronic abdominal pain is the reason for 25-50% of all visits to gastroenterology offices. The most common cause of chronic abdominal pain are functional gastrointestinal disorders such as irritable bowel syndrome, functional dyspepsia, and functional biliary pain. Chronic abdominal pain

resulting from organic diseases is most often caused by chronic inflammatory bowel diseases, peptic ulcers of the stomach and duodenum, celiac disease, adhesions, chronic inflammation of the pancreas, and neoplasms. Chronic pain associated with defecation occurs in irritable bowel syndrome, chronic postprandial pain in functional dyspepsia and chronic mesenteric ischemia, and chronic pain associated with the menstrual cycle in endometriosis and other gynecological diseases [8].

Functional abdominal pain syndrome belongs to the group of functional gastrointestinal disorders, which are diagnostically defined by the Rome criteria (Roma IV: CAPS - centrally mediated abdominal pain syndrome). Despite extensive

Acute abdomen is a synonym for sudden diseases of abdominal organs, characterized by severe abdominal pain, nausea with or without vomiting, signs of peritoneal irritation, and more or less pronounced general impairment. Due to the urgency of the condition, often only a rough definition of the disease is possible, but not a reliable and final diagnosis. The necessity of therapeutic action thus prevails over a more precise diagnosis. Causes of acute abdominal pain can be surgical or non-surgical (Table 3)

Table 3: Surgical and non-surgical causes of acute abdomen

SURGICAL CAUSES	NON-SURGICAL CAUSES
Acute inflammations of surgical organs (acute appendicitis, acute cholecystitis...)	Endocrine and metabolic disorders (uremic, diabetic, and Addisonian crisis, acute intermittent porphyria...)
Perforations of hollow organs (perforation of gastric or duodenal ulcer, iatrogenic perforations...)	Hematological diseases (crisis in sickle cell anemia, acute leukemia...)
Disorders of intestinal patency (ileus, intussusception, volvulus...)	Poisonings (lead, heavy metals, crises due to opioid withdrawal...)
Bleeding into GIT (bleeding from peptic ulcer, bleeding from varices...)	Heart and lung diseases (pneumonia, pleuritis, myocardial infarction, pericarditis...)
Bleeding into the abdominal cavity (rupture of aortic aneurysm, aortic dissection...)	Neurological diseases (tabes dorsalis, syringomyelia...)
Disorders of blood supply to abdominal organs (mesenteric ischemia...)	Other (hematoma of the rectus abdominis muscle fascia, herpes zoster...)

In the initial assessment of a patient with abdominal pain, it is particularly important

to timely recognize potentially life-threatening conditions, as shown in Table 4..

Table 4. Five potentially life-threatening causes of abdominal pain

isease / condition	Clinical warning signs	First-choice diagnostic procedure
Rupture or dissection of abdominal aortic aneurysm	Sudden severe pain in abdomen or back, hypotension, pulsatile abdominal mass	Emergency ultrasound of abdomen or CT angiography
Acute mesenteric ischemia	Severe pain disproportionate to palpation findings, nausea, vomiting, metabolic acidosis	CT angiography of mesenteric arteries
Perforation of hollow organ	Sudden pain, signs of peritoneal irritation, "board-like" abdomen	Abdominal X-ray (free air), CT abdomen
Acute pancreatitis (severe form)	Intense epigastric pain radiating to back, nausea, vomiting	Serum amylase/lipase, CT abdomen
Ectopic pregnancy	Lower abdominal pain in woman of reproductive age, amenorrhea, vaginal bleeding	β -hCG and transvaginal ultrasound

EVALUATION OF THE PATIENT WITH ABDOMINAL PAIN

History

A thorough history and systematic clinical examination represent the foundation of the diagnostic approach to a patient with abdominal pain and determine the rational choice of laboratory and imaging tests. In a significant number of patients, the diagnosis can be made based on clinical assessment alone, while in a smaller proportion of patients the cause remains unclear despite extensive diagnostics.

Although abdominal pain is most often a consequence of gastrointestinal diseases, extra-abdominal causes (cardiovascular, respiratory, metabolic, urological, and gynecological) should always be considered in the differential diagnosis. Early recognition of life-threatening conditions has particular priority, because the time interval from the appearance of symptoms to adequate therapeutic intervention is directly related to the treatment outcome.

Demographic data (age and sex), comorbidities, previous surgeries and hospitalizations, current therapy, allergies, lifestyle habits, and family history significantly guide differential-diagnostic reasoning.

Analysis of pain must be systematic and include: localization, onset, progression, duration, intensity, character, migration, and irradiation, as well as factors that provoke or alleviate the pain. It is necessary to actively inquire about accompanying symptoms: nausea, vomiting, diarrhea or constipation, weight loss, fever, jaundice, dyspnea, chest pain, palpitations, as well as urogenital complaints. In patients with abdominal pain, it is important to recognize the so-called "Red Flags," i.e., alarm symptoms, which indicate potentially life-threatening conditions and require urgent diagnostics [10]. The significance of alarm symptoms is shown in Table5.

Table 5. Alarm signs and clinical significance

Alarm sign	Clinical significance
Unintentional weight loss	Suspicion of malignancy or chronic systemic disease
Dysphagia / odynophagia	Possible obstructive or inflammatory pathology of the esophagus
Melena / hematemesis	Bleeding from upper GIT
Persistent vomiting	Obstruction, metabolic disorder, intracranial pathology
Palpable abdominal mass	Tumor, abscess, aneurysm
Anemia	Chronic or acute bleeding
Persistent or progressive pain (> 2 weeks)	Need to exclude malignancy or chronic inflammation

Special categories of patients require increased clinical caution:

Elderly patients – often have an atypical, sparse, or masked clinical picture.

Women of reproductive age – pregnancy and its complications must be excluded.

Immunocompromised – increased risk of opportunistic infections and malignancies.

Clinical examination

Assessment begins already at the first contact with the patient – general appearance, body position, level of consciousness, and orientation often indicate the severity of the condition. Vital parameters (blood pressure, pulse, respiratory rate, temperature, oxygen saturation) enable rapid assessment of hemodynamic and respiratory stability. In patients with vomiting, diarrhea, fever, or bleeding, assessment of hydration status is necessary.

Abdominal examination includes:

Inspection - Assessment of the shape and symmetry of the abdomen, distension, postoperative scars, skin changes, and visible masses.

Palpation - Performed systematically, starting away from the site of greatest tenderness. Superficial palpation is performed first, then deep palpation. The following are assessed:

local tenderness

muscle defense

rebound tenderness

presence of palpable masses

Muscle defense represents a sign of irritation of the parietal peritoneum and is most pronounced in perforations of gastroduodenal ulcer (chemical peritonitis). It is milder in inflammatory processes, while in intraperitoneal bleeding it may be discrete. In bleeding into the lumen of the digestive tract, defense is absent.

Percussion - Used to assess free fluid and pneumoperitoneum.

Auscultation - Assessment of peristalsis and possible vascular murmurs.

Rectal examination is an integral part of the evaluation. Gynecological or urological examination is performed as indicated [2].

Typical clinical signs that help in establishing the diagnosis are shown in Table 6, and the localization of the most common causes of abdominal pain in Table 7.

Table 6. Typical clinical signs that help in establishing the diagnosis

NAME OF SIGN	DESCRIPTION AND MEANING
Murphy's sign	Sign of acute inflammation of the gallbladder. We place the left hand under the right rib arch, while the thumb gently presses on the gallbladder. When the patient inhales, a positive sign is sudden interruption of inspiration due to pain.
McBurney's sign	Sign of acute appendicitis. Pain on direct pressure at the midpoint between the umbilicus and the right anterior superior iliac spine.
Rovsing's sign	Sign of appendicitis. We press with both hands on the descending colon. Due to the movement of gases in the direction of the cecum, its stretching occurs, which causes pain in the area of inflammation of the cecum.
Blumberg's sign	We press deeply with the hand in the left iliac region. We then suddenly lift the hand. The wave of abdominal wall causes pain at the site of inflammation upon sudden release of pressure.
Psoas sign	Patient lies on the left side. He can extend the right leg and thereby cause pain in the inflamed retrocecal appendix.
Obturator sign	Positive if there is pelvic localization of the appendix, due to internal rotation of the bent leg, pain is provoked in the abdomen.
Carnett's sign	Indicates the source of pain in the abdominal wall (e.g., hematoma of the rectus abdominis muscle). The sign is positive if the patient lies on his back, the pain intensifies when he lifts his head and shoulders off the surface. A negative sign means that during the same maneuver the intensity of pain decreases.
Kehr's sign	Pain at the tip of the left shoulder that occurs due to irritation of the diaphragm, most often indicates rupture of the spleen, and may manifest itself in the heart and liver after colonoscopy or as a complication.
Howship-Romberg sign	Irritation of the obturator nerve in the obturator canal, usually causes referred pain in the obturator nerve, causes pain in the medial part of the thigh down to the knee.
Closed eyes sign	In acute abdominal pain, examinees usually have their eyes wide open during the examination, because they are frightened and watch where the doctor is pressing. When it comes to functional pain, during the examination they often tend to keep their eyes closed.

Table 7. Most common causes of abdominal pain by localization

Localization of pain	Most common causes
Epigastrium	Peptic ulcer of stomach or duodenum, gastritis, functional dyspepsia, acute pancreatitis, myocardial infarction (lower wall), abdominal aortic aneurysm
Right upper quadrant	Cholelithiasis, acute cholecystitis, gastritis, hepatitis, abscesses, liver tumors, lower lobe pneumonia
Left upper quadrant	Spleen lesions (rupture, infarct), gastritis, pancreatitis, subphrenic abscess
Periumbilical region	Early appendicitis, enteritis, small bowel obstruction, mesenteric ischemia
Right lower quadrant	Acute appendicitis, ileitis (Crohn's disease), mesenteric lymphadenitis, ectopic pregnancy, ovarian torsion

Left lower quadrant	Diverticulitis of the sigmoid colon, colitis, colon obstruction, gynecological diseases
Suprapubic region	Cystitis, urinary retention, gynecological diseases (endometriosis, pelvic inflammatory disease), prostatitis
Flank (lumbar region)	Renal colic, pyelonephritis, perinephric abscess
Diffuse pain in the whole abdomen	Peritonitis, ileus, mesenteric ischemia, metabolic disorders

Laboratory diagnostics

The basic laboratory panel includes:
complete blood count with differential
electrolytes and kidney function

glycemia

liver function tests

amylase and lipase

inflammation parameters

urinalysis

Based on clinical indication, the following are determined:

troponin (suspicion of acute coronary syndrome)

D-dimer (suspicion of pulmonary embolism)

blood gases and lactate (suspicion of ischemia or sepsis)

pregnancy test is mandatory for women of reproductive age

Tumor markers have no role in the initial diagnosis of abdominal pain due to insufficient sensitivity and specificity, but serve for monitoring already diagnosed malignant disease [3].

Imaging diagnostics

The choice of method depends on the clinical suspicion:

Native abdominal X-ray – pneumoperitoneum, ileus.

Abdominal ultrasound – pathology of the gallbladder, urinary tract, gynecological diseases, assessment of the abdominal aorta.

CT abdomen with contrast – perforations, abscesses, malignancies, complicated inflammatory diseases.

In case of suspicion of thoracic etiology, a chest X-ray or echocardiography is indicated.

Endoscopic procedures have a diagnostic, and often therapeutic role.

TREATMENT OF PATIENTS WITH ABDOMINAL PAIN

The Latin saying "Dolorem sedare, medici divinum opus est" emphasizes the basic principle of medical practice – alleviating pain represents not only a therapeutic but also an ethical obligation of the physician.

The therapeutic approach to a patient with acute abdominal pain can be:

Causal (etiological) – directed at the underlying disease.

Symptomatic (supportive) – directed at stabilizing vital functions and controlling symptoms.

In urgent conditions, initial stabilization of the patient has priority (principles of the ABC approach), in parallel with diagnostic evaluation.

Supportive treatment

Supportive measures include:

fluid and electrolyte replacement (oral or parenteral)

hemodynamic support (vasopressors and inotropes as indicated)

analgesic therapy

antiemetic therapy

oxygen therapy

correction of metabolic disorders

In case of suspicion of an acute surgical condition, timely consultation with an abdominal surgeon is necessary [11].

Analgesic therapy

Modern data indicate that the use of opioid analgesics in acute abdominal pain does not reduce the diagnostic value of the clinical examination, nor does it negatively affect the treatment outcome. Therefore, adequate analgesia should not be delayed for fear of "masking" the clinical picture.

The choice of analgesic depends on the intensity of pain and the general condition of the patient and may include:

nonsteroidal anti-inflammatory drugs

opioids

spasmolytics

Long-term use of opioids in chronic or functional abdominal pain is not recommended due to the risk of dependence and opioid-induced hyperalgesia.

Treatment of functional pain

In situations where, after adequate diagnostic evaluation, no organic cause of pain is established, a functional or centrally conditioned etiology is considered. In such cases, the following may be indicated:

psychological or psychiatric evaluation
 use of tricyclic antidepressants (TCA)
 selective serotonin reuptake inhibitors (SSRI)
 serotonin and norepinephrine reuptake
 inhibitors (SNRI)

These drugs act through modulation of central
 pain perception, independent of their
 antidepressant effect [12].

Rational use of antibiotics

Empirical use of antibiotics in patients with
 abdominal pain must be clearly indicated and
 based on clinical suspicion of bacterial infection
 or intra-abdominal inflammatory process.
 Routine use of antibiotics in undifferentiated
 abdominal pain is not justified.

Antibiotic therapy is indicated in:
 suspicion of intra-abdominal infection (e.g.,
 perforation of hollow organ, abscess,
 complicated diverticulitis)
 acute cholangitis
 peritonitis
 septic condition of unclear abdominal origin
 severe forms of pancreatitis with evidence of
 infection
 immunocompromised patients with a clinical
 picture of infection

The choice of antibiotic should cover the most
 common causes of intra-abdominal infections
 (Gram-negative enterobacteria, anaerobes),
 taking into account local resistance patterns and
 individual risk factors.

Therapy should be:
 timely (especially in case of septic shock),
 adequately dosed,
 time-limited in accordance with clinical
 response.

Prolonged or inadequate use of antibiotics
 increases the risk of developing resistance,
Clostridioides difficile infection, and other
 complications, so regular re-evaluation of the
 need for continued therapy is recommended
 [13].

Patients at increased risk of unfavorable
 outcome
 Increased morbidity and mortality are expected
 in:

patients older than 65 years
 immunocompromised
 polymorbid patients
 patients after abdominal operations or recent
 endoscopic procedures
 pregnant women (especially in the first
 trimester)
 patients with sudden onset of severe, constant
 pain
 patients with signs of peritonitis or
 hemodynamic instability

Indications for hospitalization

Hospital treatment is indicated in patients with:
 suspicion of peritonitis
 obstruction or perforation of the intestine
 acute intra-abdominal or gastrointestinal
 bleeding
 hemodynamic instability
 uncontrolled pain despite adequate oral therapy
 need for parenteral therapy or invasive
 supportive measures [14]

CONCLUSION

A patient with abdominal pain
 represents a diagnostic challenge that requires a
 systematic, rational, and time-efficient approach
 due to the extensive differential diagnosis, which
 includes both harmless pathological processes
 and many that threaten life. The foundation of
 the evaluation is a carefully taken history and a
 detailed clinical examination, which guide
 further laboratory and imaging diagnostics.
 Early recognition of life-threatening conditions,
 adequate risk assessment, and timely
 consultation with a surgeon or attending
 physician are of crucial importance for the
 treatment outcome.

Monitoring and treatment of patients
 with functional gastrointestinal diseases today
 represents an increasing challenge. Supportive
 measures and analgesia should not be delayed,
 while etiological therapy is carried out
 purposefully, in accordance with the established
 and probable diagnosis.

Rational use of antibiotics and
 avoidance of unnecessary therapy represent an
 important part of modern clinical practice. By
 integrating clinical experience, diagnostic tools,
 and a multidisciplinary approach, it is possible
 to optimize the management of patients and
 reduce morbidity and mortality associated with
 abdominal pain..

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FROM POLYCYSTIC OVARY SYNDROME (PCOS) TO POLYENDOCRINE METABOLIC OVARIAN SYNDROME (PMOS) – RECONSIDERING THE NOMENCLATURE IN LIGHT OF CURRENT KNOWLEDGE

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Abstract: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age and a heterogeneous multisystem syndrome with reproductive, endocrine and metabolic manifestations. Current knowledge has called into question the appropriateness of the existing name of the disease, which is why in 2026 the international Global Name Change Consortium proposed a new term – *polyendocrine metabolic ovarian syndrome* (PMOS). The historical development of the PCOS concept, current diagnostic criteria, the reasons for changing the name to PMOS, and the possible advantages and limitations of the new nomenclature are presented. A narrative review of the literature was performed, including international guidelines, consensus documents and relevant review articles addressing the pathophysiology, diagnosis, phenotypic heterogeneity and nomenclature of the syndrome. Current evidence confirms that polycystic ovarian morphology is neither a mandatory nor a specific feature of the syndrome, while reproductive manifestations represent only one part of a complex endocrine-metabolic disorder. The proposed name PMOS better reflects the multisystem nature of the disease and may contribute to a better understanding of its metabolic and cardiovascular risk. However, due to marked phenotypic heterogeneity, the insufficient precision of certain terms and the long-standing entrenchment of the name PCOS in clinical practice and the scientific literature, the change in nomenclature continues to provoke professional debate. The change of name from PCOS to PMOS reflects the evolution of the current understanding of this complex syndrome, but it does not change the existing diagnostic criteria or therapeutic recommendations. Regardless of the renaming process, the modern approach must remain focused on women's overall health, with an integrated assessment of the reproductive, endocrine, metabolic and cardiovascular aspects of the disease.

Keywords: polycystic ovary syndrome; PCOS; PMOS; hyperandrogenism; insulin resistance; diagnostic criteria; nomenclature.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in women of reproductive age and one of the leading causes of anovulatory infertility [1,2]. It is estimated to affect approximately 10–13% of women of reproductive age, depending on the diagnostic criteria applied and the characteristics of the population studied [1,3]. The current understanding of PCOS goes beyond the concept of an isolated reproductive disorder and defines it as a complex multisystem endocrine-metabolic syndrome associated with hyperandrogenism, ovulatory dysfunction, insulin resistance, obesity, metabolic syndrome, type 2 diabetes, metabolic dysfunction-associated steatotic liver disease (MASLD),

cardiovascular risk and psychological disorders [1,2,4].

The name PCOS was introduced at a time when the characteristic ovarian morphology was considered to be the principal feature of the disease. However, current knowledge shows that polycystic ovarian morphology is neither mandatory nor specific for the diagnosis. Many women with PCOS do not have the characteristic ultrasound finding, while polycystic morphology can also be found in women without clinical manifestations of the syndrome. At the same time, the development of ultrasound technology has led to repeated changes in the criteria for defining polycystic ovarian morphology [1,5,6].

This progress in understanding the disease raised the question of whether the

traditional name still adequately reflects its essence. In 2026, the international multidisciplinary Global Name Change Consortium, with the participation of academic, clinical and patient organizations, proposed the name polyendocrine metabolic ovarian syndrome (PMOS) as an alternative to the name PCOS. The aim of the proposal is to emphasize the endocrine, metabolic and ovarian components of the disease and to reduce the confusion that the term “polycystic” may cause [7].

The history of PCOS is an example of how the development of medical knowledge can lead to the reconsideration of a historically adopted name. In 1935, Stein and Leventhal described women with amenorrhea, infertility, hirsutism and bilaterally enlarged ovaries with numerous small follicles. At a time when modern hormone assays, ultrasound and knowledge of the role of insulin in the pathogenesis of the disorder were not available, ovarian morphology was the most striking common finding and became the basis for the name of the syndrome [8].

Over the following decades, it became clear that the clinical picture is considerably more heterogeneous. Disorders of gonadotropin secretion, increased ovarian androgen production, hyperinsulinemia and insulin resistance, as well as numerous metabolic and neuroendocrine disorders, were identified. For this reason, PCOS is today viewed not only as a disorder of the reproductive system, but as a multisystem disorder with possible long-term metabolic, cardiovascular and psychological consequences [2,4,9].

The diagnostic criteria changed in parallel. The National Institutes of Health (NIH)

criteria from 1990 emphasized hyperandrogenism and chronic anovulation, while the Rotterdam criteria from 2003 included polycystic ovarian morphology as a third diagnostic element, thereby encompassing different phenotypes of the disease [5,10].

Why is the name PCOS being questioned?

The existing name can be analyzed through its three components.

The first problem concerns the term “polycystic”. The follicles visualized on ultrasound in women with PCOS are not true cysts in the pathological sense, but numerous small antral follicles associated with disordered folliculogenesis and the absence of adequate selection of a dominant follicle. The term “polycystic” is a historical remnant from the period before the development of modern ultrasonography [2,5,7].

The second problem is the term “ovarian”. PCOS is not limited to the ovaries, but involves complex interactions of the hypothalamic-pituitary-ovarian axis, the pancreas and insulin secretion, the liver, adipose tissue, skeletal muscle, the adrenal glands and other regulatory systems. The consequences of the disease include metabolic and cardiovascular disorders, as well as psychological complications [2,4,5,9].

The third part of the name – “syndrome” – is still appropriate, because PCOS represents a set of interrelated clinical, hormonal, metabolic and reproductive disorders that can manifest in various combinations and intensities. Phenotypic heterogeneity is one of its fundamental characteristics [2,5].

Table 1. Why is the name PCOS being questioned?

Part of the name	Problem	Current explanation
Polycystic	These are not true cysts	Ultrasound shows numerous small antral follicles with disordered folliculogenesis
Ovarian	The disease is not limited to the ovaries	PCOS is a multisystem endocrine-metabolic disorder
Syndrome	The term is still appropriate	It reflects the heterogeneity of clinical, hormonal, metabolic and reproductive manifestations

A particularly important problem is the variability of ultrasound criteria. Modern high-resolution probes allow visualization of a larger number of antral follicles than earlier devices, which is why the criteria for polycystic ovarian morphology have changed over time. This shows that this feature also depends on the technology

used to assess it, and not only on the biology of the disorder [1,6].

Diagnostic criteria and phenotypic heterogeneity of PCOS

The diagnosis of PCOS in adult women is still based on the modified Rotterdam criteria. After excluding other causes of

hyperandrogenism and ovulatory dysfunction, the presence of at least two of the three criteria is required to establish the diagnosis [1,2,10]:

1. clinical and/or biochemical hyperandrogenism;
2. ovulatory dysfunction;
3. polycystic ovarian morphology determined by ultrasound examination or, in adult women, an elevated concentration of anti-Müllerian hormone (AMH) as an alternative to the ultrasound criterion.

AMH should not be used as a stand-alone diagnostic test, nor simultaneously with ultrasound to confirm the same criterion. When both hyperandrogenism and ovulatory dysfunction are present, ovarian ultrasound or AMH measurement is not necessary to establish the diagnosis [1].

Clinical hyperandrogenism most commonly manifests as hirsutism, while acne and androgenic alopecia, especially when they occur in isolation, have lower diagnostic specificity. For biochemical assessment, measurement of total and free testosterone, or calculation of the free androgen index, is primarily recommended. Androstenedione and dehydroepiandrosterone sulfate (DHEAS) may be measured when testosterone is not elevated, but they have lower specificity for ovarian hyperandrogenism [1].

Ovulatory dysfunction in adult women is most commonly recognized on the basis of menstrual irregularities, including cycles longer than 35 days, shorter than 21 days, or fewer than eight cycles per year. Nevertheless, ovulatory dysfunction may also exist with apparently regular cycles, so in unclear cases ovulation can

be assessed by measuring progesterone in the luteal phase [1].

In adult women, with modern ultrasound equipment and adequate image quality, polycystic ovarian morphology is defined by the presence of at least 20 follicles measuring 2–9 mm in diameter in at least one ovary. When older equipment or a transabdominal approach is used, or when reliable counting of all follicles is not possible, an ovarian volume of at least 10 mL or at least 10 follicles in a single ovarian section may be used. The dominant follicle, corpus luteum and pathological cysts are not included in the assessment [1,6].

In adolescents, the diagnosis is made more restrictively. The simultaneous presence of ovulatory dysfunction, defined according to the time elapsed since menarche, and clinical and/or biochemical hyperandrogenism is required, with exclusion of other causes. Polycystic ovarian morphology and AMH are not recommended for establishing the diagnosis in adolescence due to insufficient specificity [1].

Before establishing the diagnosis, other causes of hyperandrogenism and menstrual cycle disorders must be excluded, primarily thyroid disease, hyperprolactinemia and non-classic congenital adrenal hyperplasia. Depending on the clinical picture, Cushing's syndrome, androgen-producing tumors, hypogonadotropic hypogonadism, primary ovarian insufficiency and iatrogenic causes should also be considered. Sudden onset or rapid progression of hyperandrogenism, virilization and markedly high androgen concentrations require extended differential diagnosis [1,2,5].

Table 2. Phenotypes of polycystic ovary syndrome according to the Rotterdam criteria

Phenotype	Hyperandrogenism	Ovulatory dysfunction	Polycystic ovarian morphology (PCOM)	Common name
A	+	+	+	Full or classic phenotype
B	+	+	–	Classic phenotype without PCOM
C	+	–	+	Ovulatory phenotype
D	–	+	+	Non-hyperandrogenic phenotype

Phenotypes A and B are, on average, associated with more pronounced reproductive and metabolic disorders, while C and especially D may have a milder metabolic profile. Nevertheless, the phenotype is not an

unchangeable category, nor can it replace individual risk assessment [5].

The existence of different phenotypes is an important limitation of the name PCOS. In phenotype B, polycystic ovarian morphology is

not present, while in phenotype D there is no clinical or biochemical hyperandrogenism. Thus, no single reproductive, biochemical or morphological feature is common to all patients [5,10].

Proposal for a new nomenclature – PMOS

In 2026, the Global Name Change Consortium published the results of a multistep international consensus process aimed at reconsidering the name of PCOS. The process involved experts in endocrinology, gynecology, reproductive medicine and other fields, researchers and patient representatives, with the engagement of 56 academic, clinical and patient organizations. Polyendocrine metabolic ovarian syndrome (PMOS) was proposed as the new name [7].

The PMOS proposal seeks to retain the initial letter P and a certain continuity with the existing terminology, while at the same time removing the term “polycystic” and emphasizing the endocrine and metabolic components of the disease. The term polyendocrine indicates the involvement of multiple endocrine systems, metabolic the metabolic characteristics, while ovarian retains the link with ovarian and reproductive dysfunction [7,9].

The authors of the proposal emphasize that the change of name in itself does not represent a change in diagnostic criteria or therapeutic recommendations. Its purpose is primarily to align the nomenclature with the current understanding of the disease and to improve communication, education and clinical awareness of its multisystem consequences [7].

Table 3. Reasons for the proposed name change

Phenotype	Hyperandrogenism	Ovulatory dysfunction	Polycystic ovarian morphology (PCOM)	Common name
A	+	+	+	Full or classic phenotype
B	+	+	–	Classic phenotype without PCOM
C	+	–	+	Ovulatory phenotype
D	–	+	+	Non-hyperandrogenic phenotype

One of the main arguments in favor of changing the name is that the name of a disease should reflect its current pathophysiological essence. PCOS involves disorders of the hypothalamic-pituitary-ovarian axis, insulin regulation, ovarian steroidogenesis, adipose tissue and liver metabolism, as well as various metabolic and vascular consequences [2,5,9].

It is particularly important that women with PCOS have an increased risk of glucose regulation disorders, type 2 diabetes, dyslipidemia, arterial hypertension, MASLD and other cardiometabolic complications. For this reason, the modern approach cannot be limited to menstrual disorders, infertility or the ultrasound appearance of the ovaries [1,2,11].

According to proponents of the change, the name PMOS could help ensure that in women with this syndrome, body weight and waist circumference, blood pressure, glucose regulation, an oral glucose tolerance test (OGTT)

when needed, lipid status and cardiometabolic risk are considered earlier [1,2].

Arguments against the name change

The PMOS proposal has not been accepted unanimously. One of the main arguments against the change is the marked heterogeneity of PCOS. In some women, reproductive manifestations and hyperandrogenism predominate, while in others metabolic disorders may be in the foreground. There are also women of normal body weight with minimally expressed metabolic disorders, which raises the question of whether the term “metabolic” can adequately encompass all phenotypes [5,9].

A similar question concerns the term polyendocrine, which is not widely established in the existing nomenclature. Without additional explanation, it could cause new terminological uncertainties and different interpretations [7].

A further argument is that the change of name in itself does not change the way the

disease is treated. Without appropriate education of physicians and patients, the new name will not automatically lead to earlier recognition of metabolic complications or to better quality of treatment [7].

Historical continuity is also an important practical problem. The name PCOS has been used for almost nine decades and is

present in a large number of scientific publications, clinical guidelines, databases and electronic health systems. A change in nomenclature could make it more difficult to search earlier literature, compare studies and maintain continuity of scientific communication [7].

Table 4. Arguments for and against the name change

Arguments for PMOS	Arguments against PMOS
It better reflects the current multisystem pathophysiology	No name can encompass all phenotypes
It emphasizes the endocrine and metabolic nature	The term polyendocrine is not sufficiently established
It reduces confusion about "cysts"	The metabolic component is not dominant in all patients
It may encourage more systematic metabolic screening	The name change does not change diagnosis or therapy
It may improve communication and education	There is a problem of historical and scientific continuity

The essential question, therefore, is not only whether the name PCOS is terminologically outdated, but whether its replacement would lead to a measurable improvement in the understanding, diagnosis and treatment of the disease. A change in nomenclature makes sense only if it contributes to better clinical practice, and is not an end in itself [7].

The role of ultrasound in the current concept of PCOS

The development of ultrasound diagnostics has particularly demonstrated the limitations of relying on ovarian morphology. Modern medicine allows precise assessment of the antral follicle count and ovarian volume, but no international diagnostic criterion requires polycystic morphology in all women with PCOS [1,10].

At the same time, polycystic morphology is not specific to PCOS and can be found in women without the syndrome, especially at a younger age. The ultrasound finding alone is therefore not synonymous with the disease [5,6].

This, however, does not diminish the importance of ultrasound. Ultrasound examination remains important in assessing ovarian morphology, excluding other ovarian disorders, assessing reproductive status and in certain therapeutic procedures [1,6]. The essential question is not whether ultrasound is important, but whether the finding in a single organ should form the basis for the name of a complex multisystem syndrome.

Therapeutic implications of the name change

The change of name from PCOS to PMOS does not in itself change the diagnostic criteria

or therapeutic recommendations. Treatment should still be tailored to the patient's dominant symptoms, reproductive plans and metabolic profile [1].

The basis of the therapeutic approach is lifestyle modification, including appropriate diet, physical activity and weight reduction in women who are overweight or obese. These interventions can have a favorable effect on reproductive, metabolic and cardiovascular outcomes [1].

In women who are not planning pregnancy, combined oral contraceptives are one of the basic pharmacological options for regulating the menstrual cycle and treating clinical hyperandrogenism. Antiandrogens may be used in selected patients together with appropriate contraception[1].

Metformin has an important place in women with metabolic disorders, particularly impaired glucose regulation, prediabetes or type 2 diabetes, as well as in certain patients with increased metabolic risk. Glucagon-like peptide-1 (GLP-1) agonists may be considered in selected women with obesity, especially when the goal is greater weight reduction and improvement of metabolic parameters. Inositols may have a place in some patients, although their optimal use and clinical significance require further evaluation [1].

In women who wish to become pregnant, the goal of treatment is to establish ovulation and increase the likelihood of conception. According to current international guidelines, letrozole is the first-line therapy for ovulation induction in anovulatory women with PCOS [1].

The change in nomenclature, therefore, should not lead to a change in therapeutic algorithms, but possibly to a broader consideration of the patient's needs. If the name PMOS were to contribute to greater awareness of the metabolic and cardiovascular consequences of the disease, its potential benefit would lie primarily in a change of clinical perspective, rather than in the introduction of new therapy.

Conclusion

The name polycystic ovary syndrome originated at a time when the morphological appearance of the ovaries was the most noticeable feature of the disease. Over almost a century, the development of reproductive endocrinology, molecular biology and ultrasound diagnostics has completely changed the understanding of this disorder. Today it is clear that PCOS is a heterogeneous, multisystem syndrome in whose pathogenesis complex interactions of genetic, epigenetic, neuroendocrine, metabolic and inflammatory mechanisms participate, while polycystic ovarian morphology is only one of its possible manifestations.

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THE IMPORTANCE OF THE MEDITERRANEAN DIET IN THE PREVENTION OF CARDIOVASCULAR DISEASES

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Summary: Cardiovascular diseases (CVD) are a heterogeneous group of diseases, with a leading share in morbidity and mortality worldwide. The rapid upward trend of these diseases requires preventive measures aimed at reducing cardiovascular risk factors, among which unhealthy dietary trends are of particular importance.

In recent decades, cultural globalization and urbanization have led to lifestyle changes, which have been particularly reflected in unhealthy dietary trends that include a low intake of whole grains, fruit, fiber, legumes, nuts and seeds, omega-3 fatty acids, polyunsaturated fatty acids, vegetables, milk and calcium, and a high intake of sodium, trans fats, red or processed meat and sugar-sweetened beverages. This phenomenon has created the so-called “nutrition transition”, in which obesity, CVD and diet-related chronic diseases represent new challenges for public health systems.

An unhealthy diet is a modifiable risk factor for the development of CVD. In the prevention of this group of diseases, emphasis is placed on the importance of the Mediterranean dietary model, as the healthiest and most complete nutritional model, which contributes to a significant reduction in the incidence, prevalence and mortality of CVD.

Keywords: Mediterranean diet, cardiovascular diseases, prevention.

In the context of healthy eating habits, a dietary pattern inspired by the principles of the Mediterranean diet is associated with multiple health benefits, due to its protective effects against a wide range of chronic and metabolic diseases, including obesity, diabetes mellitus (DM), CVD, neurodegenerative diseases and cancer [1].

The term “Mediterranean diet” was introduced in the mid-1970s in the United States of America (USA) by Ancel Keys (1904–2004), one of the most prominent scientists of our time, and his wife Margaret Haney. In their publications, they were the first in the English-speaking world to demonstrate the value of the Mediterranean diet on the basis of their scientific research combined with culinary art. Thanks to their studies, the World Health Organization (WHO) was later encouraged to promote the Mediterranean diet in order to improve global health and to use the Mediterranean diet pyramid as a pedagogical tool illustrating its basic rules [2].

The Mediterranean diet was recognized as an “intangible cultural heritage of France and Italy, Greece, Spain and Morocco by the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 2010 [3]. The basis of

the Mediterranean diet is a balanced intake of nutrients (carbohydrates, proteins, fats, vitamins and minerals) that are rich in plant-based proteins, complex carbohydrates and fiber, monounsaturated fatty acids and polyunsaturated fatty acids [4]. The Mediterranean diet, which is based on the traditional diet of the Mediterranean countries, has a significant positive impact on health. It reduces the risk of a wide range of diseases, especially CVD, type 2 diabetes mellitus (T2DM), obesity and certain types of cancer [5]. The results of the conducted studies indicate that a two-point increase in the score of adherence to the Mediterranean diet determines a 9% reduction in total mortality, a 9% reduction in CVD mortality, a 6% reduction in the incidence of or mortality from neoplasms, and a 13% reduction in the incidence of Parkinson’s disease and Alzheimer’s disease [6]. This dietary regimen has favorable effects on the endocrine and metabolic balance, contributes to the regulation of insulin sensitivity, blood pressure, lipid profile, lipoprotein particles, oxidative stress, inflammation and the prevention of carotid atherosclerosis. Unsaturated fats and polyphenols, which characterize the Mediterranean diet, form the basis of CVD prevention, especially in dietary regimens rich in

vegetables, showing lower levels of total cholesterol and lower levels of systolic blood pressure. Also, this dietary regimen has favorable effects in reducing glycoxidative damage and the inflammatory response, compared with a diet based on the consumption of saturated fatty acids [7].

Assessing the impact of Mediterranean food choices on the serum metabolic profile in healthy adolescents performing physical activity of different intensity levels, it was shown that active subjects who consume typical Mediterranean food have a better serum metabolic profile, which suggests that adherence to the Mediterranean pattern and the performance of physical activity lead to a significant reduction in the glucose and lipid profile, thus making the Mediterranean diet and physical activity a winning combination for health status [8].

Conducted studies have shown that practicing the Mediterranean diet is a significant factor in the prevention of malignant diseases. In persons who practiced this dietary regimen, an increase in the plasma concentration of several binding proteins was recorded, such as insulin-like growth factor binding protein (IGFBP)-1, IGFBP-2 and sex hormone-binding globulin,

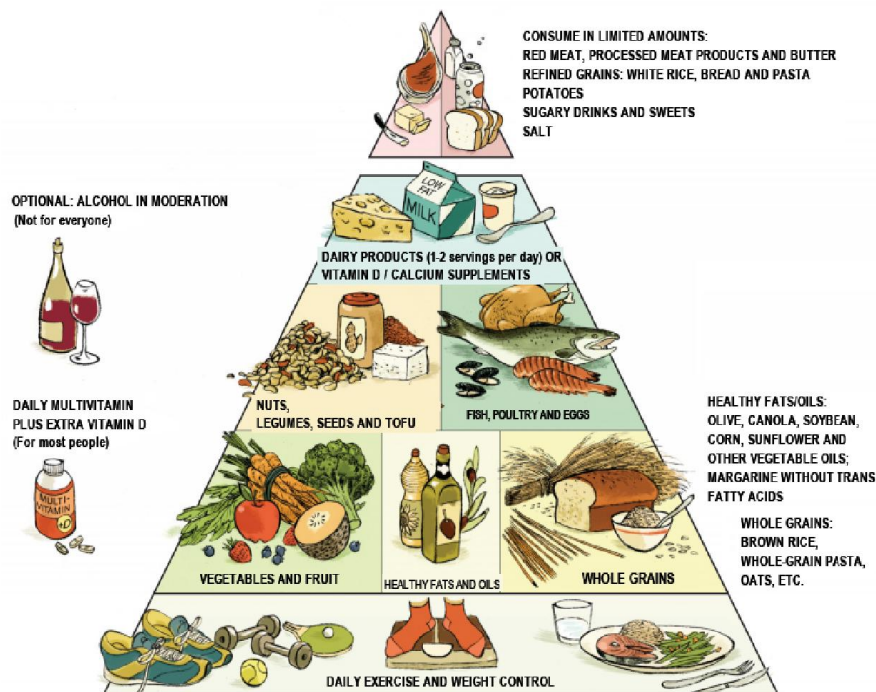
which resulted in a reduction in the biological activity of IGF-1, testosterone and estradiol. Insulin, estrogens, androgens and IGF-1 are powerful cellular mitogens, associated with the development and growth of several tumors, including cancer of the breast, colon, prostate, pancreas and endometrium [9].

The Mediterranean diet pyramid

The Mediterranean diet pyramid is representative of the Mediterranean diet and was developed on the basis of the dietary habits of long-lived adults in the Mediterranean region. The pyramid follows general guidelines on the choice of foods, but does not prescribe their exact quantity. Nutritionists, sociologists, anthropologists and farmers have collectively contributed to the development of what we currently call the Mediterranean diet, adapting the pyramid to the new lifestyle of the Mediterranean region [10]. The Mediterranean diet pyramid (Figure 1.) includes ingredients from all food groups in appropriate proportions and frequencies and is intended for the generally healthy adult population. However, it is flexible enough to also meet the needs of pregnant women, children and people with various pathophysiological conditions [11].

Figure 1. The Mediterranean diet pyramid

Source: <https://dijetapro.org/wp-content/uploads/2015/12/piramida-1-1.png>



Cereals form the basis of the Mediterranean diet, providing calories, macronutrients, micronutrients, dietary fiber, minerals and a multitude of phytochemicals. These nutritional factors are necessary for the homeostasis of human metabolism and the function of multiple organs. The intake of cereals, especially whole grains, contributes to the preservation of health and the prevention of CVD, cerebrovascular disorders, DM, malignant diseases and a reduction in the rate of total mortality [12]. In the context of preserving the cardiovascular and cerebral systems, regular intake of cereals reduces the risk of coronary heart disease, myocardial infarction, heart failure, small- and large-vessel stroke and ischemic stroke [13]. They achieve their cardioprotective potential by lowering blood pressure, total cholesterol and low-density lipoprotein cholesterol and by regulating glucose levels [14]. Regular use of cereals in the diet also exhibits antioncogenic potential, especially in tumors of the gastrointestinal tract. This antioncogenic potential is particularly manifested by a reduced risk of pancreatic cancer in middle-aged men [15]. Conducted studies point to the importance of cereals, especially rice, for maintaining ideal weight and preventing obesity. Rice achieves its anti-obesity effect through its influence on vascular function and on the condition of the liver and pancreas, by reducing adipocyte hypertrophy and lipid accumulation, whereby the inflammatory and antioxidant systems are improved and fecal elimination of cholesterol is increased. It exerts particularly protective effects at the level of the host microbiota and contributes to the restoration of eubiosis [16]. An optimal daily intake of cereals in the range of 3 to 7 servings per day, which is equivalent to 90 to 210 g of whole-grain products, is associated with the lowest risk of mortality from all causes, coronary heart disease, T2DM and colorectal cancer [17]. Pasta is made from refined grains, which may contribute to its perception as "fattening", but unlike many other refined grains, the unique structure of pasta makes it a carbohydrate with a low glycemic index. Low glycemic index/load diets have been shown to be beneficial for weight loss or weight maintenance in adults and children, even when the low glycemic index diet includes pasta [18]. Bread is an integral part of the diet worldwide, with a significant contribution to key nutrients. Although evidence

on the impact of bread consumption on health is still lacking and depends on the overall diet, whole-grain breads have shown consistent beneficial effects on human health [19]. Bread provides several nutrients such as sugar, proteins, iron, calcium and various vitamins. An average daily intake of 300 g of bread can provide the nutrients needed by the body and create the desired nutritional status. Bread can provide 1,2% of protein, 60% of thiamine and niacin, 40% of calcium and 80% of the daily iron requirement of an adult [20].

According to WHO recommendations, consuming adequate amounts of fruit and vegetables is one of the basic elements of a healthy diet, which reduces the risk of chronic non-communicable diseases and ensures an optimal daily intake of dietary fiber [21]. The importance of fruit and vegetables in the diet is reflected in the high percentage of fiber, minerals, vitamins and phytochemicals they contain [22]. These nutritional components have a favorable effect on the body through the regulation of oxidative stress, inflammatory processes and insulin resistance. The high fiber content of fruit and vegetables has a favorable effect on the regulation of cholesterol levels and arterial blood pressure [23]. The consumption of vegetables, as well as the combination of fruit and vegetables, has a favorable effect on reducing the risk of metabolically unhealthy obesity, especially in young people who are obese. In a study conducted by Guedes et al. [24], in a population of university students, it was found that inadequate intake of fruit and vegetables was present in 87% of respondents, with a prevalence of overweight of over 39%, whereby the risk of overweight was two to three times higher in respondents who did not have an adequate intake of fruit and vegetables. In recent years, it has been established that the consumption of fruit and vegetables has a preventive effect against certain types of cancer, especially gastrointestinal cancers, due to their high content of fiber and antioxidants. In a large meta-analysis of cohort studies, increased consumption of fruit alone and in combination with vegetables corresponds to a reduction in the probability of gastric cancer by 13% and 25% [25]. The recommended daily intake is at least 200 g of fruit and 150-200 g of vegetables, i.e. at least 1-2 servings of fruit and 3-4 servings of vegetables per day. Consumption of phytosaccharides (>450 g/day) and fruit intake

reduce the risk of CVD by 14,2% and 6,7% [26-28].

Olive oil is located at the center of the Mediterranean diet pyramid. It is an ideal source of monounsaturated fats, vitamin E, polyphenols, chlorophyll and phytosterols, micronutrients that exert numerous benefits on the body, including anti-inflammatory, antioxidant, neuroprotective, anticancer, antidiabetic, antimicrobial and antisteatotic effects [29-30]. They exhibit a particular protective potential at the level of the cardiovascular system, because it contributes to the regulation of lipid status, blood pressure, insulin sensitivity and glycemic control. Olive oil shows great potential in the positive modulation of the composition of the gut microbiota and of microbially produced products, which is associated with the prevention of cardiometabolic diseases [31]. Daily use of olive oil in the diet can significantly reduce the risk of CVD, stroke and T2DM, but also of overall mortality. The maximum benefit can be achieved by consuming between 20 and 30 g per day. In a study conducted by Donat-Vargas et al., it was found that an additional intake of olive oil of 25g/day reduces the risk of CVD by 16% and the risk of T2DM by 22% [32].

According to the Mediterranean diet pyramid, milk and dairy products are foods whose consumption is recommended daily. Dairy products are rich in high-quality proteins, vitamins (riboflavin, vitamin D, vitamin B-12), calcium, potassium and magnesium, which are important for maintaining muscle mass, improving vascular function, bone mineralization and neuromuscular function, and contribute to overall cardiovascular health [33]. Fermented or cultured dairy products, such as yogurt, contain probiotic bacterial cultures that are assumed to reduce the production of trimethylamine-N-oxide, a metabolite that is an early predictor of metabolic syndrome, implicated as a cause of atherosclerosis and CVD [34]. The results of conducted studies suggest that the intake of fermented dairy products for every 20 g reduces the risk of the incidence of and mortality from CVD [35]. In studies conducted by Guo [36] et al. in 2021, and Lu Y. et al. in 2025 [37], it was found that the consumption of dairy products has a significant impact on reducing the incidence of hypertension and cerebrovascular diseases, and favorable effects on serum cholesterol, triacylglycerides and blood pressure. Daily

consumption of dairy products has a positive effect on anthropometric parameters, specifically on waist circumference, especially in women. Women who consume more than 1,9 servings of dairy products per day are 53% less likely to have a waist circumference greater than 80 cm [38].

Thanks to their rich bioactive composition, nuts exert numerous positive effects on the body. A high percentage of monounsaturated and polyunsaturated fatty acids, tocopherols and tocotrienols, phytosterols, sphingolipids, carotenoids, chlorophyll and alkyl phenols, and phenolic compounds (including flavonoids, phenolic acids, stilbenes, lignans) exert positive effects on the cardiovascular, central nervous, respiratory and endocrine systems, with a significant role in reducing the risk of developing malignant diseases [39]. A nut intake of the recommended 28 g/day is associated with a 21% reduction in the risk of CVD (including the incidence of and mortality from coronary heart disease, atrial fibrillation and stroke mortality), an 11% reduction in the risk of death from cancer and a 22% reduction in all-cause mortality [40]. Each increase in total nut consumption of 5 g/day is associated with a 3%, 6% and 25% lower risk of pancreatic and colon cancer [41]. Nut intake contributes to the regulation of all biochemical parameters associated with DM, including fasting glycemia, plasma insulin, glycated hemoglobin (HbA1c) and the oral glucose tolerance test (OGTT) [42].

The Mediterranean region has a rich fishing tradition, which results in significant fish consumption. Fish meat is rich in many polyunsaturated fatty acids that exert favorable effects on the cardiovascular system. Polyunsaturated fatty acids include long-chain Ω -3, especially eicosapentaenoic acid and docosahexaenoic acid, obtained primarily from fish and seafood, as well as alpha-linolenic acid, obtained from various plant sources. Polyunsaturated fatty acids exert a protective role on the cardiovascular system by increasing the level of high-density lipoproteins, reducing inflammatory factors, improving heart rhythm and blood pressure, regulating left ventricular diastolic filling and increasing vagal tone. [43]. Consumption of fish 3-4 times a week reduces the risk of developing coronary diseases by about 12%, while a lower weekly fish intake of about 100-150 g also reduces the risk of coronary diseases, but by a significantly smaller

percentage, of 4-7% [44]. In a study conducted by Mihan et al., the risk of CVD was lowest with a moderate amount of fish (i.e. at least 175 g/week, or approximately 2 servings/week), with no further apparent reduction in risk with a higher fish intake (i.e. >350 g/week, or >3-4 servings/week) [45].

From a nutritional point of view, meat contains all the essential amino acids (which makes it a complete protein), is rich in some key micronutrients, such as vitamin B12, iron, zinc, selenium, iodine and vitamin D, and also has non-negligible amounts of essential fatty acids, especially in the lean parts (e.g. monounsaturated fatty acids, long-chain omega-3 polyunsaturated fatty acids, as well as conjugated linoleic acid) [46]. White meat, which differs in its nutritional composition from red meat in terms of a lower percentage of fat and iron, has a favorable effect on health. White meat achieves its favorable effect on the body by reducing the risk of developing CVD, DM, stroke, cancer, as well as all-cause mortality [47]. Potentially beneficial effects are achieved if fresh, unprocessed and lean white meat is used in the diet [48]. A particularly important effect of white meat is reflected in the prevention of cancer. Higher consumption of red meat is associated with an 84% increased risk of hepatocellular carcinoma, while white meat is associated with a 39% reduced risk; red meat consumption is associated with a higher risk of breast cancer, while the use of white meat in the diet can reduce this risk [49]. White meat also has a positive effect on body weight regulation, in terms of a favorable effect on the reduction of excess body weight, especially in women who are overweight or obese [50].

Eggs are a well-known source of dietary cholesterol, which is why their excessive use in the diet was disputed at the end of the last century. The American Heart Association (AHA), in its 2000 revision, recommended a cholesterol intake of less than 300 mg/day in order to reduce the increase in blood cholesterol, despite the lack of concrete evidence that egg consumption can cause elevated cholesterol levels. The latest Dietary Guidelines for Americans no longer set limits on egg consumption, but instead advocate egg consumption as part of a healthy diet [51]. An egg contains 177 mg of cholesterol, but only 1.3 g of saturated fat [52]. The lipids in egg yolks comprise a mixture of healthy unsaturated fatty

acids, including triglycerides, phospholipids, cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL) and very-low-density lipoproteins (VLDL). LDL makes up two thirds of the total yolk and is responsible for its emulsifying properties, while proteins provide essential amino acids. Egg yolks serve as a significant source of essential vitamins such as A, B2, B6, B12, biotin, folic acid, D, E and K, together with minerals such as calcium, zinc, iron, potassium, magnesium, iodine, fluoride, selenium and phosphorus. These vitamins and minerals play a key role in maintaining vision, contributing to bone and muscle growth, promoting well-being and strengthening immunity. In addition, they contain antioxidants such as lutein and zeaxanthin. The proteins found in eggs exert numerous beneficial effects on the body, which are reflected in the prevention of malnutrition, improvement of skeletal muscle function, and anti-infective, hypotensive, anticancer and anti-obesity properties [53]. When it comes to the potential protective effect on the cardiovascular system, the emphasis is placed on the amount of eggs consumed. The results of a study conducted by Godos et al. [54] revealed that a moderate egg intake (4/week) did not increase the risk of CVD, while a high egg intake (1/day) was associated with heart failure. Another study showed that a moderate egg intake (5-6 per week) was associated with a reduced risk of CVD, including a 26% lower risk of hemorrhagic stroke and a 12% lower risk of coronary heart disease [55].

The harmful effect of red meat on cardiovascular health has been widely demonstrated, primarily due to its higher content of saturated fatty acids and cholesterol. Red meat consumption is associated with the risk of CVD, primarily coronary heart disease, as well as with an increased risk of all-cause mortality. Reducing red meat intake by 3 servings per week reduces the risk of the incidence of acute myocardial infarction, stroke and T2DM [56]. Additional harmful factors accompanying the use of red meat in the diet are increased amounts of salt, nitrates and peroxynitrites, which can influence the development of atherosclerosis and vascular dysfunction, which are predictors of CVD, with a particular influence on the development of ischemic heart disease [57]. Red meat consumption is a risk factor for the development of hypertension. Replacing one serving per day

of red meat with white meat, fish, eggs or dairy products reduces the risk of developing hypertension by 8-15% [58].

A category of foods that, according to the guidelines of the Mediterranean diet, should be limited are sweets. Sweets and other sweetened foods have a high content of energy and added sugar, while their content of essential micronutrients is generally low [59]. The consumption of sweets has numerous negative health effects, including the risk of obesity, DM, CVD and hypertension. According to WHO recommendations, sugar consumption should be limited to less than 5% of total energy intake [60].

CONCLUSION

CVD continue to be the leading cause of morbidity and mortality in the world, with an unhealthy diet playing a significant role among changeable or modifiable risk factors. The modern lifestyle and changes in dietary habits have contributed to an increased frequency of obesity, diabetes mellitus and other metabolic disorders that form the basis for the development of CVD.

The Mediterranean diet is one of the best-studied and scientifically confirmed models

of healthy eating. Its basic characteristics include a high intake of whole grains, fruit, vegetables, legumes, nuts, olive oil and fish, with a moderate intake of dairy products, eggs and white meat, and limited consumption of red meat, industrially processed food and sweets. Numerous epidemiological, cohort and intervention studies have shown that adherence to the Mediterranean dietary pattern contributes to an improved lipid profile, regulation of arterial blood pressure, reduction of inflammation and oxidative stress, better glycemic control and a reduced risk of atherosclerotic changes.

The available scientific evidence indicates that the Mediterranean diet significantly reduces the incidence of and mortality from CVD, but also the risk of other chronic non-communicable diseases, including T2DM, obesity and certain malignant diseases. Therefore, its application can be considered one of the most effective non-pharmacological strategies in the primary and secondary prevention of cardiovascular diseases. Promoting the principles of the Mediterranean diet through public health programs, health education and everyday clinical practice can contribute to improving the health status of the population and reducing the burden of CVD

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SEVERE DECOMPENSATED HEART FAILURE WITH ANASARCA ,PRESERVED EJECTION FRACTION and GLOBAL LONGITUDINAL STRAIN, CAUSED BY TRANSIENT CONSTRICTIVE PERICARDITIS AND AN ASSOCIATED CHRONIC MYELOPROLIFERATIVE PROCESS – report of a controversial case with complete cardiac compensation under therapy

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Summary: Introduction. Constrictive pericarditis is a complex clinical and hemodynamic syndrome characterized by restricted diastolic filling of the heart due to pathological changes of the pericardium - loss of tissue elasticity, and, less often, it may occur in a transient form. In advanced constriction, the clinical presentation is systemic venous congestion with ascites, hepatomegaly and anasarca, with preserved left ventricular systolic function, which is why, in the differential diagnosis, it may mimic heart failure with preserved ejection fraction (HFpEF), restrictive cardiomyopathy or other causes of predominantly right-sided heart failure, but also with pleural effusions and pulmonary congestion as a sign of additional left ventricular failure. Echocardiographic assessment plays a central role in recognizing constrictive pathophysiology, but a definitive diagnosis in complex cases requires a multimodality approach, sometimes including pericardial biopsy. **Case report.** We present a 73-year-old female patient with previous conditions of arterial hypertension, pericardial adhesions and a small encapsulated pericardial effusion from 2014, mild mitral regurgitation (since 2014), chronic renal failure, type 2 diabetes mellitus on insulin therapy and hypothyroidism, who developed severe global heart failure with dominant signs of systemic venous congestion. At her own request, she was discharged from the Internal Medicine Department of the Zaječar Health Center. The clinical picture consisted of orthopnea, bilateral pleural effusions, ascites, hepatosplenomegaly, peripheral edema and anasarca. Echocardiography revealed preserved left ventricular systolic function (EF 60–70%), paradoxical movements of the interventricular septum, pericardial thickening of 6–9 mm, parallel movements of the pericardial layers, right ventricular dilatation and dysfunction, significant tricuspid regurgitation and pulmonary hypertension with a maximum recorded right ventricular systolic pressure (RVSP) of 76 mmHg. After intensive decongestive therapy, including intravenous diuretics and inotropic support with dobutamine infusions, corticosteroid and anti-inflammatory therapy was given according to the algorithm for the treatment of constrictive pericarditis. Bilateral evacuating pleural punctures were also performed, and significant clinical and hemodynamic improvement was finally achieved. In parallel with corticotherapy, a nonsteroidal anti-inflammatory antirheumatic drug and colchicine were introduced. The overall therapeutic effect was the loss of dyspnea, complete clinical cardiac compensation with a reduction in body weight from 77 kg to 52 kg over 28 days, with complete resolution of pleural effusions, ascites and peripheral edema, as well as a reduction in RVSP from 76 to 44 mmHg. During follow-up, progressive leukocytosis from $50 \times 10^9/L$ to over $90 \times 10^9/L$, known since 2024, was recorded. A peripheral blood smear showed the presence of all developmental forms of the granulocytic lineage with a predominance of myelocytes and metamyelocytes and less than 2% blasts, which indicated a chronic myeloproliferative process. A hematologist was consulted, but the patient refused hospitalization at the hematology department of a higher-level institution. **Conclusion.** In patients with marked systemic venous congestion, hepatosplenomegaly, ascites and preserved left ventricular systolic function with pleural effusions and pulmonary congestion, constrictive pericarditis should be considered as a possible cause of heart failure. The simultaneous presence of marked leukocytosis, severe splenomegaly and a finding compatible with a chronic myeloproliferative process raises the possibility of secondary pericardial involvement by a hematological disease. This case highlights the importance of a multidisciplinary approach and the need for a complete hemodynamic and hematological evaluation, which is sometimes impossible in practice.

Keywords: constrictive pericarditis; HFpEF; right-sided heart failure; pulmonary hypertension; hepatosplenomegaly; pleural effusion; leukocytosis; myeloproliferative process.

INTRODUCTION

Constrictive pericarditis. Pericardial constriction is a chronic condition characterized by a thickened, heavily fibrotic and inelastic, and often calcified, pericardium, which leads to impaired diastolic filling of the heart. The term constrictive pericarditis (CP) should be used when pericardial constriction is associated with pericarditis [1]. Constrictive pericarditis is a consequence of chronic inflammation of the pericardium and is characterized by scarring, fibrosis and complete loss of pericardial elasticity. The main symptoms are dyspnea, edema, orthopnea and fatigue. The classic clinical picture is most often characterized by isolated right-sided heart failure, with normal or near-normal natriuretic peptide levels. Signs of venous congestion, hepatomegaly, pleural effusions and ascites may occur [2,3,4]. Constrictive pericarditis should initially be treated with empirical anti-inflammatory therapy for at least 3 to 6 months according to the 2025 recommendations of the European Society of Cardiology [1,5]. Patients in whom medical treatment has not led to improvement, as well as patients with pericardial constriction not associated with pericarditis, should be referred without delay for cardiac surgical treatment, i.e. pericardiectomy [1,5]. Severe hypotension may be a sign of chronic pericarditis with constriction and cardiac tamponade (CTP – constrictive tamponade physiology), which clinically manifests as Beck's triad: hypotension, jugular venous distension and muffled heart sounds.

Transient constrictive pericarditis. Transient constriction is a form of constrictive pericarditis (CP) with active inflammation present, which may resolve after anti-inflammatory therapy or regress spontaneously. It develops during pericarditis with or without pericardial effusion (effusive-constrictive pericarditis). In more than 50% of cases, constriction resolves after anti-inflammatory therapy [6,7,8]. In patients with newly diagnosed constrictive pericarditis, a trial of anti-inflammatory therapy lasting 3 to 6 months is recommended before referral for pericardiectomy [9,10]. To demonstrate active pericardial inflammation, the use of biomarkers (e.g. elevated C-reactive protein) and multimodality imaging is necessary, including cardiovascular magnetic resonance (CMR) [10,11].

Constrictive pathophysiology

It is important to distinguish constrictive pathophysiology from actual symptoms of heart failure [3,6,7,12]. Echocardiographic and hemodynamic signs of constriction may be present, such as: "septal bounce" (paradoxical or abrupt movement of the interventricular septum), respiratory phase-dependent shift of the interventricular septum and Doppler features of constriction, while the patient may be free of heart failure symptoms. The non-inflammatory phenotype of pericarditis is a form whose pathogenesis, with normal C-reactive protein levels, is unknown, and these cases are often therapeutically challenging and more difficult to treat [13].

Treatment of constriction

The algorithm for the treatment of constriction uses clinical data, biomarkers and imaging methods, including CMR (cardiovascular magnetic resonance), CT (computed tomography) and ECG (electrocardiogram) [1,5].

Empirical anti-inflammatory therapy is justified only in patients with evidence of pericarditis based on clinical criteria, biomarkers and/or imaging findings. Stratification of constrictive pericarditis by response to therapy

- *Low risk:* clinical remission after therapy, normalization of imaging findings.
- *Intermediate risk:* improvement of symptoms without complete remission, partial regression of signs of constriction.
- *High risk:* persistent symptoms, permanent signs of constriction on imaging.

Constrictive pericarditis is a complex clinical syndrome resulting from impaired diastolic filling of the cardiac ventricles due to thickening, fibrosis, inflammatory changes or other pathological changes of the pericardium. The clinical picture depends on the degree and duration of constriction, and signs of systemic venous congestion often dominate, including peripheral edema, ascites, hepatomegaly, pleural effusions and exercise intolerance. At the same time, left ventricular systolic function may remain preserved, which can make differentiation from HFpEF and restrictive cardiomyopathy difficult [1,14].

Echocardiography plays a central role in the initial recognition of the constrictive physiological pattern. Of particular importance are paradoxical movements of the interventricular septum, respiratory variations

in diastolic filling, the so-called annulus reversus: a higher tissue Doppler velocity of medial e' than of lateral e' , and certain hepatic vein flow patterns. A combination of several echocardiographic parameters increases diagnostic reliability, while individual signs are not sufficient for a definitive diagnosis [13].

In patients with preserved ejection fraction, heart failure may result from impaired diastolic function and elevated filling pressures, whereby secondary pulmonary hypertension and right ventricular failure may also play a significant role. Current criteria for HFpEF therefore require, in addition to symptoms and preserved ejection fraction, objective evidence of structural or functional abnormalities and/or elevated filling pressures [16].

A particular diagnostic problem in this case is the simultaneous presence of marked leukocytosis, hepatosplenomegaly and pathological changes of the pleura and pericardium. In such a context, a hematological process may play a significant role in the differential diagnosis, including infiltrative and extramedullary processes. However, the peripheral blood finding alone is not sufficient to establish a definitive diagnosis of myeloproliferative neoplasm [17-21].

The aim of this report is to present the complex clinical course of a patient with severe systemic congestion, preserved left ventricular systolic function, echocardiographic signs of suspected constrictive pericardial physiology, pulmonary hypertension and a concurrent finding of marked leukocytosis compatible with a myeloproliferative process, as well as the diagnostic difficulties due to the patient's non-cooperation.

CASE REPORT:

MEDICAL HISTORY: We present a 73-year-old female patient with long-standing cardiovascular problems: hypertension, mitral regurgitation, pericardial adhesions and a small pericardial effusion from 2014. Based on the documentation she brought, newly developed G3 kidney disease is recorded; for 10 years she has had type 2 diabetes mellitus on insulin therapy, as well as hypothyroidism and marked leukocytosis. In May 2026, the patient was hospitalized at the Internal Medicine Department of the Zaječar Health Center due to a feeling of shortness of breath (dyspnea) and received therapy from which she did not feel any significant improvement. During the 2 months after this hospitalization in 2026, a pronounced clinical picture of systemic venous congestion developed, with orthopnea, bilateral pleural effusions, ascites, peripheral edema and hepatosplenomegaly, and typical ANASARCA. On 13.07.2026, i.e. the day before admission to the "Dr Bastać" Practice, she was discharged at her own request from the Internal Medicine Department of the Zaječar Health Center.

MAIN COMPLAINTS are marked fatigue, inability to walk, instability, episodes of fainting, a feeling of severe suffocation, difficulty breathing, shortness of breath, occasional stabbing chest pain and leg swelling.

The first contact was back in 2014 - at that time, echocardiography revealed mild mitral regurgitation, separation of the pericardial layers, with adhesions (Figures 1 and 2) on the lateral wall - signs of adhesive pericarditis, and a small encapsulated effusion behind the posterior wall of 2 mm. Tissue Doppler showed that: systolic and diastolic annular velocities were reduced, E/e' ratio 10,6 borderline. In the laboratory findings, only thrombocytopenia dominates, and since then she has been on bisoprolol 2,5 mg. Thrombocytopenia,

Figure 1. small encapsulated effusion behind the posterior wall 2 mm, 2014

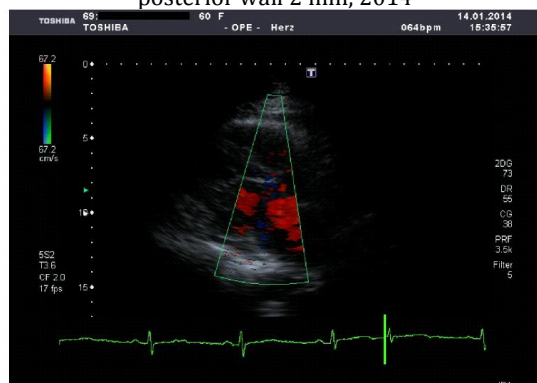
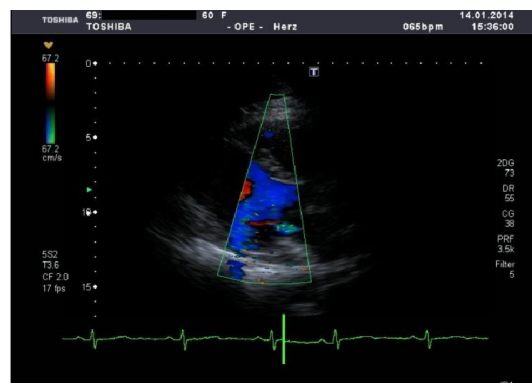


Figure 2. mild mitral regurgitation, 2014



Now, on admission, she gives no information and has no documentation that she was hospitalized at the hematology department of the Clinical Center Niš in 2024. It was later learned from the heteroanamnesis that a bone marrow biopsy had been performed, but the sample was not diagnostic. She refused the proposed further treatment and was discharged with a diagnosis of splenomegaly and suspected chronic myeloid leukemia. She also had laparoscopic gallbladder surgery with complications and conversion to classic laparotomy due to a calculus in the common bile duct.

CURRENT previous therapy: spironolactone 100mg 2x1, Bisoprolol 2,5mg 1x1, Empagliflozin 10mg 1x1, Ramipril- 5mg 1x1/2, Thyroxine 25mcg 2x1, Furosemide forte 500mg 1x1.

STATUS PRAESENS ON ADMISSION: 14.07.2026 - inspection reveals extreme dyspnea, Tachypnea, distended neck veins, orthopnoea- can lie down, examination difficult overall. Blood pressure was 130/70 mmHg, body weight 77 kg, and SpO₂ 95%. She refuses hospitalization and referral to a tertiary institution (written statement).

COR: HR 75 min, heart sounds muffled, rhythm regular, systolic regurgitant murmur over Erb's point 2/6. **PULMO:** breath sounds diminished bilaterally at the bases, dullness to percussion up to both scapular angles, early and late

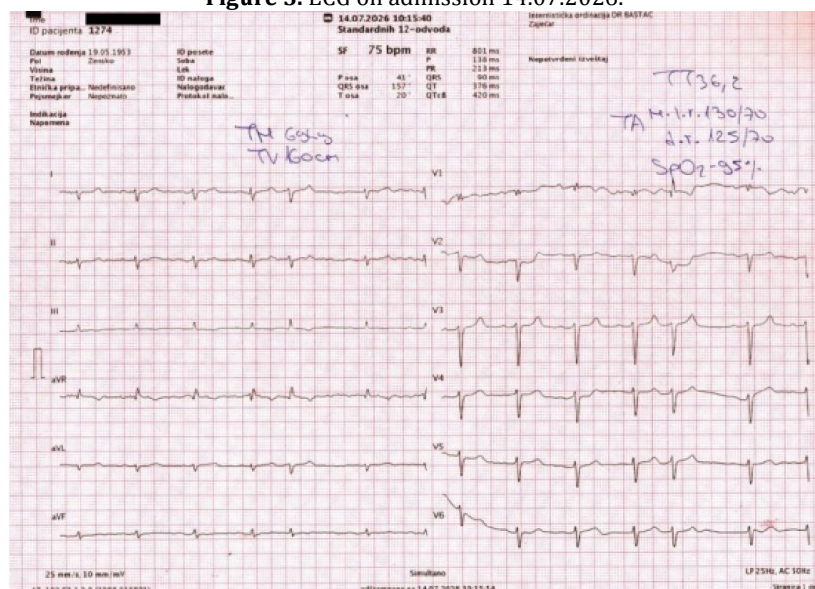
inspiratory crackles above the dullness, signs of large bilateral pleural effusions (hydrothorax). **ABDOMEN:** Soft and non-tender on palpation. The liver is palpable 4 cm below the RCM, the spleen is palpable up to 4 cm below the LCM. **EXTREMITIES:** large cold doughy edema of the lower legs 3+, circumference measurement: left leg 50/39/27cm, right leg 47/36/27cm, peripheral arterial pulses are symmetrically palpable.

LABORATORY ANALYSES ON ADMISSION 14.07.2026.

Urgent "point of care" laboratory analyses performed at the "Dr Bastać" Internal Medicine Practice **dominated by:** very high N-terminal pro-B-type natriuretic peptide (NT-proBNP 1175 pg/mL), signs of renal dysfunction with creatinine 122 µmol/L and GFR 37 mL/min/1,73 m², as well as hyponatremia of 130 mmol/L. hyperuricemia: 774 µmol/L, albumin normal 37 g/L, leukocytes 55x10⁹/cm³, neutrophilia 84%.

ECG ON ADMISSION: sinus rhythm with frequent supraventricular extrasystoles SVES, HR 75/min, low voltage of R waves, no R progression to v6 with deep S, extreme right axis with incomplete right bundle branch block, QRS duration 90ms and QTc interval 420ms normal, overall depolarization vector right-sided, rS in D1-2, aVL. rsr in V1, no R progression to V6, deep S in V2-V6 and no ST changes.

Figure 3. ECG on admission 14.07.2026.



Ultrasonography of the pleura and lungs and echocardiography on admission (technically difficult due to orthopnea)

left - pleural effusion thickness approx. 9,7cm x 12,4cm x 7,6cm, right - effusion approx. 5,3cm x 9,1cm x 4,4cm

Minimal ascites on the right between the liver and kidney 11 mm -12 mm, in the pouch of Douglas 9 mm (Figures 4 and 5).

Echocardiographic examination revealed a dilated left atrium, moderate mitral regurgitation (MR), MR vena contracta 4mm, with normal left ventricular dimensions. The interventricular septum showed paradoxical movements - septal bounce shift, and preserved

left ventricular systolic function was recorded, (Teicholtz EF=76%, and EF Biplane Simpson rule 65%, Figure 4). Diastolic dysfunction - impaired relaxation and compliance - was also measured ($E/e' = 21,8$, $E/A = 2,0$ and $DTE = 113ms$) (Figure 5). The right ventricle was mildly dilated, with **TAPSE reduced to 12 mm** and significant tricuspid regurgitation TR 3+ and signs of moderate pulmonary hypertension: elevated right ventricular systolic pressure RVSP=52 mmHg, **The pericardial layers were separated and moved in parallel, with pericardial thickening: behind the posterior wall of the left ventricle 7-8 mm-/** (Figures 6 and 7) / [12,2,13].

Figure 4. Collapsed lung parenchyma in the effusion 14.07.2026.

Figure 5. Large "dense" pleural effusion 14.07.2026.

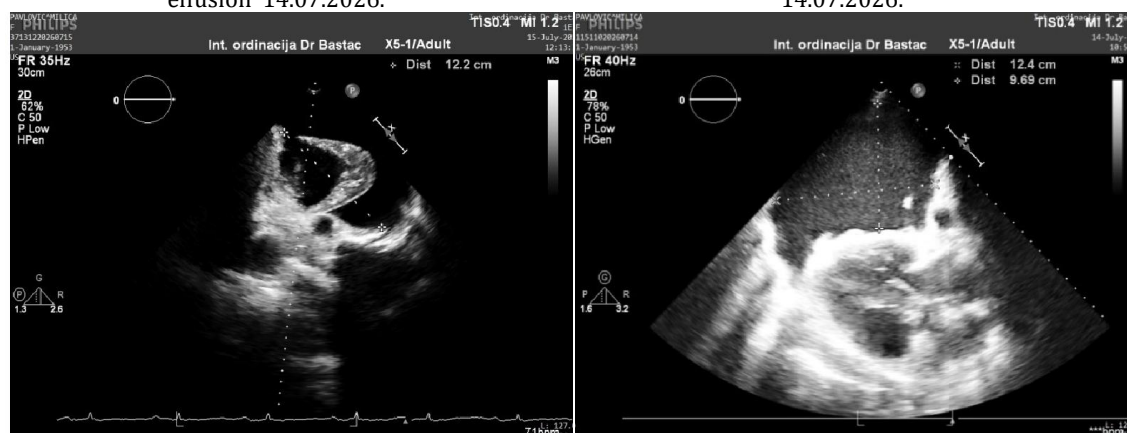


Figure 6. Paradoxical septal movements
14.07.2026.

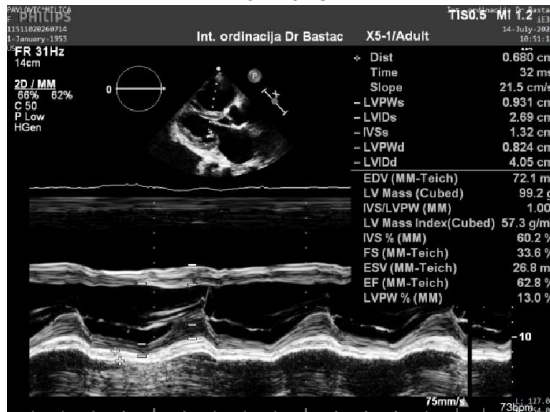
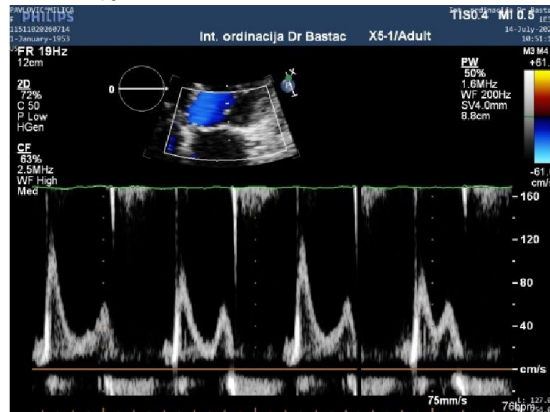


Figure 7. Increased respiratory variation of mitral flow >30% 14.07.2026.



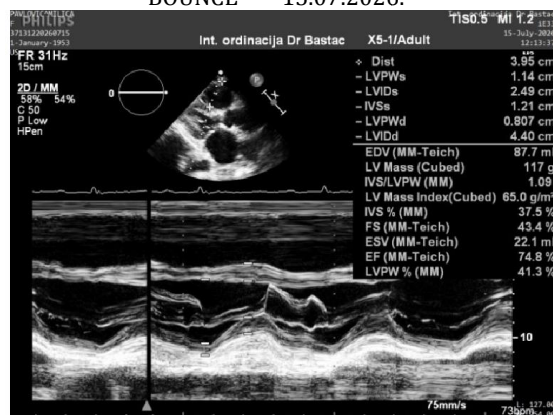
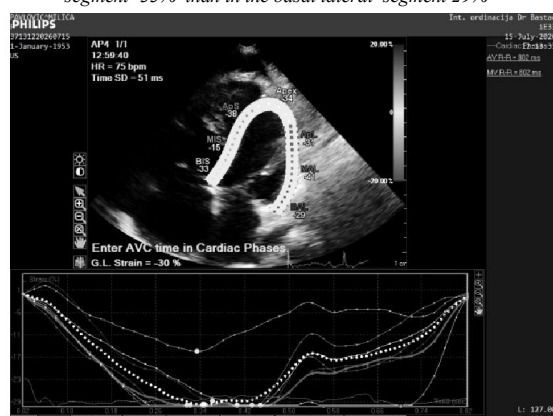
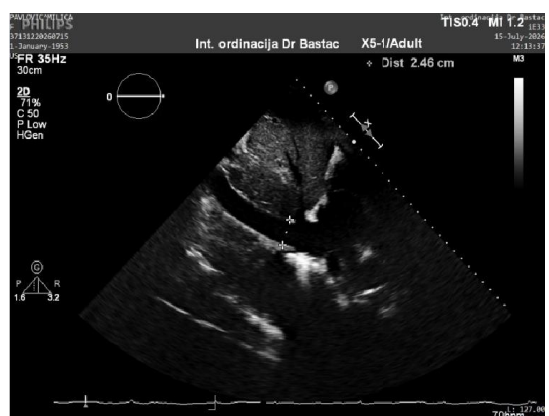
The next day, 15.07.2026, the patient was still orthopneic, 3 kg lighter and with anasarca.

At that time the echocardiographic examination was supplemented (Table 1). Echocardiography revealed preserved left ventricular systolic function, EF 60 to 70%, paradoxical movements of the interventricular septum, (Figures 6 and 8) and pericardial thickening of 6–9 mm, parallel movement of the pericardial layers, right ventricular dilatation and dysfunction, (Figure 9) significant tricuspid regurgitation and

pulmonary hypertension with an increase in RVSP to 76 mmHg. The finding was interpreted as a syndrome of global decompensated heart failure with preserved left ventricular ejection fraction (HFpEF) with predominant right ventricular failure, secondary pulmonary hypertension and signs of constrictive pericardial pathophysiology - strain reversus (Figure 8) and respiratory variation of Doppler flow greater than 25% (Figures 7 and 9). Constrictive pericarditis was suspected [1,13,14].

Table 1. supplemented echocardiographic examination tISSUE DOPPLER AND STRAIN

	1	2	REF VAL 1	REF VAL 2
Septal e' (mitral annulus velocity Tissue dop PW) / S' systolic velocity [cm/s]	4,6/26	7,6	≥ 8	> 6
Lateral e' (mitral annulus velocity Tissue dop PW) / S' systolic velocity [cm/s]	6,5/16,7	8	≥ 10	> 6
E/e' average (normal ≤8)	21,3		borderline 9 - 13	elevated ≥14
Tricuspid annulus S' / Tricuspid annulus E' [cm/s]	3,8	5,8	9,5 - 18	> 10
4C longitudinal strain is greater in the basal septal segment -33% than in the basal lateral segment 29% STRAIN REVERSUS SIGN				

Figure 8. Paradoxical septal movements SEPTAL BOUNCE 15.07.2026.**Figure 9.** Right ventricular dilatation, larger than the left ventricle 15.07.2026.**Figure 10.** sign strain reversus for constrictive pericarditis 4C longitudinal strain is greater in the basal septal segment -33% than in the basal lateral segment 29%**Figure 11.** Dilatation of the inferior vena cava 25 mm without 50% inspiratory collapse . 15.07.2026.

After both evacuating pleural punctures, a biochemical analysis of the pleural fluid was performed 15.07.2026. clear transudate,

and at the same time abdominal ultrasound revealed splenomegaly, with a spleen diameter of about 17–18 cm [4,17,18].

Table. 2. biochemical analysis of the pleural fluid

Total protein IN FLUID	18	g/L	60 - 85
Albumin IN FLUID	13	g/l	33-55
Globulins	5	g/l	12-40

COURSE AND THERAPY

Initial urgent parenteral therapy in the form of a day hospital at the Int. practice of Dr Bastac

Due to the clinical picture of anasarca, ascites and bilateral hydrothorax, intensive decongestive therapy was introduced, including intravenous furosemide, spironolactone and an SGLT2 inhibitor, with further adjustment of

therapy according to the clinical condition [1,16].

Therapeutic course: Intensive decongestive therapy, supported by bilateral therapeutic evacuating pleural punctures (500 ml and 350 ml), led to a turnaround in treatment and complete loss of dyspnea on day 4 of treatment, with good regression of edema with high doses of furosemide, spironolactone and

empagliflozin, (with antihypertensives paused during treatment within the day hospital due to more severe episodes of hypotension), and was accompanied by significant clinical improvement.

Key dynamics of therapy and of the therapeutic response to intensive intravenous therapy (IV th) within the day hospital of the "DR BASTAĆ" Internal Medicine Practice (Table 3).

Table 3. Overview of the clinical course and the main intensive IV th within the day hospital of the "DR BASTAĆ" Practice

	13 and 14.07..	15 and 16.07.	17.07.	FURTHER ON
	Dose 4 amp (80 mg) IV Furosemide /100 ml 0,9%NaCl, II dose -6 amp (120 mg) Furosemide Methylprednisolone 40 mg + 40 mg dose 8amp (160mg) Furosemide +potassium +Mg	50 mg Dobutamine IN 200 ml 0,9% NaCl OVER 4 HOURS, Amp furosemide 3 x 80mg METHYLPREDNISOLONE 40mg + K+Mg PLEURAL PUNCTURE RIGHT 500 ML PUNCTURE LEFT 350 ML 500 ML	50 mg Dobutamine IN 200 ml Na Cl OVER 4 HOURS, Amp furosemide 3 x 80mg METHYLPREDNISOLONE 40 mg + K+ Mg THEN THE CONDITION IMPROVES and intensive diuresis is established	Switch to Per os th: Bisoprolol, Amiodarone, Dilacor, Forxiga, Entresto, Spironolactone, Furosemide forte 500 mg Euthyrox, Pronison, Allopurinol, Colchicine, Plavix, Nolpaza, K, Mg, ,
DIURESIS according to body weight reduction	1 kg less	3 kg less	total 6 kg lower body weight	25 kg in 28 days
BP	130/70	100/65	100/65	105/60
PULSE	87/min	92/min	79/min	92/min
BREATHING	ORTHOPNEA	ORTHOPNEA	dyspnea	No dyspnea
EDEMA , LIVER, ASCITES , PULMO	Lower leg edema ++, ascites present, bilateral pleural effusion	Lower leg edema +, bilateral pleural effusion	Lower leg edema +, no ascites, bilateral pleural effusion	No edema, no pleural effusion, no ascites

Over the following days, clinical improvement was recorded with intensive diuresis and significant regression of symptoms (Table 3).

Table 4. 17.07.2026. Tissue Doppler and right ventricular function - Weakly expressed but still present sign - ANNULUS REVERSUS.

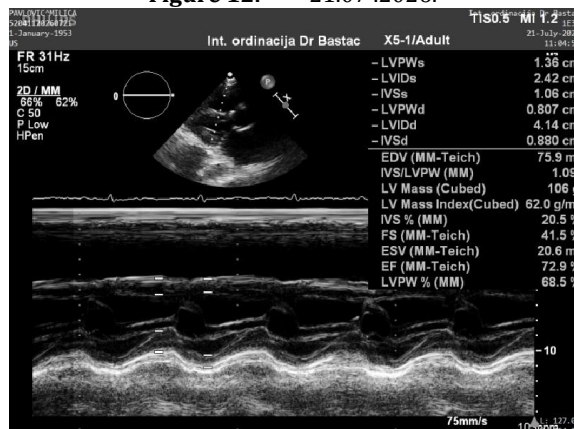
Septal e' (mitral annulus velocity Tissue dop PW) / S'systolic velocity [cm/s]	5,7		≥ 8
Lateral e' (mitral annulus velocity Tissue dop PW)/ S'systolic velocity [cm/s]	4,5		≥ 10
TAPSE	15	>17mm	
Right atrial (RA) area [cm ²]	25	<18	

FOLLOW-UP
21.07.2026.

Echocardiography still showed preserved left ventricular systolic function, EF 73% by Teicholz and approximately 60% by Simpson, with impaired relaxation and reduced compliance. The right ventricle was LESS dilated,

EXAMINATION

RVSP was 76 mmHg, with TR 3+, while the pericardium remained thickened, with a thickness of up to 9 mm. Diastolic dysfunction persists: E/e' was 21,8. On 21.07.2026, body weight was 68 kg. The patient reports less fatigue and reduced leg edema [1,13].

Figure 12. 21.07.2026.

At the examination on 21.07.2026 (Figure 12), preserved left ventricular systolic function was again described, with a finding interpreted as constrictive pericarditis, with marked tricuspid regurgitation, pulmonary hypertension and right ventricular failure.

The combination of clinical systemic congestion, pericardial thickening and paradoxical septal motion justifies the suspicion of constrictive physiology, but the morphological change of the pericardium alone is not sufficient for a definitive diagnosis [1,2,13].

Table 5. Serial echocardiographic follow-up (14.07–11.08.2026.)

Parameter	14.07.	17.07.	21.07.	25.07	11.08.
LV EDD (mm)	40 b mode	49	41	41/4c40	44
LV ESD (mm)	27	23	24	22	29
EF (%)	69	76	73	78	63
LV mass (g)	99	118	106	90	140
LVMI (g/m ²)	57	67	62	54	92
E wave (m/s)	1,1	1,2	0,75	1,14	0,80
E/A ratio	1,3	2,0	1,4	1,8	1,7
e' medial septal			3,0	8,7	
e' lateral					
E/e'	21,3	21,8	21,8	21,9	15,0
GLS 4c	-30			-21	
TAPSE (mm)	-	12	9		16
RV basal diameter (mm)	39	45	46	45	45
RA area (cm ²)	-	25	24		21
TR Vmax (m/s)	3,8	2,8	3,7	4,0	3,3
TR Gmax (mmHg)	57	32	56	64	44
RVSP/SPDK (mmHg)	77	52	76	74	44
IVC exp./insp. (mm)	-	26/16	23/17	20/10	17/7
Liver CC (cm)	17,8	15	17	17	16
Mitral regurgitation	2+ mild	2+ mild	2+ mild	2+mild	2-3+ moderate
Tricuspid regurgitation	3+ moderate -	3+ moderate	3-4+	3+	at least moderate
Ascites	+	minimal	none	None	None

Chest CT scan finding (Dr Stanislav Tadić): hydrothoraces, pulmonary congestion, no pulmonary infiltrates and marked hepatomegaly and, splenomegaly, small ascites [1,13].

Serial echocardiographic evaluation initially showed an increase in pulmonary hypertension with improvement of left ventricular function and decongestion on

21.07.2026 (RVSP 76 mmHg, TAPSE 9 mm, TR Gmax 56 mmHg), and with excellent clinical improvement (right atrial dilatation 25 mm and 44 ventricles, significant reduction of hepatomegaly and of signs of systemic venous congestion..

BLOOD LABORATORY ANALYSES

Findings brought from 13.07.2026. - Marked leukocytosis was recorded. The leukocyte count

was $55,0 \times 10^9/L$, with 84% granulocytes, while recorded, with 75,2% granulocytes.
on 21.07.2026. $58,8 \times 10^9/L$ leukocytes were

Table 6. Dynamics of laboratory parameters (13–21.07.2026.)

Parameter	13.07.2026	14.07.2026	21.07.2026
Erythrocytes ($\times 10^{12}/L$)	-	5,0	5,4
Hemoglobin (g/L)	143	152	159
Leukocytes ($\times 10^9/L$)	55	Error	58,8
Neutrophils / Granulocytes (%)	84	error	75,2
Lymphocytes (%)	10	error	16,4
Platelets ($\times 10^9/L$)	293	163	166
CRP (mg/L)	-	17	41,9
Glucose (mmol/L)	5,1	4,76	11,4
Urea (mmol/L)	8,1	14,3	10,8
Creatinine ($\mu\text{mol}/L$)	97	122	69
GFR ($\text{mL}/\text{min}/1,73 \text{ m}^2$)	48	37	72,3
Uric acid ($\mu\text{mol}/L$)	-	774	536
AST (U/L)	36	31	30
Albumin (g/L)	41	37	40
Total protein (g/L)	-	59	66
LDH (U/L)	962	-	-
TSH (mIU/L)	36,84	-	-
FT4 (pmol/L)	10,77	-	-
FT3 (pmol/L)	3,39	-	-
NT-proBNP (pg/mL)	-	1175	-

The immunological work-up performed on 23.07.2026 did not show laboratory indicators of a systemic autoimmune disease:

ANA 0,8 COI, anti-CCP <3,5 U/mL and dsDNA 12,1 U/mL.

Table 7. Immunological work-up.

	<i>obtained val.</i>	<i>units</i>	<i>reference values</i>
s-Antibodies to cyclic citrullinated peptides (anti-CCP)	<3,5	U/ml	<5,0
ANA antinuclear ab	0,8	COI	Negative : <1,0 Borderline positive : 1,0-1,2 Positive : >1,2
Ds DNA ab	12,1	U/ml	<20,0

Figure 13. Major reduction of the pleural effusion after puncture 25.07.2026.



Figure 14. Major reduction of the pleural effusion after puncture 25.07.2026.



During follow-up until 11.08.2026, a significant reduction in right ventricular systolic pressure (RVSP or SPDK 44 mmHg) and an improvement in right ventricular function (TAPSE 16 mm) were recorded, with a reduction in the dimensions of the liver and the inferior vena cava, i.e. excellent regression of congestion. Left ventricular diastolic function is improving, E/e' (from 21 to 15), and there is a mild ANNULUS REVERSUS SIGN, moderate mitral regurgitation (2-3+) and residual pulmonary hypertension, indicating persistent diastolic dysfunction and chronic right heart overload [1,13].

At the follow-up on 11.08.2026, the clinical condition was significantly better, with almost complete resolution of peripheral edema and absence of bilateral pleural effusion on echocardiographic examination. At the same time, an improvement in right ventricular function parameters and a reduction in the estimated right ventricular pressure from 76 to 44 mmHg were recorded.

According to documented measurements, body weight decreased from 77 kg to 52 kg. This weight loss should be interpreted primarily in the context of marked

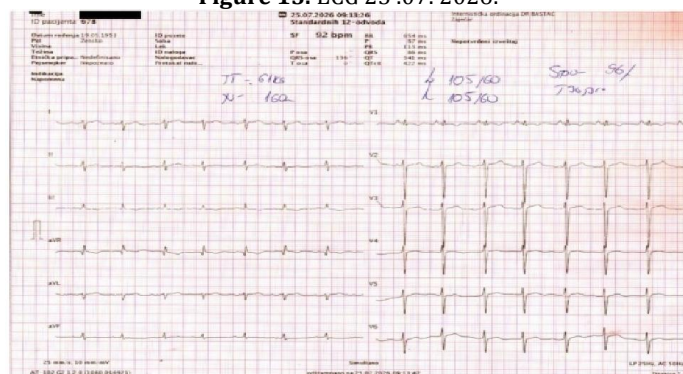
previous fluid retention and intensive decongestive therapy. Pleural effusions were no longer recorded [1,13].

HEMATOLOGIST - However, the hematological problem persisted. On 13.08.2026, a peripheral blood smear showed the presence of all elements of the granulocytic lineage, with a predominance of myelocytes and metamyelocytes and blasts up to 2%. Erythrocytes and platelets were morphologically described as normal, while all elements of the granulocytic lineage were represented, with a predominance of myelocytes and metamyelocytes. Blasts accounted for up to 2%. The finding was assessed as compatible with a myeloproliferative process, with a recommendation for referral to the Clinic of Hematology for further diagnostics.

Considering current classifications of myeloid neoplasms, this finding does not represent a definitive hematological diagnosis, but rather a basis for further morphological, molecular and clinical evaluation [17,18].

The finding was assessed as compatible with a myeloproliferative process, with a recommendation for further diagnostics.

Figure 15. ECG 25.07.2026.



Overview of the oral home therapy given at discharge from the day hospital of the Dr Bastać Practice (Table 8)

Table 8. oral home therapy .11.08.2026.

drug	morning	noon	evening	comment
Bisoprolol tab 2,5 mg	1+1/2			after meals
Amiodarone tab	0		0	
Digoxin tab	1/2			
Dapagliflozin 10 MG	1			after meals
spironolactone 100mg ,	1/2			after meals
furosemide forte 500 mg	1			
Euthrox 25mcg ,	1		1	before meals
Clopidogrel 75 MG	1			after meals
Allopurinol 100 mg	2		2	

Colchicine 0,5 mg	1		1	
Pronizon 20 mg	1			
Pantoprazole 40 mg	1		1	after meals
potassium powder 1 g		1		
Insulin 12 U				in the evening
magnesium 400 mg	1			

Follow-up 03.10.2026. - 80 days after the onset of the disease

At our invitation, the patient came in, stating that she feels very well, and denies complaints of significance for the cardiovascular system. In the period between the last two follow-ups, she was hospitalized for 2 weeks at the Zaječar General Hospital due to progression of leukocytosis (CBC during hospitalization Leu 147×10^9), but without a final diagnosis and with an indication for further evaluation by a hematologist, which the patient again refuses.

Clinical examination - slight deterioration compared to 11 August, when she was fully cardiac compensated.

Cor: HR 75/min, heart sounds clear, rhythm irregular, frequent SVES, systolic regurgitant murmur 3/6, p.max over Erb's point. Pulmo: breath sounds normal, diminished at the right base, early and late inspiratory crackles, basal crepitations, Expiration not prolonged. Abdomen: soft and non-tender on palpation. Liver of soft consistency, mobile with respiration, palpable 10 cm below the RCM, spleen of firm consistency, palpable 19 cm below the LCM. Extremities: doughy edema of the lower legs ++, peripheral arterial pulses are symmetrically palpable.

CRP 6.4, (normal up to 5 mg/l), mildly elevated

CBC: Hgb106, Er 3.57, Le 65.0, Creatinine 170, GFR 25.6, Uric acid 508, K ion 5.9, HbA1c 5.6, BNP 395.

Conclusion: Significant improvement is maintained,

reduced pulmonary hypertension, improved diastolic function, IAS bulging toward the left atrium. TR 3+ is recorded, the septum makes paradoxical movements. The pericardium is now of reduced thickness on three-dimensional echocardiography 3D/4D, 3,6 to 5,8 mm, unevenly thickened (also compared to 8 to 9 mm at the onset of the disease) and separated, without pericardial effusion.

Mild to moderate mitral regurgitation MR 2+ is recorded. Diastolic function parameters: impaired relaxation and reduced compliance. Left ventricle of normal endocavitary dimensions WITHOUT myocardial hypertrophy and with preserved global systolic function. EF=78%.

Pleural ultrasonography: minimal bilateral pleural effusions. On the left, pleural effusion in the mid-scapular line basally above the liver 2cm, in the mid-axillary 5mm, in the posterior axillary 11mm, in the anterior axillary line 4mm. On the right, effusion in the mid-scapular line 2,4 cm, posterior axillary line 14 mm, mid-axillary 15 mm

Lung ultrasonography: Basally about 8 B-lines. right and left, B-lines 7, from the scapular angle A-lines - no congestion.

Since the patient discontinued NSAIDs, corticotherapy and colchicine on her own initiative, a slight improvement occurred, so it was explained to the patient that it is very important to take this therapy for up to 6 months.

Figure 16. Minimal pleural effusion 03.10.2026.

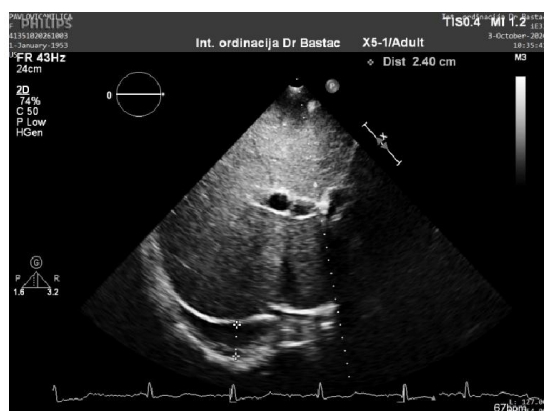


Figure 17. No respiratory variations over the mitral valve 03.10.2026

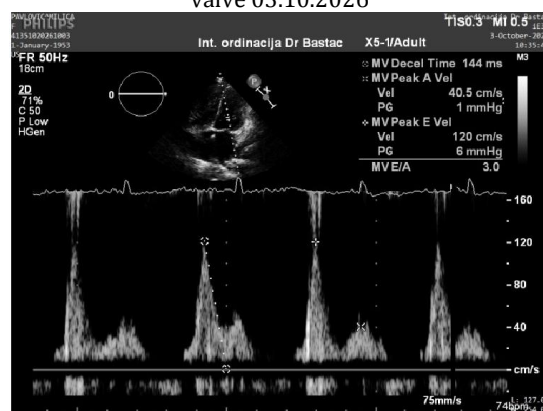


Figure 18. 03.10.2026
TD of the lateral annulus

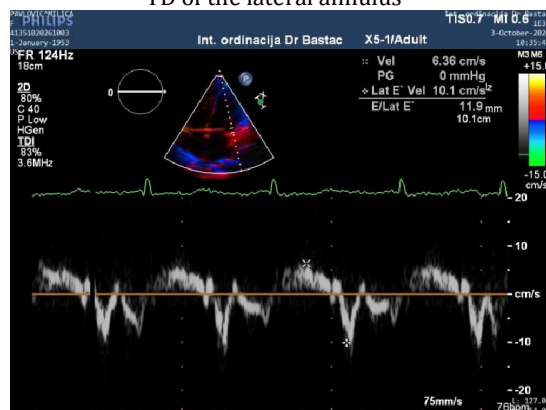


Figure 19. 03.10.2026
TD of the medial annulus Loss of annulus reversus

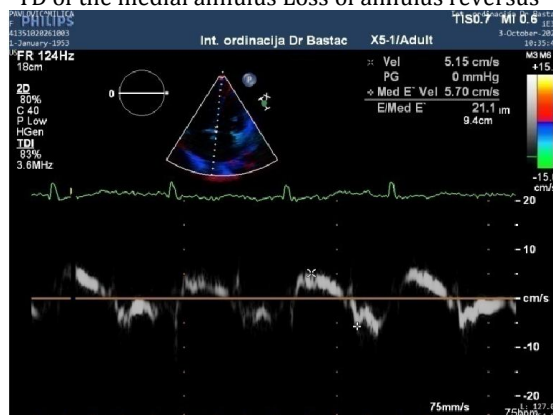
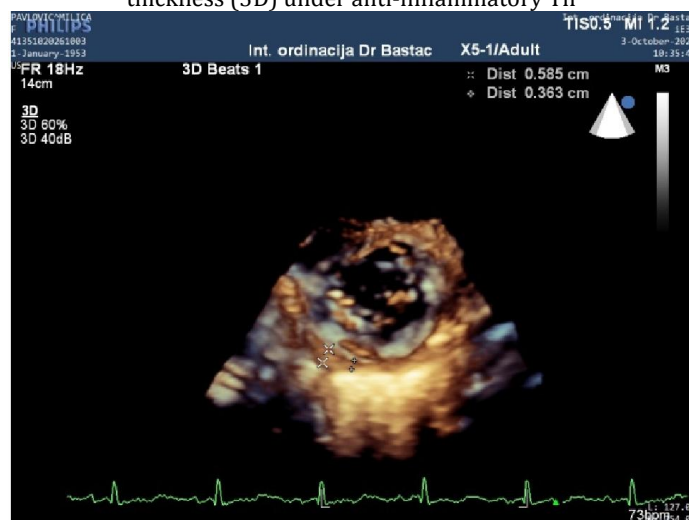


Figure 20. 03.10.2026. Reduction of pericardial thickness (3D) under anti-inflammatory Th



DISCUSSION

The presented case is characterized by a marked discrepancy between the preserved left ventricular systolic function and the severity of the clinical congestion syndrome. During the most severe phase of the disease, LVEF was preserved, while at the same time there were left ventricular diastolic dysfunction, significant tricuspid regurgitation, pulmonary hypertension, right ventricular dysfunction, right atrial dilatation and signs of elevated filling pressures.

The key diagnostic problem is distinguishing constrictive pericarditis from other conditions that can produce a similar hemodynamic phenotype, primarily HFpEF and

restrictive cardiomyopathy. Constrictive pericarditis can lead to predominant systemic venous congestion with relatively preserved left ventricular systolic function, which is why the clinical picture may be very similar to other forms of right-sided heart failure [1,14].

In this patient, several echocardiographic findings supported the possibility of constrictive pathophysiology. Particularly notable were paradoxical movements of the interventricular septum (septal shift and bounce), pericardial thickening, diastolic filling abnormalities, dilatation of the right heart chambers and significant tricuspid regurgitation. At the same time, left ventricular systolic function remained preserved, with EF

values of approximately 60–76% and normal global longitudinal strain [1,2,13].

The Mayo Clinic echocardiographic criteria include a combination of respiration-related septal shift, medial e' and changes in hepatic venous flow. Combining several criteria increases the specificity for constrictive physiology. [13]

In the presented case, however, it was not possible to carry out a complete hemodynamic protocol for definitive confirmation of constriction. The patient declined further hospitalization, and invasive pressure assessment was not performed [1,15]. Therefore, it is more appropriate to designate this finding as **echocardiographically suspected constrictive pericardial pathophysiology physiology**, rather than as definitively confirmed constrictive pericarditis [1,13].

An important element of the case is the marked leukocytosis. The leukocyte count was $55,0 \times 10^9/L$ as early as 13.07.2026, and $58,8 \times 10^9/L$ on 21.07.2026, with marked granulocytosis. In addition, splenomegaly was present. A later peripheral blood examination showed the presence of all elements of the granulocytic lineage, with a predominance of myelocytes and metamyelocytes and blasts up to 2%, and the finding was designated as compatible with a myeloproliferative process [17-21].

This finding is significant because it shows that the leukocytosis was not merely a transient laboratory change during the acute worsening of heart failure. However, based on the submitted documentation, it is not possible to definitively determine the type of hematological disease. Current classifications of myeloid neoplasms require the integration of clinical, morphological and molecular data [17,18].

It is precisely in this context that the question arises of a possible association of the hematological process with the changes in the pericardium and pleura. In the differential diagnosis, infiltrative processes, extramedullary hematopoiesis and other inflammatory or serositis mechanisms may be considered [22-24].

Extramedullary hematopoiesis in the pericardium is a very rare phenomenon, but it has been described in patients with myeloproliferative neoplasms. Haroun et al.

described extramedullary hematopoiesis involving the pericardium in a patient with polycythemia vera, with the development of cardiac tamponade [22]. Mahadevan et al. presented a case of pericardial extramedullary hematopoiesis with cardiac tamponade and reviewed previously published cases [23]. In 2025, Hayar et al. described a rare case of extramedullary hematopoiesis with pericardial involvement in a patient with a myeloproliferative disease [24].

These data provide a possible pathophysiological framework for considering a hematological-pericardial association in our case, but **they do not constitute evidence that the pericardial thickening in the presented patient is a consequence of extramedullary hematopoiesis**. Such a conclusion would require additional radiological, morphological and/or histological evidence [22-24].

Particularly significant is the therapeutic response to decongestive therapy, heart failure therapy and anti-inflammatory therapy. Intensive diuresis and evacuation of the pleural effusions led to a marked reduction in body weight and resolution of peripheral edema and pleural effusions. At the same time, a reduction in RVSP from 76 to 44 mmHg and an improvement in TAPSE from 9 to 16 mm were recorded [1,16]. Such a response confirms the importance of volume overload in the clinical picture, but by itself neither confirms nor excludes constrictive pericarditis [1,13]. Also, according to the recommendations for probable constrictive pericarditis from the European guideline for myopericardial diseases and the algorithm, triple anti-inflammatory therapy should be introduced: a corticosteroid, a nonsteroidal anti-inflammatory drug and colchicine for up to 6 months. If transient constrictive pericarditis is established, with clear clinical and imaging improvement and disappearance of the constrictive pathophysiology, then pericardiectomy is not required as a definitive treatment measure. Transient constriction is a form of constrictive pericarditis (CP) with active inflammation present, which may resolve after anti-inflammatory therapy or even regress spontaneously. It develops during pericarditis with or without pericardial effusion (effusive-constrictive pericarditis). In more than 50% of cases, constriction resolves after anti-inflammatory therapy [6,7,8]. In patients with

newly diagnosed constrictive pericarditis, a trial of anti-inflammatory therapy lasting 3 to 6 months is recommended before referral for pericardiectomy [9,10]. The presence of active pericardial inflammation was confirmed by inflammatory biomarkers (C-reactive protein, which was initially 42 mg/L and then fell to 7 mg/L), as well as by cardiovascular magnetic resonance (CMR), which showed pericardial edema and late gadolinium enhancement (LGE) [10,11]. In HFpEF with marked congestion and preserved ejection fraction, the assessment of filling pressures, right ventricular function and the pulmonary circulation is an important part of the diagnostic process [16].

For definitive confirmation of constrictive pericarditis in such a complex presentation, additional modalities would be of importance, including an ultrafast MDCT scanner or a photon-counting scanner and cardiovascular magnetic resonance, and, if necessary, right heart catheterization for direct hemodynamic assessment [1,2,15].

Precisely such further work-up was recommended to the patient, but it had not been carried out by the last follow-up, because she feels well and refuses hospitalization at a higher-level institution in cardiology or hematology.

CONCLUSION and EPILOGUE OF THE CASE:

In patients with marked systemic venous congestion, hepatosplenomegaly, ascites and anasarca and preserved left ventricular systolic function, but with signs of severe HFpEF with reduced left ventricular stroke volume and pulmonary congestion with pleural effusions, constrictive pericarditis should be considered in the differential diagnosis [1,13]. Constrictive

pericarditis was suggested by echocardiography: pericardial thickening, parallel movement of the pericardial layers and paradoxical septal movements and other Doppler signs of CP [1,2,13]. However, echocardiographic findings alone are not sufficient for definitive confirmation of the diagnosis without hemodynamic confirmation. The etiological diagnosis could be related to the existing chronic myeloproliferative process [17,18,22-24].

Despite the initial therapeutic failure in this patient with decompensated heart failure, with huge doses of diuretics, inotropic support, dobutamine AND corticosteroids, after bilateral pleural punctures, after 4 days of treatment a gradual recovery occurs. The peripheral edema and both pleural effusions disappear, as detected by lung ultrasound. She is later switched to per os th, and there is a reduction in body weight from 77 kg to 52 kg - a total of 25 kg over a period of 28 days. A reduction of RVSP to 44 mmHg also occurs. and an improvement in other echocardiographic dimensions and parameters [1,16]. At the same time, progressive leukocytosis is recorded, up to values above $90 \times 10^9/L$, while the examination of the peripheral blood smear by a hematologist showed a predominance of myelocytes and metamyelocytes with less than 2% blasts, which was compatible with a CHRONIC myeloproliferative process. The patient refuses further treatment at the hematology department of a higher-level institution and follow-up visits, and in a telephone conversation claims that she feels well. **After almost 2 months, she comes with moderate deterioration because she discontinued the anti-inflammatory therapy of her own accord.**

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From Koch to mRNA vaccines — Nobel Prizes and the development of medicine with a comparative analysis of the achievements of the 20th and 21st centuries (1901–2025)

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Summary: The Nobel Prize in Physiology or Medicine is one of the most important international recognitions for scientific achievements that have shaped the development of modern medicine. Since it was first awarded in 1901, the prize has recognized scientific discoveries that have fundamentally changed the understanding of the human organism, the origin of diseases and the possibilities for their treatment. **The aim** of this paper on the history of medicine is to present the development of medical science through an analysis of the Nobel Prizes in Physiology or Medicine during the 20th and 21st centuries, with special reference to the most important discoveries and their impact on everyday clinical practice. The key achievements of the 20th century that laid the foundations of modern medicine — the discovery of insulin, penicillin and the structure of DNA — are analyzed, as well as their contribution to the development of endocrinology, infectious diseases, molecular biology and personalized medicine. An overview of the most important Nobel Prizes of the 21st century is also presented, among which research on the cell cycle, apoptosis, RNA interference, stem cells, immunotherapy of malignant diseases, mRNA technology and microRNA stand out. Today, checkpoint inhibitors (PD-1, PD-L1, CTLA-4) enable long-term survival in many patients with melanoma, lung cancer, kidney cancer and other tumors. The comparative analysis shows that in the 20th century Nobel Prizes were mainly directed toward discovering the causes of diseases and developing antibiotics, hormones and diagnostic methods, while in the 21st century research on molecular and cellular mechanisms, gene regulation, immunology and precision medicine dominates. From the discovery of insulin and penicillin to mRNA vaccines and tumor immunotherapy, Nobel laureates have contributed significantly to extending life expectancy and improving the quality of life of millions of people. There are several oversights by the Nobel Committee with regard to ultrasound diagnostics, innovative surgical techniques and new inventive drugs and therapies. Although these methods have saved or improved the quality of life of millions of patients, the Nobel Committee has traditionally rewarded fundamental biological discoveries much more often than the development of diagnostics, pharmacological therapy and surgical techniques. There is a significant difference between a scientific discovery and its clinical translation into everyday medical practice. That is why many scientific achievements of enormous public health importance remain outside its scope. The history of medicine cannot be viewed exclusively through the Nobel Prizes, but also through an assessment of the real impact of individual diagnostic and therapeutic methods on survival, quality of life and the reduction of the burden of disease in the general population. **CONCLUSION:** If the 20th century was the century of the scientific discovery of organs, microbes, hormones and antibiotics, then the 21st century is the century of molecular medicine, genomics and personalized treatment. In the 20th century, medicine answered the question "What causes disease?", and in the 21st century it is trying to answer the question "Why does the disease develop in this particular patient and how can it be treated in a targeted way?".

Keywords: Nobel Prize; history of medicine; insulin; penicillin; DNA; immunotherapy; mRNA vaccines; personalized medicine; molecular biology.

INTRODUCTION

The Nobel Prize is one of the most prestigious international recognitions for scientific, literary and peace achievements. Its history begins with the will of Alfred Nobel, a Swedish inventor and industrialist, who bequeathed his fortune to establish a fund that would reward "those who, during the preceding year, have conferred the greatest benefit to humankind" [1].

Alfred Nobel was born in 1833 in Stockholm. He spent most of his life as a chemist

and inventor. He patented a total of 355 inventions [2]. His best-known invention, dynamite, patented in 1867, brought him enormous wealth, but also his concern about the destructive use of explosives [2,3]. It is believed that precisely these reasons, as well as the influence of Bertha von Suttner, a prominent peace activist, prompted Alfred Nobel to dedicate most of his fortune to prizes that would serve the progress of humankind [4].

In his will, signed in 1895, Nobel specified that the income from his fortune should be divided into five equal parts and

awarded for outstanding achievements in the fields of physics, chemistry, physiology or medicine, literature and peace [1]. The prize in physiology or medicine was to go to the person who had made the most important discovery in these fields. For a large part of his life and business, Nobel was connected with France. He had a laboratory and an estate near Paris. His last will was signed precisely in Paris on 27 November 1895. Alfred Nobel died on 10 December 1896 in San Remo, and it was precisely this date that was later chosen as the day of the prize award ceremony [5]. With it, he practically dedicated most of his remaining fortune to a fund from whose income prizes would be awarded every year.

After lengthy negotiations (about 5 years), both with the French government and with members of the Nobel family, the first Nobel Prize award ceremony was held on 10 December 1901 [6]. That year, prizes were awarded in all five categories, and the first recipient of the Nobel Prize in Physiology or Medicine was Emil Adolf von Behring, a German physician and bacteriologist, for the discovery of serum therapy against diphtheria [3,7]. This discovery marked a turning point in the development of modern immunization methods and saved countless lives around the world [7].

The Nobel Prize in Physiology or Medicine, awarded since 1901, has become synonymous with the highest achievements in the biomedical sciences. During more than a century of its existence, this prize has recognized discoveries that have fundamentally changed the way we understand the human body, diseases and treatment [7].

The importance of the Nobel Prize in Medicine is reflected in several key aspects. First of all, the prize has recognized discoveries that directly contributed to saving millions of lives — from the discovery of insulin in 1923, through penicillin in 1945, to the development of mRNA vaccines in 2023 [7]. **Second, the Nobel Prize has served as a kind of map of the development of medical science, reflecting changes in research priorities — from the study of infectious diseases in the early decades, through molecular biology and genetics in the second half of the 20th century, to contemporary research at the subcellular and molecular level [8].**

In addition, the prize has institutionalized and affirmed scientific

excellence, encouraging international cooperation and the exchange of knowledge. An analysis of the laureates shows that most laureates came from the United States of America, Great Britain and Germany, but the discoveries had a global impact on medical practice [9]. Also, the prize has evolved from recognizing individual researchers toward recognizing teamwork — in the period from 1901 to 2019, as many as 71 of the total of 110 prizes in medicine were awarded to two or three scientists jointly [8].

The Nobel Prize in Physiology or Medicine is more than a mere recognition — it is a mirror of the progress of medical science and a witness to humankind's continuous striving for a better understanding of life and health. From the first recognition to Emil von Behring for serum therapy to the latest discoveries in the field of immunology and gene therapy, this prize documents the history of medicine and at the same time illuminates the path for future generations of researchers.

MATERIAL AND METHODS

This paper presents an overview of the development of medicine through an analysis of the Nobel Prizes in Physiology or Medicine, i.e. biomedical scientific achievements, awarded in the period from 1901 to 2025. Data on Nobel Prize laureates, years of award and the explanations of the awarded achievements were collected from the official database of the Nobel Prize Foundation and from the available scientific literature [1,2].

The analysis included discoveries that had a significant impact on the development of the biomedical sciences, diagnostic methods, therapeutic procedures and preventive medicine. Nobel Prize laureates were classified according to the dominant field of research (microbiology, immunology, genetics, molecular biology, pharmacology, neurology, cardiology and other fields), as well as according to their contribution to contemporary clinical practice.

A qualitative comparative analysis of the Nobel Prizes awarded during the 20th and 21st centuries was applied, with the aim of examining changes in the research priorities of medicine. Particular attention was paid to discoveries that led to a significant improvement in the diagnosis, treatment and prevention of diseases, as well as to their impact on life

expectancy and the quality of life of the population.

For the purposes of this paper, Nobel Prizes that led to changes in everyday clinical practice were analyzed in particular, including the discovery of insulin, blood groups, penicillin, electrocardiography, cardiac catheterization, the structure of DNA, computed tomography, magnetic resonance imaging, new surgical techniques and organ transplantation, immunotherapy of malignant diseases and mRNA technology.

NOBEL PRIZES OF THE 20TH CENTURY: Key discoveries that laid the foundations of modern medicine (Table 1)

Modern medicine, as we know it today, is the result of a series of revolutionary discoveries that have fundamentally changed the way we understand the human body, diseases and treatment. Among the most important achievements that shaped medical science in the 20th century, the discoveries of insulin, penicillin and the structure of DNA stand out. For most historians of medicine, the three greatest turning points are:

1. **Insulin (1923)** — saved millions of patients with diabetes.
2. **Penicillin (1945)** — dramatically reduced mortality from infections.
3. **The structure of DNA (1962)** — opened the era of molecular and personalized medicine.

The discovery of insulin (1921–1923)

The discovery of insulin is one of the greatest achievements of 20th-century medical science and the first time that modern medical science succeeded in providing a life-saving therapy for a disease that had previously been universally fatal [10]. Diabetes mellitus, a condition described as early as 1550 BC in the Ebers Papyrus, had been a medical mystery for thousands of years [11].

The research that led to the discovery of insulin was carried out in Toronto in 1921–1922 and was led by Frederick Banting and John Macleod, with the key contribution of Charles Best and James Collip [12]. Their revolutionary work demonstrated that a pancreatic extract could consistently lower blood glucose levels in diabetic dogs [12]. This discovery marked a turning point in the understanding of the

endocrine regulation of nutrient metabolism and the functions of other organs [12].

For this achievement, Banting and Macleod were awarded the Nobel Prize in Physiology or Medicine in 1923, and they shared their prize with Best and Collip [12]. The importance of the discovery of insulin is reflected in the fact that it has saved the lives of millions of people with type 1 diabetes worldwide [12]. This discovery also initiated a whole century of research aimed at the purification, isolation, structural characterization and genetic sequencing of insulin, which has continuously improved therapeutic formulations [10].

The discovery of penicillin (1928–1945)

The discovery of penicillin represents a turning point in the fight against infectious diseases and one of the most important contributions to modern medicine [13]. The history of penicillin comprises three key phases of development: Fleming's discovery, the success of Florey and his colleagues in obtaining penicillin in a relatively pure form and demonstrating its clinical application, and the American success in mass production of the drug [14].

Sir Alexander Fleming discovered penicillin by chance in 1928, but his discovery did not attract significant attention for more than a decade, and the active substance was not isolated [13]. It was only in 1939 that Sir Howard Walter Florey, together with Ernst Boris Chain, led a team of British scientists who successfully produced the drug from the liquid medium in which penicillin grows [13].

During the Second World War, penicillin production took place under extremely difficult conditions. In the Netherlands, scientists of the NG&SF company continued secret research despite the German occupation. Using Fleming's 1929 publication as a basis, they managed to isolate a substance which they code-named "Bacinal" in order to conceal its identity from the German authorities [15]. An interesting detail from this period is that the scientists kept a German guard tipsy during their work by "treating" him to gin, which enabled them to continue production [15].

In 1945, Fleming, Florey and Chain were awarded the Nobel Prize in Physiology or Medicine for the discovery of penicillin and its therapeutic value [16,17]. The development of

penicillin represents a turning point in the fight against infectious diseases and laid the foundations for the antibiotic era [13].

The discovery of the structure of DNA (1953)

The discovery of the molecular structure of deoxyribonucleic acid (DNA) is one of the most important scientific achievements of the 20th century and the foundation of modern molecular biology [18]. This discovery transformed the understanding of cell function and revolutionized fields such as medicine, forensics, bioinformatics and nanotechnology [19].

On 25 April 1953, James Watson and Francis Crick published in the journal *Nature* their revolutionary model of the DNA double helix [19]. In their paper they concluded that “the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material” [19]. This insightful statement marked the beginning of a new era in the understanding of heredity and the transmission of genetic information. The double helix model was the result of a synthesis of numerous studies. Watson and Crick used the data of many researchers, including Oswald Avery, who proved that DNA, and not proteins or

RNA, is the carrier of hereditary information, as well as Erwin Chargaff, who showed that in DNA the amount of adenine corresponds to the amount of thymine, while the amount of guanine corresponds to the amount of cytosine [20]. A key role was also played by Rosalind Franklin, a British biophysicist and crystallographer, whose X-ray images provided key information that Watson and Crick used to build their model [19]. The structure of the double helix is antiparallel and complementary, with the bases located inside the molecule, adenine bonded to thymine and guanine to cytosine by hydrogen bonds, while the phosphates and deoxyribose are on the outside [20]. This structure in itself reveals its function — the way in which genetic information is copied and passed on to offspring [20].

Watson, Crick and Maurice Wilkins, their collaborator from King's College, were awarded the Nobel Prize in Physiology or Medicine in 1962 for this epochal discovery [16,17,19]. Elucidating the structure of DNA enabled the development of molecular biology into its “golden age”, creating structural biology and laying the foundations for the sequencing of the human genome twenty years later [18].

Table 1. The Nobel Prize in Physiology or Medicine (1901–2000)

Year	Laureate(s)	Discovery / contribution
1901	Emil von Behring	Serum therapy against diphtheria
1902	Ronald Ross	Transmission of malaria by mosquitoes
1903	Niels Finsen	Phototherapy (light treatment)
1904	Ivan Pavlov	Physiology of digestion
1905	Robert Koch	Tuberculosis and its causative agent
1906	Camillo Golgi, Santiago Ramón y Cajal	Structure of the nervous system and neurons
1907	Alphonse Laveran	Protozoa as causes of disease
1908	Ilya Mechnikov, Paul Ehrlich	Immunity (cellular and humoral)
1909	Theodor Kocher	Physiology and surgery of the thyroid gland
1910	Albrecht Kossel	Nucleic acids and cell chemistry
1911	Allvar Gullstrand	Optics of the eye
1912	Alexis Carrel	Vascular anastomoses and transplantation
1913	Charles Richet	Anaphylaxis
1914	Robert Bárány	Vestibular apparatus and balance
1915–1918	—	Prize not awarded
1919	Jules Bordet	Immunology and the complement system
1920	August Krogh	Regulation of capillary circulation
1921	—	Prize not awarded
1922	Archibald Hill, Otto Meyerhof	Energy metabolism of muscle
1923	Frederick Banting, John Macleod	Discovery of insulin
1924	Willem Einthoven	Electrocardiography (ECG)
1925	—	Prize not awarded
1926	Johannes Fibiger	Experimental carcinogenesis*
1927	Julius Wagner-Jauregg	Malaria therapy of neurosyphilis
1928	Charles Nicolle	Typhus
1929	Christiaan Eijkman, Frederick Hopkins	Vitamins and deficiency diseases
1930	Karl Landsteiner	ABO blood groups

1931	Otto Warburg	Cellular respiration
1932	Charles Sherrington, Edgar Adrian	Function of neurons
1933	Thomas Hunt Morgan	Chromosomes and heredity
1934	George Whipple, George Minot, William Murphy	Treatment of pernicious anemia
1935	Hans Spemann	Embryology and the organizer of development
1936	Henry Dale, Otto Loewi	Chemical transmission of nerve impulses
1937	Albert Szent-Györgyi	Vitamin C and cellular metabolism
1938	Corneille Heymans	Regulation of respiration
1939	Gerhard Domagk	Sulfonamides (Prontosil)
1940– 1942	—	Prize not awarded
1943	Henrik Dam, Edward Doisy	Vitamin K
1944	Joseph Erlanger, Herbert Gasser	Functions of nerve fibers
1945	Alexander Fleming, Ernst Chain, Howard Florey	Penicillin
1946	Hermann Muller	Mutations induced by X-rays
1947	Carl Cori, Gerty Cori, Bernardo Houssay	Glucose and glycogen metabolism
1948	Paul Müller	DDT as an insecticide
1949	Walter Hess, Egas Moniz	Hypothalamus; psychosurgery
1950	Edward Kendall, Tadeus Reichstein, Philip Hench	Corticosteroids and their application
1951	Max Theiler	Yellow fever and vaccine development
1952	Selman Waksman	Streptomycin
1953	Hans Krebs, Fritz Lipmann	Krebs cycle and coenzyme A
1954	John Enders, Thomas Weller, Frederick Robbins	Cultivation of poliovirus in tissue cultures
1955	Hugo Theorell	Oxidation enzymes
1956	André Cournand, Werner Forssmann, Dickinson Richards	Cardiac catheterization
1957	Daniel Bovet	Antihistamines
1958	George Beadle, Edward Tatum, Joshua Lederberg	Role of genes in biochemical processes
1959	Severo Ochoa, Arthur Kornberg	Biosynthesis of RNA and DNA
1960	Frank Macfarlane Burnet, Peter Medawar	Acquired immunological tolerance
1961	Georg von Békésy	Mechanism of hearing
1962	Francis Crick, James Watson, Maurice Wilkins	Structure of DNA
1963	John Eccles, Alan Hodgkin, Andrew Huxley	Ionic mechanisms of the nerve impulse
1964	Konrad Bloch, Feodor Lynen	Metabolism of cholesterol and fatty acids
1965	François Jacob, André Lwoff, Jacques Monod	Genetic regulation of enzyme synthesis
1966	Peyton Rous, Charles Huggins	Tumor viruses and hormonal treatment of prostate cancer
1967	Ragnar Granit, Haldan Hartline, George Wald	Physiology of vision
1968	Robert Holley, Har Gobind Khorana, Marshall Nirenberg	Deciphering of the genetic code
1969	Max Delbrück, Alfred Hershey, Salvador Luria	Replication and genetics of viruses
1970	Julius Axelrod, Ulf von Euler, Bernard Katz	Neurotransmitters and synaptic transmission
1971	Earl Sutherland	cAMP as a second messenger
1972	Gerald Edelman, Rodney Porter	Structure of antibodies
1973	Karl von Frisch, Konrad Lorenz, Nikolaas Tinbergen	Foundations of ethology
1974	Albert Claude, Christian de Duve, George Palade	Structure and organization of the cell
1975	David Baltimore, Renato Dulbecco, Howard Temin	Interaction of tumor viruses and genetic material
1976	Baruch Blumberg, Daniel Gajdusek	Hepatitis B and new mechanisms of infectious diseases
1977	Roger Guillemin, Andrew Schally, Rosalyn Yalow	Hypothalamic hormones and radioimmunological methods
1978	Werner Arber, Daniel Nathans, Hamilton Smith	Restriction enzymes
1979	Allan Cormack, Godfrey Hounsfield	Computed tomography (CT)
1980	Baruj Benacerraf, Jean Dausset, George Snell	Genetic control of the immune response (MHC/HLA)
1981	Roger Sperry, David Hubel, Torsten Wiesel	Functional organization of the brain
1982	Sune Bergström, Bengt Samuelsson, John Vane	Prostaglandins
1983	Barbara McClintock	Mobile genetic elements
1984	Niels Jerne, Georges Köhler, César Milstein	Monoclonal antibodies
1985	Michael Brown, Joseph Goldstein	Cholesterol metabolism and LDL receptors
1986	Stanley Cohen, Rita Levi-Montalcini	Cell growth factors (NGF, EGF)
1987	Susumu Tonegawa	Genetic mechanisms of antibody diversity
1988	James Black, Gertrude Elion, George Hitchings	Rationally designed drugs
1989	J. Michael Bishop, Harold Varmus	Proto-oncogenes
1990	Joseph Murray, E. Donnall Thomas	Organ and cell transplantation

1991	Erwin Neher, Bert Sakmann	Function of single ion channels
1992	Edmond Fischer, Edwin Krebs	Reversible protein phosphorylation
1993	Richard Roberts, Phillip Sharp	Discovery of split genes (introns)
1994	Alfred Gilman, Martin Rodbell	G proteins and cell signaling
1995	Edward Lewis, Christiane Nüsslein-Volhard, Eric Wieschaus	Genetic control of early embryonic development
1996	Peter Doherty, Rolf Zinkernagel	Specificity of the cell-mediated immune response
1997	Stanley Prusiner	Prions
1998	Robert Furchgott, Louis Ignarro, Ferid Murad	Nitric oxide (NO)
1999	Günter Blobel	Signal sequences for protein transport
2000	Arvid Carlsson, Paul Greengard, Eric Kandel	Signal transduction in the nervous system

The importance of fundamental scientific discoveries for the development of cardiology **The five Nobel Prizes with the greatest impact on cardiology:**

- 1924 — Einthoven (ECG) — the most frequently used diagnostic method in cardiology.
- 1956 — Cardiac catheterization — enabled coronary angiography, PCI and modern invasive cardiology.
- 1964 — Cholesterol metabolism — the basis for the prevention of atherosclerosis.

- 1985 — LDL receptor — the direct scientific foundation of statins, ezetimibe and PCSK9 inhibitors.
- 1998 — Nitric oxide (NO) — changed the understanding of endothelial dysfunction, coronary disease and pulmonary hypertension.

The most important discoveries in the history of medicine in the 20th century (Table 2).

Table 2. The most important discoveries in the history of medicine

Year	Laureate(s)	Discovery	Impact on everyday medical practice
1901	Emil von Behring	Serum therapy	The beginning of modern immunotherapy and vaccinology.
1905	Robert Koch	Tuberculosis	Founded medical microbiology and the etiological diagnosis of infections.
1908	Mechnikov and Ehrlich	Immunity	The basis of modern immunology, vaccines and biological therapy.
1923	Banting and Macleod	Insulin	Turned type 1 diabetes from a fatal into a chronic disease.
1924	Willem Einthoven	Electrocardiogram (ECG)	The foundation of modern cardiological diagnostics.
1930	Karl Landsteiner	ABO blood groups	Enabled safe transfusions and the development of transplantation.
1945	Fleming, Chain and Florey	Penicillin	A revolution in the treatment of bacterial infections.
1952	Selman Waksman	Streptomycin	The first effective drug against tuberculosis
1956	Forssmann, Courmand and Richards	Cardiac catheterization	The basis of invasive cardiology, coronary angiography and hemodynamics
1960	Burnet and Medawar	Immunological tolerance	Enabled the development of transplant medicine.
1962	Watson, Crick and Wilkins	Structure of DNA	The foundation of molecular medicine, genetics and personalized therapy)
1964	Bloch and Lynen	Cholesterol metabolism	Laid the foundations for statins and the prevention of atherosclerosis.
1968	Holley, Khorana and Nirenberg	Genetic code	The basis of genetic engineering and modern biotechnology.
1977	Rosalyn Yalow	Radioimmunoassays (RIA)	The forerunner of modern laboratory diagnostics of hormones and biomarkers.
1979	Cormack and Hounsfield	Computed tomography (CT)	A revolution in radiological diagnostics
1984	Köhler, Milstein and Jerne	Monoclonal antibodies	The foundation of biological therapy in oncology, rheumatology and hematology.
1985	Brown and Goldstein	LDL receptor	Understanding of hyperlipidemia and the development of modern lipidology.
1988	Black, Elion and Hitchings	Rational drug design	Contributed to the development of beta-blockers, anti-ulcer drugs and numerous other drugs.
1990	Murray and Thomas	Organ transplantation	Routine transplantation of the kidney, heart, liver and bone marrow.
1998	Furchgott, Ignarro and Murad	Nitric oxide (NO)	Understanding of endothelial function, hypertension and atherosclerosis, and the development of sildenafil therapy.

**WINNERS OF THE NOBEL PRIZE IN MEDICINE
IN THE 21ST CENTURY**

The twenty-first century has brought accelerated development of the biomedical

sciences, and the Nobel Prize in Physiology or Medicine has become a mirror of that progress (Table 3). From discoveries that shed light on the basic mechanisms of the functioning of cells,

through the understanding of the immune system, to revolutionary therapies that saved millions of lives during the COVID-19 pandemic,

the laureates of the 21st century have continued the tradition of exceptional achievements that have shaped modern medicine.

Table 3. Nobel Prizes in Medicine in the 21st century (2001–2025)

Year	Laureates	Discovery	Clinical significance
2001	Hartwell, Hunt, Nurse	Regulation of the cell cycle	Understanding the origin of malignant diseases
2002	Brenner, Horvitz, Sulston	Programmed cell death (apoptosis)	Oncology, neurodegenerative diseases
2003	Lauterbur, Mansfield	Magnetic resonance imaging (MRI)	A revolution in the diagnosis of the CNS, heart and soft tissues
2004	Axel, Buck	Odorant receptors	Neurobiology and sensory medicine
2005	Marshall, Warren	<i>Helicobacter pylori</i>	Peptic ulcer becomes a curable infectious disease
2006	Fire, Mello	RNA interference	Modern gene therapy
2007	Capecci, Evans, Smithies	Knockout mice	Disease models and drug development
2008	zur Hausen; Barré-Sinoussi; Montagnier	HPV and HIV	Prevention of cervical cancer, AIDS
2009	Blackburn, Greider, Szostak	Telomeres and telomerase	Aging, carcinogenesis
2010	Robert Edwards	In vitro fertilization	Treatment of infertility
2011	Beutler, Hoffmann, Steinman	Innate immunity and dendritic cells	Vaccines and immunotherapy
2012	Gurdon, Yamanaka	Induced pluripotent stem cells	Regenerative medicine
2013	Rothman, Schekman, Südhof	Vesicular transport in the cell	Diabetes, neurological diseases
2014	O'Keefe, Moser, Moser	The brain's GPS system	Dementias and neurology
2015	Campbell, Ōmura, Tu Youyou	Therapy of malaria and parasitic diseases	Millions of lives saved
2016	Yoshinori Ohsumi	Autophagy	Cancer, neurodegeneration
2017	Hall, Rosbash, Young	Circadian rhythm	Sleep medicine, metabolism
2018	Allison, Honjo	Tumor immunotherapy	One of the greatest revolutions in oncology
2019	Kaelin, Ratcliffe, Semenza	Cellular response to hypoxia	Anemia, cancer, cardiology
2020	Alter, Houghton, Rice	Hepatitis C virus	Elimination of post-transfusion hepatitis
2021	Julius, Patapoutian	Receptors for temperature and touch	Chronic pain
2022	Svante Pääbo	Paleogenomics	Evolutionary medicine
2023	Karikó, Weissman	mRNA technology	COVID vaccines and a new era of vaccination
2024	Ambros, Ruvkun	microRNA	Regulation of gene expression
2025	Brunkow, Ramsdell, Sakaguchi	Peripheral immune tolerance	Autoimmune diseases and transplantation

Key areas of research in the 21st century

An analysis of the winners of the Nobel Prize in Physiology or Medicine in the 21st century shows several dominant directions in the development of biomedical research.

1. Gene regulation and RNA biology

The Nobel Prizes awarded for RNA interference (2006) and microRNA (2024) point to the central importance of RNA in the regulation of gene expression. These discoveries showed that the control of gene activity does not take place exclusively at the level of DNA, but also through complex mechanisms of post-transcriptional regulation. Understanding these processes has opened new possibilities for the development of diagnostic methods, targeted therapy and gene medicine. The discovery of RNA interference showed that cells possess natural mechanisms for the selective “silencing” of genes, while research on microRNA revealed an additional regulatory layer that controls protein synthesis and cell function. Today,

disorders of these mechanisms are associated with numerous diseases, including malignant, metabolic and neurodegenerative disorders.

2. Immunology

One of the most important areas of modern medicine is immunology. The Nobel Prizes of 2011, 2018 and 2025 shed light on key mechanisms of innate immunity, immune regulation and peripheral tolerance. The discoveries of Toll-like receptors and dendritic cells explained how the organism recognizes pathogens and triggers an immune response. The later identification of immune checkpoints enabled the development of modern immunotherapy of malignant diseases, while research on regulatory T lymphocytes and peripheral tolerance has significantly advanced the understanding of autoimmune diseases, transplant medicine and immune homeostasis.

3. Cell biology

Advances in cell biology have enabled a deeper understanding of the basic mechanisms

of the functioning of living systems. The Nobel Prizes for vesicle transport (2013) and autophagy (2016) clarified the processes of intracellular transport, intercellular communication and the recycling of cellular components. These mechanisms play a key role in maintaining cellular balance, the response to stress and adaptation to changes in the external environment. Their disorders are associated with the development of numerous diseases, including neurodegenerative disorders, diabetes, cardiovascular diseases and malignant tumors.

4. Radiological diagnostics, translational and applied medicine

A special characteristic of 21st-century medicine is the successful translation of fundamental scientific discoveries into clinical practice. The Nobel Prizes for magnetic resonance tomography (2003), in vitro fertilization (2010) and mRNA technology (2023) are examples of how basic research can lead to revolutionary diagnostic and therapeutic achievements.

These technologies have significantly advanced diagnostics, reproductive medicine and the prevention of infectious diseases, confirming that the greatest progress in medicine is often achieved by linking basic research with clinical application.

The winners of the Nobel Prize in Physiology or Medicine in the 21st century have continued the tradition of great scientific discoveries, but at the same time they have directed medicine toward new concepts of molecular biology, immunology and personalized therapy. Unlike many achievements of the 20th century, which were focused on individual diseases or organs, contemporary research increasingly reveals universal molecular and cellular mechanisms that link various physiological and pathological processes. Such an approach is the basis of modern precision medicine and the future development of new diagnostic and therapeutic strategies.

THE FIVE GREATEST MEDICAL REVOLUTIONS OF THE 21ST CENTURY

1. Immunotherapy of malignant diseases (Nobel 2018)

Before 2010, metastatic melanoma was one of the deadliest diagnoses in oncology. Patients with advanced melanoma had a five-year survival of only about 5%, and therapeutic

options were limited to surgery, radiation and cytotoxic chemotherapy, which rarely produced lasting results. Tumor cells managed to evade attack by the immune system by using their own “brakes” that prevent excessive activation of T cells.

The key discovery came from two independent directions in the 1990s. James Allison discovered that the CTLA-4 protein on the surface of T cells acts as an inhibitory receptor — a kind of “brake” that prevents full activation of the immune response. By blocking CTLA-4 with antibodies, his team showed that T cells can be “released” and directed to destroy tumor cells. Tasuku Honjo independently discovered another inhibitory receptor, PD-1, which binds to PD-L1 on tumor cells; this interaction sends a signal to the T cell to withdraw from the attack. Many tumors overexpress PD-L1 precisely as a strategy for evading the immune system [21,22].

Checkpoint inhibitors became the first class of drugs that does not attack the tumor directly, but rather “releases the brakes” of the immune system. In 2011, ipilimumab (anti-CTLA-4) was approved for metastatic melanoma, followed by anti-PD-1 drugs such as pembrolizumab (Keytruda) and nivolumab (Opdivo). The results were revolutionary: combined anti-PD-1 and anti-CTLA-4 therapy extended long-term survival in metastatic melanoma from 5% to about 50% in the latest reports [23]. Today, these drugs are used for melanoma, cancer of the lung, kidney, urinary bladder, head and neck, as well as for Hodgkin lymphoma [21].

However, challenges remain: only some patients have a lasting response, and the therapy can cause autoimmune side effects. New checkpoints (LAG-3, TIM-3) and combinations with other treatment modalities are being investigated [23]. Today, checkpoint inhibitors (PD-1, PD-L1, CTLA-4) enable long-term survival in many patients with melanoma, lung cancer, kidney cancer and other tumors.

2. mRNA vaccines (Nobel 2023)

For the first time in history, a vaccine does not require the cultivation of viruses or bacteria. The genetic information for producing the protective antigen is sufficient. This has opened the possibility of developing vaccines against malignant diseases, HIV and numerous infections.

Traditional vaccines required the cultivation of viruses or bacteria under laboratory conditions — a lengthy, expensive and technically demanding process. Even after identification of the pathogen, it took weeks or months to produce a sufficient amount of attenuated or inactivated virus. The mRNA approach changed this completely: instead of producing the antigen itself in the laboratory, it is enough to know the genetic sequence that encodes the protective protein, and the patient's body becomes a "factory" that produces that protein and triggers an immune response [24,25].

The key scientific breakthrough occurred in 2005, when Katalin Karikó and Drew Weissman discovered how to modify mRNA so that it does not cause an undesirable immune reaction. Namely, the synthetic mRNA that scientists produced in the laboratory was recognized by innate immune receptors (Toll-like receptors) as a foreign body, which caused a strong inflammatory reaction and degradation of the mRNA before it could reach the ribosomes. Karikó and Weissman showed that replacing uridine — one of the four basic nucleotides — with pseudouridine (its isomer) dramatically reduces immunogenicity and at the same time increases the translational efficiency of mRNA [26].

This discovery enabled the development of mRNA vaccines against COVID-19 in record time. Unlike traditional vaccines, mRNA vaccines do not require the cultivation of the virus; the genetic information is sufficient. The Pfizer-BioNTech and Moderna vaccines showed an efficacy of about 95% in preventing symptomatic COVID-19 disease, including in older people, who usually respond less well to vaccines [25]. This technology is extremely flexible: when a new variant of the virus appears, the mRNA sequence can be quickly adapted. The same principle opens the possibility of developing vaccines against HIV, Zika virus and influenza, as well as therapeutic vaccines against malignant diseases — for example, against melanoma, where mRNA can be programmed to encode neoantigens specific to the patient's tumor [24,27].

3. Genomics and molecular medicine

From the discovery of the structure of DNA in 1953 (Nobel 1962) to the present day, genomics has traveled the path from fundamental research to routine clinical

application. The Human Genome Project, completed at the beginning of the 21st century, was a turning point: for the first time, the complete sequence of the human genome was read. Today, genome sequencing is no longer a special event — it is becoming a ubiquitous resource in medicine. Whole-genome sequencing (WGS) has been recognized as a priority diagnostic method for detecting rare genetic diseases, because it enables analysis of the non-coding parts of the genome, which make up about 98,5% of our DNA and contain regulatory elements key to controlling gene expression [28,29]. In oncology, this has led to a paradigm shift: tumors are today classified not only according to the organ of origin, but according to molecular mutations. Next-generation sequencing (NGS) enables simultaneous analysis of a multitude of genes from a limited amount of sample, **identifying "driver" mutations** that drive tumor growth, translocations, amplifications and other genetic changes [30]. For example, lung cancer is routinely tested for EGFR, ALK, ROS1 and other mutations, because each of them has a corresponding targeted therapy. **Personalized cancer vaccines are designed on the basis of the unique mutations of the patient's tumor**, and liquid biopsy (analysis of circulating tumor DNA from the blood) enables early detection of recurrence [28].

Genomics also enables pharmacogenomics — adjusting the dose and choice of drugs on the basis of the genetic profile of the patient. This reduces side effects and increases the efficacy of therapy, especially in pediatrics and oncology [29]. However, challenges remain: the reference genome is incomplete and does not represent the genetic diversity of humankind well enough, which is why the concept of a "pangenome" is being developed that would encompass both copies of the chromosomes and variations within populations [28]. Interpreting the enormous amount of data also requires sophisticated bioinformatic tools and multidisciplinary teams.

4. Regenerative medicine

Until 2006, the dominant view in biology was that cell differentiation is an irreversible process — that a mature, specialized cell cannot return to the stem cell state. Shinya Yamanaka called this dogma into question. Yamanaka's induced pluripotent STEM cells made it possible to return mature cells to an

embryonic state, opening the possibility of regenerating tissues and organs.

His team showed that mature, differentiated cells can be reprogrammed into a pluripotent state by simply introducing only four transcription factors (known as the Yamanaka factors: Oct4, Sox2, Klf4 and c-Myc). The cells created in this way were named induced pluripotent stem cells (iPS cells) [31,32].

This discovery revolutionized the understanding of development and opened the door to regenerative medicine. iPS cells have two key properties: they can divide indefinitely and they can differentiate into any cell type in the body — neurons, cardiomyocytes, hepatocytes, pancreatic cells. Unlike embryonic stem cells, iPS cells can be created from the patient's own cells (e.g. from skin or blood), thereby avoiding ethical issues and the risk of immunological rejection. In 2012, Yamanaka received the Nobel Prize for this discovery, together with John Gurdon, whose pioneering nuclear transfer experiments in frogs decades earlier had laid the foundations [33,31].

The clinical potential of iPS cells is enormous. They can be used for disease modeling in the laboratory (e.g. creating neurons from patients with ALS or Parkinson's disease), for drug screening, and — most ambitiously — for the regeneration of damaged tissues and organs. The first clinical studies have already been conducted: transplantation of iPS-derived retinal cells in macular degeneration, and research for heart disease, type 1 diabetes and spinal cord injuries [33]. **However, challenges remain: the risk of tumor (teratoma) formation if remaining undifferentiated iPS cells are transplanted**, the efficiency of reprogramming, and long-term safety. Nevertheless, iPS technology has already changed the way we think about cellular plasticity and has opened the way to personalized regenerative medicine.

5. Precise gene regulation

RNA interference and microRNA have shown that genes are not just “switched on or off”, but that there is a complex network regulating their activity. This represents the basis of future gene therapies.

For a long time it was believed that genes are simply “switched on” or “switched off” — that gene expression is regulated primarily at the level of transcription, through transcription factors that bind to DNA. The discovery of RNA

interference (RNAi) in 1998 (Nobel 2006) showed that there is a completely different layer of regulation that acts at the level of the RNA itself, after transcription has already taken place [34]. Andrew Fire and Craig Mello discovered that double-stranded RNA can activate cellular mechanisms that specifically degrade the mRNA that matches it in sequence, thereby “silencing” gene expression before the protein is even formed [34].

MicroRNAs, discovered in 1993 but recognized with the Nobel Prize in 2024, represent an even finer layer of regulation [35]. These small RNA molecules (about 22 nucleotides long) do not degrade mRNA directly, but bind to it and inhibit translation or promote its gradual destruction [35]. One microRNA can regulate hundreds of different mRNAs, creating a complex network of mutual interactions [36]. The human genome encodes more than 1000 microRNAs, and their dysregulation is associated with numerous diseases — from cancer to neurodegenerative disorders [36].

These findings form the basis of future gene therapies. RNAi is already used as a research tool for gene silencing, and the first drugs based on this principle have been approved (e.g. patisiran for hereditary transthyretin amyloidosis) [37]. MicroRNAs are being investigated as therapeutic targets: inhibition of oncogenic microRNAs or the addition of tumor-suppressor microRNAs could become a new strategy for treating cancer [36]. The key challenge remains the delivery of these molecules to target cells in vivo, as well as avoiding off-target effects [37]. Nevertheless, the understanding that genes are not binary switches, but exist in a complex network of regulation, fundamentally changes the way we approach gene therapy and drug development [38].

COMPARATIVE ANALYSIS of the Nobel Prizes in Physiology or Medicine during the 20th and 21st centuries

An analysis of the Nobel Prizes in Physiology or Medicine during the 20th and 21st centuries provides a unique insight into the development of medical science and changes in research priorities over more than a century [1,2]. Viewed through the prism of the awarded discoveries, a transition can clearly be seen from research aimed at identifying the causes of diseases and basic physiological processes toward the study of molecular mechanisms, gene

regulation and an individualized approach to treatment [8].

The first half of the 20th century was marked by discoveries that laid the foundations of modern medicine. The work of Robert Koch, Ronald Ross and Alphonse Laveran enabled an understanding of the etiology and transmission of infectious diseases [1,2], while Landsteiner's discovery of blood groups, Banting's discovery of insulin and Fleming's discovery of penicillin directly changed clinical practice and significantly reduced mortality [10,12,13]. In the same period, key diagnostic methods, such as electrocardiography, emerged, which enabled an objective assessment of organ function and laid the foundations of modern diagnostics [1,2].

The second half of the 20th century represents the era of molecular biology. The discovery of the structure of DNA in 1962 marked the beginning of a new epoch in medicine [19,20]. The following decades brought an understanding of the genetic code, the mechanisms of cell signaling, cholesterol metabolism, receptor function and the regulation of the immune response [1,2]. During this period, medicine moved from the level of organs and tissues to the level of the cell and the molecule. At the same time, advanced diagnostic methods were developed, among which computed tomography represents one of the most important technological revolutions in medicine [1,2].

Unlike in the 20th century, the Nobel Prizes in the 21st century have been predominantly directed toward research on regulatory mechanisms within the cell. Discoveries of apoptosis, RNA interference, telomeres, stem cells, autophagy, microRNA and immune checkpoints have been awarded [34,35,36,40]. The common feature of this research is the study of processes that determine cell behavior, gene expression and the interaction of the organism with disease at the molecular level [8].

A particularly important trend of the 21st century is the development of personalized

medicine. While the therapeutic approaches of the 20th century were mainly based on the principle of "one disease — one drug", modern medicine strives to individualize diagnosis and therapy on the basis of the genetic, molecular and immunological characteristics of each patient [28,29]. Immunotherapy of malignant diseases, awarded the Nobel Prize in 2018, is one of the best examples of this concept, because it enables activation of the immune system against the tumor, with a significant improvement in survival in certain malignancies [21,23,38].

In addition, the Nobel Prize for the development of mRNA technology in 2023 showed how fundamental research can lead to the rapid development of new therapeutic and preventive strategies [24,25,39]. During the COVID-19 pandemic, mRNA vaccines enabled unprecedentedly rapid production of effective vaccines, thereby confirming the practical value of decades of basic research [25,27,39].

Viewed as a whole, the Nobel Prizes of the 20th century were focused on discovering the causes of diseases and developing antibiotics, hormones, vaccines and diagnostic methods, while the Nobel Prizes of the 21st century reflect the transition of medicine toward understanding the molecular and genetic mechanisms of disease [8]. This change marks the transformation of medicine from a predominantly reactive discipline toward predictive, preventive and personalized medicine [28,29].

It can be concluded that the Nobel Prizes represent a kind of history of the development, i.e. the evolution, of biology, especially physiology and medicine (Table 4.). From microorganisms, hormones and antibiotics to the genome, immunotherapy and mRNA technology, the awarded discoveries show how the focus of medicine over the last 125 years has shifted from treating manifest disease toward its early detection, prevention and an individualized therapeutic approach [1,2,8].

Table 4. The development or evolution of medicine through the Nobel Prizes

Characteristic	20th century	21st century
Dominant diseases	Infectious diseases	Chronic non-communicable diseases and malignancies
Level of research	Organ and tissue	Cell, genome and molecule
Main discoveries	Insulin, penicillin, ECG, DNA	Immunotherapy, mRNA, microRNA, stem cells
Goal of therapy	Treatment of disease	Prediction, prevention and personalization
Concept of medicine	"One drug for many"	"The right drug for the right patient"
Dominant technology	Microbiology and biochemistry	Genomics, bioinformatics and artificial intelligence

Through this table we see that the Nobel Prizes are a kind of mirror of the development of medicine from 1901 to the present day.

DISCUSSION

The Nobel Prize is awarded for a fundamental scientific mechanism in diagnostics and therapy, and not for the development of diagnostic and therapeutic methods and techniques or the development of new drugs. For example, in 2023 the prize was not awarded for a particular vaccine against COVID-19, but for the discoveries that enabled the development of mRNA vaccines.

However, in the discussion we would like to emphasize our view that there are several oversights by the Nobel Committee with regard to new modalities of ultrasound, MDCT scanner, PET scan and magnetic resonance diagnostics, as well as revolutionary innovative surgical techniques and new revolutionary inventive drugs and therapies. Although these methods have saved or improved the quality of life of millions of patients, the Nobel Committee has traditionally rewarded fundamental biological discoveries much more often than the development of diagnostics, pharmacological therapy and surgical techniques.

Table 5. The most important pioneers of ultrasound diagnostics and the Nobel Prizes

Field	Pioneers	Nobel Prize
Echocardiography (1953)	Inge Edler and Hellmuth Hertz	No
Doppler echocardiography	Shigeo Satomura	No
Pulsed Doppler	Peter Wells, Paul Peronneau, Donald Baker	No
Two-dimensional echocardiography	Bom, Lancée, Roelandt, Kisslo and others	No
Color Doppler	Developed by several research groups during the 1970s and 1980s	No
Three-dimensional echocardiography	Dekker, Roelandt and numerous later researchers	No
Strain / Speckle Tracking	Developed during the 1990s and 2000s by several groups	No

While other revolutionary diagnostic methods in medicine received this prestigious recognition, echocardiography and medical ultrasound remained without a Nobel Prize, despite the fact that they completely changed modern clinical practice [41,42].

Although Inge Edler (a cardiologist) and Hellmuth Hertz (a physicist) successfully applied

Thus, there is a significant difference between a scientific discovery and its clinical translation into everyday medical practice. The Nobel Prize traditionally favors fundamental mechanisms and biological principles, while many achievements of enormous public health importance remain outside its scope. Therefore, the history of medicine cannot be viewed exclusively through the Nobel Prizes, but also through an assessment of the real impact of individual therapies on survival, quality of life and the reduction of the burden of disease in the general population.

ULTRASOUND DIAGNOSTICS. None of the key pioneers of medical ultrasound, echocardiography, Doppler, color Doppler, three-dimensional echocardiography and speckle-tracking (strain) echocardiography, or of ultrasound-guided therapeutic interventions, received the Nobel Prize in Physiology or Medicine, or in Physics, for these achievements [41,42]. In fact, ultrasound diagnostics is one of the most important medical technologies that has never been awarded a Nobel Prize [41] (Table 5).

ultrasound to examine cardiac structures as early as 1953 at Lund University, and Shigeo Satomura soon afterwards developed the Doppler technique for analyzing blood flow, the Nobel Committee never awarded them [41]. The two of them (Inge Edler and Hellmuth Hertz) received the prestigious Lasker Award in 1977, which is often called the “American Nobel Prize for medicine” [41].

Table 6. Comparison with other major imaging methods that *were* awarded the Nobel Prize in Physiology or Medicine (or Physics)

Diagnostic method	Laureates	Year of award	Contribution
X-radiation (X-rays)	Wilhelm Conrad Röntgen	1901. (Physics)	Discovery of X-rays, which enabled the first insight into the interior of the human body.
Electrocardiography (ECG)	Willem Einthoven	1924.	Invention of the ECG apparatus and recording of the electrical activity of the heart.
Computed tomography (CT)	Allan Cormack and Godfrey Hounsfield	1979.	Development of computer-assisted tomography for three-dimensional imaging of tissues.
Magnetic resonance imaging (MRI)	Paul Lauterbur and Peter Mansfield	2003.	Discoveries concerning the visualization of structures by means of magnetic resonance.

Historians of medicine cite several reasons why a Nobel Prize was never awarded for ultrasound: the gradual evolution of the technology, the focus on clinical application, and the fact that ultrasound diagnostics is not the work of one person but of a large number of physicists, engineers and physicians over several decades, so it was difficult to designate one or at most three laureates, as the Nobel rules require [41,42]. Gradual evolution of the technology — medical ultrasound developed step by step, through the adaptation of existing industrial and military technology (such as sonar for detecting submarines), so it may have been difficult for the Committee to single out one or two individuals who made a definitive scientific breakthrough [41]. Focus on clinical application — the Nobel Prize in Physiology or Medicine often favors fundamental, basic scientific discoveries (such as genetics, immunology or cell biology) over engineering and technological achievements in medical practice [41,42].

Nevertheless, in medical circles the absence of this prize for ultrasound is considered one of the greatest oversights in the history of the Nobel Committee, given that it is the most accessible, completely safe (non-ionizing) and today irreplaceable method for examining the heart and the whole body [41].

The most important pioneers of medical ultrasound who did not receive the Nobel Prize

1. Karl Theodor Dussik (Austria) - He is considered one of the first researchers to attempt to use ultrasound to image the human body. As early as 1942, he used ultrasonic waves in an attempt to diagnose brain tumors with a method he called "hyperphonography".
2. George Ludwig (USA) - He was the first to show that ultrasound can be used to detect gallstones and other structures in tissues. His work from the late 1940s is considered the first practical medical application of ultrasound.
3. John J. Wild (1914–2009) - Often called **"the father of medical ultrasound"**. He was the first to use ultrasound to distinguish normal from tumor tissue, especially in the breast and the gastrointestinal tract. He developed the first ultrasound images of breast tumors and participated in the development of transrectal and transvaginal probes.
4. John Reid - An engineer who, together with Wild, constructed the first practical ultrasound devices for imaging breast tumors. He later also

participated in the development of Doppler technology.

5. Douglas Howry (1920–1969) - A radiologist who developed B-mode ultrasound imaging and produced the first high-quality two-dimensional cross-sectional images of the human body. He is considered one of the founders of modern abdominal ultrasonography.

6. Joseph Holmes - Together with Howry, he developed the first 2D B-mode scanners and laid the foundations of modern imaging of the abdominal organs.

7. Ian Donald (1910–1987) - Known as **"the father of obstetric and gynecological ultrasound"**. His work enabled the routine use of ultrasound in pregnancy and in the diagnosis of abdominal masses and gynecological diseases. In 1958, he published a famous paper on the use of ultrasound in the diagnosis of abdominal tumors and cysts.

8. Tom Brown - An engineer who, with Ian Donald, developed the first practical contact B-mode scanners, without the need to immerse the patient in water.

Scientists working on the Doppler effect found themselves in a similar situation. The Doppler effect was described by the Austrian physicist Christian Doppler as early as 1842. He did not receive the Nobel Prize because he died long before the Nobel Prizes were established (1901). The 1919 Nobel Prize in Physics was not awarded to Doppler, but to Johannes Stark for experimental research on the Doppler effect in canal rays and for the Stark effect [1,2].

Revolutionary surgical techniques and operations

It is also a great oversight in the awarding of the Nobel Prize, in our opinion and in the opinion of many historians of medicine, that the innovative surgeons who revolutionized operative medicine in the second half of the 20th century and in the 21st century did not receive the Nobel Prize, although their methods changed everyday surgical practice more than many Nobel-awarded discoveries. Outside transplant surgery, very few surgeons have received the Nobel Prize for the development of operative techniques: Alexis Carrel – Nobel Prize in Medicine 1912 for vascular suturing and transplant surgery; Joseph Murray – Nobel 1990 for organ transplantation.

However, no Nobel Prize has been awarded for laparoscopy, minimally invasive surgery, video surgery, endoscopic surgery,

arthroscopy, robotic surgery or modern oncological operations, despite the fact that their revolution in surgery has permanently changed almost all surgical disciplines and has become the standard of modern operative medicine [43,44].

Pioneers of laparoscopy who did not receive the Nobel Prize:

1. Kurt Semm (1927–2003) - Most often considered one of the most important figures in the history of minimally invasive surgery: first laparoscopic appendectomy (1980), developed the electronic CO₂; developed numerous laparoscopic instruments; developed training simulators for laparoscopic training. His work was initially ridiculed, and later became the basis of modern laparoscopic surgery.

2. Erich Mühe (1938–2005) - Performed the first laparoscopic cholecystectomy in 1985 in Germany. Initially he was not recognized by the surgical community, and his pioneering work was officially recognized only many years later.

3. Philippe Mouret (1942–2008) - A French surgeon who in 1987 popularized laparoscopic cholecystectomy and launched the worldwide "laparoscopic revolution".

4. Camran Nezhat - One of the pioneers of video laparoscopy. His idea of performing the operation while watching a monitor instead of looking directly through the optics represented a turning point that enabled the development of modern laparoscopic surgery.

Many of these surgeons received the highest professional recognitions: the SAGES Pioneer in Endoscopy Award, the Jacobaeus Award, the Semm Award, honorary memberships of the world's leading surgical societies, medals of the American College of Surgeons (ACS), and European and world awards for minimally invasive surgery. Toward the end of his life, Kurt Semm received the "**Pioneer in Endoscopy**" recognition, which is considered one of the highest recognitions in the field of endoscopic surgery. Nor did the pioneers of the following fields receive the Nobel Prize: arthroscopy (Masaki Watanabe); modern colorectal total mesorectal excision (Bill Heald); laparoscopic hernioplasty; video-assisted thoracoscopic surgery (VATS); endovascular surgery; robotic surgery (the da Vinci era).

Although these methods have saved or improved the quality of life of millions of patients, the Nobel Committee has traditionally rewarded fundamental biological discoveries

much more often than the development of surgical techniques [43,44].

Revolutionary innovative drugs

Many inventors of drugs in the 20th and 21st centuries did receive the Nobel Prize, but most often not for the drug itself as a product, but for the discovery of the biological mechanism or principle on which the drug is based. The Nobel Committee has traditionally valued **a fundamental discovery** more than the development of an individual preparation. In Nobel's will, the key terms are "the most important discovery" and "the greatest benefit to humankind".

Drugs and therapies that brought the Nobel Prize:

Insulin – Banting and Macleod (1923).

Penicillin – Fleming, Chain and Florey (1945).

Sulfonamides (Prontosil) – Gerhard Domagk (1939).

Streptomycin (the first effective drug against tuberculosis) – Selman Waksman (1952).

Corticosteroids – Hench, Kendall and Reichstein (1950).

Beta-blockers and H₂ antagonists – James Black (1988).

Rational drug design – Gertrude Elion and George Hitchings (1988), whose work led to numerous drugs (azathioprine, allopurinol, acyclovir and others).

Aspirin, prostaglandins and mechanisms of action – John Vane (1982).

Cancer immunotherapy (checkpoint inhibitors) – James Allison and Tasuku Honjo (2018).

mRNA vaccines – Katalin Karikó and Drew Weissman (2023).

Why, then, did many great drug inventors not receive the Nobel Prize?

The first reason: the Nobel is awarded for a discovery, not for the development of a product. For example, the development of statins, ACE inhibitors or ARB drugs involved dozens of research groups, companies and clinical trials. It is difficult to single out at most three people, and the Nobel can be shared among at most three laureates. **The second reason** is that many drugs are created through teamwork. In the 21st century, the development of a new drug often involves hundreds of researchers, pharmacologists, biochemists and clinicians. The Nobel system was created at the beginning of the 20th century, when discoveries were more often linked to individuals. **The third reason** is the long-term testing and monitoring of drug effects,

and decades are needed to confirm the importance of the effects and adverse effects of drugs, so the Nobel Committee often waits 20–40 years to see whether a discovery has really changed medicine. Because of this, many researchers die before they could be awarded, and the Nobel is generally not awarded posthumously. An important fact is that the Nobel Prize is awarded for the fundamental scientific mechanism of action of a drug and not for the development of the drug. For example, in 2023 the prize was not awarded for a particular vaccine against COVID-19, but for the discoveries that enabled the development of mRNA vaccines.

Many cardiologists consider the discovery of statins to be among the greatest achievements of modern medicine, comparable in impact to insulin. The Japanese biochemist Akira Endo discovered the first HMG-CoA reductase inhibitor, but never received the Nobel Prize. However, he received numerous other prestigious international awards.

SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin and others) represent one of the greatest therapeutic revolutions of the last 20 years. They were originally developed as antidiabetic drugs, and it was then shown that they reduce hospitalizations for heart failure, slow the progression of chronic kidney disease and reduce cardiovascular risk even in patients without diabetes. Interestingly, however, it is still not fully clarified even today which is the dominant mechanism of their cardioprotective and nephroprotective action.

GLP-1 receptor agonists (liraglutide, semaglutide, dulaglutide and others) also have a strong case for the Nobel Prize. This group of drugs has changed the treatment of: type 2 diabetes, obesity, cardiovascular risk in obese persons. However, it is more likely that Nobel recognition, if it comes, would be linked to: the discovery of the incretin system, the biology of the GLP-1 receptor, new knowledge about the regulation of appetite and body weight,

The list of the greatest therapeutic discoveries of the 20th and 21st centuries by impact on mortality comprises: Insulin, Antibiotics (penicillin and later antibiotics), Vaccines, statins, diuretics and antihypertensive therapy, corticosteroids, antiplatelet and anticoagulant therapy, Antiretroviral therapy for HIV, Immunotherapy of malignant diseases SGLT

inhibitors and GLT agonists. However, only some of these achievements have been awarded the Nobel Prize, because the Nobel primarily rewards **the discovery of a scientific principle**, and not necessarily the therapy that later had the greatest clinical effect.

Great medical achievements without a Nobel Prize

The history of medicine shows that the Nobel Prize, despite its enormous importance, has not encompassed all the achievements that have fundamentally changed the course of modern clinical practice. The reason for this lies in the fact that the Nobel Prize is most often awarded for fundamental scientific discoveries, while many revolutionary achievements arise as the result of the long-term work of large research teams, decades of technological development and the gradual improvement of existing methods. [53,54]. One of the most important examples is statins. The discovery of the first HMG-CoA reductase inhibitor by the Japanese biochemist Akira Endo opened a new era in the prevention and treatment of atherosclerotic cardiovascular disease. Over the last few decades, statins have contributed to a significant reduction in the incidence of myocardial infarction, stroke and cardiovascular mortality worldwide. However, the Nobel Prize was not awarded for the discovery of statins as such; instead, Brown and Goldstein were awarded for fundamental discoveries of the mechanisms regulating cholesterol metabolism, which enabled the development of modern lipid-lowering therapy [50,54].

A similar example is angiotensin-converting enzyme inhibitors (ACE inhibitors). The work of David Cushman and Miguel Ondetti led to the development of captopril, the first ACE inhibitor, which started a new era in the treatment of arterial hypertension, heart failure and diabetic nephropathy. Despite its enormous impact on reducing morbidity and mortality, this achievement was not awarded the Nobel Prize.

Beta-blockers represent an interesting exception. Although the Nobel Prize was not awarded for propranolol itself, rather James Black was awarded in 1988 for discovering the basic principles of rational drug development that led to the creation of beta-blockers and H2 antagonists. In this way, the Nobel Committee rewarded a scientific concept rather than an individual drug [49,54].

The development of heart transplantation represents another achievement that fundamentally changed medicine. After the first successful heart transplant performed by Christiaan Barnard in 1967, transplant surgery became a standard therapeutic option for end-stage heart failure. However, the Nobel Prize was never awarded for this achievement, partly due to the fact that numerous researchers and surgeons contributed to the development of transplant medicine, including Norman Shumway, Richard Lower and many others.

Coronary revascularization represents one of the greatest therapeutic successes of cardiovascular medicine. The development of coronary artery bypass grafting (CABG), associated with René Favaloro, enabled effective surgical treatment of coronary heart disease. Later, Andreas Grüntzig developed percutaneous transluminal coronary angioplasty (PCI), which marked the beginning of modern interventional cardiology, particularly refined with the development of coronary STENT technology. Both methods have significantly extended the lifespan of millions of patients, but their creators did not receive the Nobel Prize. *sve.*

The first Stents were **self-expanding Wallstent** systems. In 1986 the first coronary stent in humans was developed by **Ulrich Sigwart and Jacques Puel**. The first Wallstent implantations were performed in **Lausanne (Switzerland) and Toulouse (France)**. **Jacques Puel** was the first to implant a Wallstent in a coronary artery in **Toulouse**, while **Ulrich Sigwart** was simultaneously performing the first implantations in **Lausanne**. Their stent was a **self-expanding mesh metal prosthesis**, unlike the later balloon-expandable stents. **Julio Palmaz**, together with **Richard Schatz**, developed one of the most important early **balloon-expandable coronary stents – the Palmaz-Schatz stent**. The concept originated in the late 1970s, and clinical development took place during the 1980s. The first **Palmaz-Schatz stent in a coronary artery** was implanted in **1987 in São Paulo, Brazil**, by a team consisting of Julio Palmaz, Richard Schatz and Eduardo Sousa. However, even earlier in 1987, the first implantations of other balloon-expandable stents were performed.

Similarly, the implantable cardioverter-defibrillator (ICD), developed by Michel Mirowski, enabled the prevention of sudden cardiac death in high-risk patients and

represents one of the most important achievements of modern arrhythmology. The first successful implantable cardioverter-defibrillator in a human was implanted on 4 February 1980 at Johns Hopkins Hospital in Baltimore, USA. The device was developed by the cardiologist **Michel Mirowski**, together with Morton Mower and colleagues. The first implantation was performed by the cardiac surgeon **Levi Watkins Jr.** Despite its enormous clinical importance, this discovery was not awarded the Nobel Prize.

A special example is in vitro fertilization (IVF). For the development of this method, Robert Edwards received the Nobel Prize in 2010, after his method had enabled the birth of millions of children around the world and opened a completely new chapter in reproductive medicine. This example shows that the Nobel Committee occasionally also rewards clinical innovations when their importance becomes indisputable and confirmed in the long term [54]. During the last decades, antiretroviral therapy for HIV infection has also gained great importance. Although Françoise Barré-Sinoussi and Luc Montagnier received the Nobel Prize for the discovery of HIV in 2008, the development of modern combined antiretroviral therapy, which turned HIV infection from a fatal into a chronic disease, was not the subject of Nobel recognition [54].

An analysis of these examples shows that there is a significant difference between a scientific discovery and its clinical translation into everyday medical practice. The Nobel Prize traditionally favors fundamental mechanisms and biological principles, while many achievements of enormous public health importance remain outside its scope. Therefore, the history of medicine cannot be viewed exclusively through the Nobel Prizes, but also through an assessment of the real impact of individual therapies on survival, quality of life and the reduction of the burden of disease in the general population [49,50,51,53,54].

From the perspective of the history of medicine, among the modern therapies that have the potential to one day be associated with the Nobel Prize because of their impact on mortality and morbidity, the following are often cited:

- SGLT2 inhibitors and their cardiorenal mechanisms.
- GLP-1 receptor agonists and the regulation of metabolism/obesity.

- Immunotherapy of malignant diseases (already awarded in 2018).
- mRNA platforms (already awarded in 2023).
- CRISPR gene therapy (Nobel Prize in Chemistry 2020, but medical applications are yet to come).

If the long-term effects of SGLT2 inhibitors on the heart and kidneys prove comparable to the historical impact of statins or ACE inhibitors, this group of drugs could represent one of the greatest therapeutic achievements of the beginning of the 21st century, regardless of whether their creators ever receive the Nobel Prize - **they represent a potential area of future Nobel-awarded discoveries**. The current literature particularly emphasizes that the mechanisms of cardiorenal protection of SGLT2 inhibitors have not yet been fully clarified.

SGLT2 inhibitors and GLP-1 receptor agonists – potential candidates for future Nobel recognition

SGLT2 inhibitors represent one of the most important pharmacotherapeutic achievements of the beginning of the 21st century. Although they were originally developed as drugs for lowering blood glucose concentration in patients with type 2 diabetes mellitus, large randomized clinical trials have shown that their benefit goes far beyond glycemic control. This group of drugs reduces the risk of hospitalization for heart failure and slows the progression of chronic kidney disease, and certain effects are also seen in patients without diabetes [55–58]. It is particularly important that the results of the EMPA-REG OUTCOME study with empagliflozin showed a reduction in cardiovascular and total mortality, as well as in hospitalizations for heart failure, in patients with type 2 diabetes and high cardiovascular risk. These results were unexpected, because the benefit was considerably greater than could be explained by improved glycemic control alone [55]. Further research showed that SGLT2 inhibitors provide cardiorenal protection independently of the presence of diabetes. In the DAPA-HF and DAPA-CKD studies and other large randomized trials, their benefit was confirmed in patients with heart failure and chronic kidney disease, including populations without diabetes [56–58].

The mechanism by which SGLT2 inhibitors achieve such broad effects has not yet

been fully clarified. Increased natriuresis and osmotic diuresis, a reduction in intravascular volume and arterial blood pressure, restoration of tubuloglomerular feedback and a reduction in intraglomerular pressure are considered important. In addition, effects on the energy efficiency of the myocardium and kidneys, tissue oxygenation, metabolism of energy substrates, inflammation and cardiac remodeling have been proposed [55,59,60].

Precisely the fact that a single group of drugs shows simultaneous metabolic, cardiac and renal effects represents a particularly interesting scientific problem. Current data indicate that their action cannot be reduced merely to the inhibition of glucose reabsorption in the proximal tubule, but that there is a complex interaction between the kidneys, heart, metabolism and neurohumoral mechanisms [59–61].

Therefore, any future Nobel recognition would more likely be associated with the discovery of a fundamental mechanism explaining the broad cardiorenal effects of SGLT2 inhibition than with the development of an individual drug itself, such as empagliflozin or dapagliflozin. Such a scenario would be consistent with the traditional pattern of the Nobel Prize, which is primarily awarded for fundamental discoveries and new biological principles, and not for the commercial development of an individual pharmaceutical product.

The second great therapeutic revolution of the beginning of the 21st century is associated with GLP-1 receptor agonists. Understanding the incretin system and the physiological role of GLP-1 enabled the development of drugs that simultaneously affect insulin secretion, glucagon, gastric emptying, food intake and the regulation of body weight [62]. GLP-1 receptor agonists, including liraglutide, dulaglutide and semaglutide, were first developed for the treatment of type 2 diabetes, but their use expanded significantly after evidence of a pronounced effect on body weight and cardiovascular outcomes. The development of this therapeutic group is an example of how fundamental research on hormone physiology can lead to a completely new class of drugs [62,63]. Of particular importance are the results of the SELECT study, in which semaglutide reduced the incidence of major cardiovascular events compared with placebo in overweight or

obese persons without diabetes. These results further extended the importance of GLP-1 receptor agonists beyond the traditional treatment of diabetes and pointed to the possibility that pharmacological control of body weight is an important component of cardiovascular prevention [63,64]. Therefore, the GLP-1 system can be viewed as another potentially important candidate for a future fundamental discovery that could be recognized with the highest scientific honors. However, any Nobel Prize would more likely be linked to a new fundamental understanding of the regulation of metabolism, appetite, energy homeostasis and the action of the GLP-1 receptor than to semaglutide itself or any other individual drug. SGLT2 inhibitors and GLP-1 receptor agonists thus represent an interesting example of modern medicine in which the boundary between diabetology, cardiology, nephrology and metabolic medicine is increasingly blurred. Their clinical importance has already been confirmed by large randomized studies, while the fundamental mechanisms of their pleiotropic effects remain the subject of intensive research [55–64].

If future research identifies a fundamental biological mechanism that explains the broad spectrum of metabolic, cardiovascular and renal effects of these therapeutic groups, it is precisely such a discovery, and not the drug itself, that could form the basis for one of the future great recognitions in the field of physiology or medicine.

CONCLUSION

Viewed from the perspective of modern medicine, the most influential therapeutic achievements of the 20th and early 21st centuries by impact on mortality include antibiotics, insulin, vaccines, corticosteroids, organ transplantation, statins, antihypertensive drugs, coronary revascularization, ICD therapy, antiretroviral drugs, immunotherapy of malignant diseases, Immunotherapy of malignant diseases with checkpoint inhibitors, sodium-glucose cotransporter type 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, mRNA vaccines and siRNA directed at the degradation of PCSK9 mRNA - gene therapy . However, only some of these achievements have been awarded the Nobel Prize, because the Nobel primarily rewards **the discovery of a scientific principle**, and not

necessarily the therapy that later had the greatest clinical effect, which confirms that the importance of an individual medical discovery need not always be proportional to its Nobel recognition [45–54].

If the 20th century saved millions of people thanks to insulin, antibiotics, blood transfusion, the ECG and transplantation, the 21st century strives to provide each patient with therapy based on their genome, immunological profile and the molecular characteristics of the disease [1,2,8].

The 20th century discovered the causes of diseases. The 21st century is learning how to treat them precisely, in a targeted and individualized way [8,28,29].

The key differences between the 20th and 21st centuries are:

- *Focus on basic mechanisms:* While discoveries in the 20th century were often directed at specific diseases and their causes (e.g. penicillin, poliovirus), the 21st century is increasingly focused on understanding the basic biological mechanisms underlying health and disease [8].
- *Genetics and molecular biology:* The 21st century has brought a revolution in genetics. Discoveries such as RNA interference (2006) and the role of genes in the development of cells and diseases (e.g. the discovery of FOXP3 gene mutations that lead to autoimmune diseases) represent enormous progress compared with earlier understandings of genetics [34,35,36].
- *Immunology and therapy:* The understanding of the immune system has significantly advanced. The discovery of regulatory T cells and peripheral immune tolerance (2025) is key to understanding autoimmune diseases and developing new therapies [40]. Also, the discovery of HIV (2008) and the development of mRNA vaccines (2023) are examples of the direct application of this knowledge in medicine [24,25,39].
- *Technological progress:* The development of new technologies has enabled scientists to investigate things that were previously unimaginable. An example is the sequencing of

Neanderthal DNA (2022), which opened a completely new field in the study of

human evolution [41].

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

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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 declared for 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 a scientific project).

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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:
Coffee drinking and cancer of the pancreas [editorial]. *BMJ.* 1981; 283 628.

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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.

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Conference Articles:
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Article published electronically before the printed version:
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Online monograph:

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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/>.

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