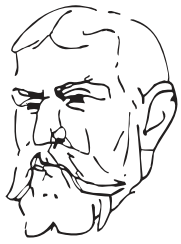
# Wiadomości Lekarskie

Czasopismo Polskiego Towarzystwa Lekarskiego

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# Wiadomości Lekarskie





**Managing Editor:**
Agnieszka Rosa amarosa@wp.pl

**International Editor:**
Lesia Rudenko l.rudenko@wydawnictwo-aluna.pl

**Distribution and Subscriptions:**
Bartosz Guterman prenumerata@wydawnictwo-aluna.pl

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ORIGINAL ARTICLE
PRACA ORYGINALNA

# KLINICZNE I DEMOGRAFICZNE PREDYKTORY ŁAGODNYCH ZABURZEŃ POZNAWCZYCH – BADANIE PRZEKROJOWE

# CLINICAL AND DEMOGRAPHIC PREDICTORS OF MILD COGNITIVE IMPAIRMENT - CROSS-SECTIONAL STUDY

**Anna Rajtar-Zembaty[1], Andrzej Sałakowski[3], Jakub Rajtar-Zembaty[2], Katarzyna Olszewska[1], Roksana Epa[1], Gabriela Tomczyk-Knop[4], Anna Starowicz-Filip[1], Barbara Bętkowska-Korpała[1], Anna Skalska[2]**

[1]ZAKŁAD PSYCHOLOGII LEKARSKIEJ, KATEDRA PSYCHIATRII, UNIWERSYTET JAGIELLOŃSKI, COLLEGIUM MEDICUM W KRAKOWIE, KRAKÓW, POLSKA
[2]KATEDRA CHORÓB WEWNĘTRZNYCH I GERONTOLOGII, UNIWERSYTET JAGIELLOŃSKI, COLLEGIUM MEDICUM W KRAKOWIE, KRAKÓW, POLSKA
[3]NZOZ NOWA REHABILITACJA W KRAKOWIE, KRAKÓW, POLSKA
[4]NZOZ CENTRUM DOBREJ TERAPII W KRAKOWIE, KRAKÓW, POLSKA

## STRESZCZENIE

**Wstęp:** Obniżenie sprawności funkcji poznawczych stanowi poważny problem zdrowotny oraz społeczny osób w wieku podeszłym. Skuteczne zapobieganie i leczenie dysfunkcji poznawczych należy do wyzwań współczesnej medycyny. W literaturze przedmiotu brakuje dostatecznej liczby spójnych danych dotyczących związku różnych czynników klinicznych i demograficznych z funkcjonowaniem poznawczym osób w różnym przedziale wiekowym.

**Cel pracy:** Analiza klinicznych i demograficznych predyktorów łagodnych zaburzeń poznawczych w zależności od grupy wiekowej.

**Materiał i metody:** Analizą objęto 817 osób w wieku podeszłym (669 z prawidłowym funkcjonowaniem poznawczym i 148 osób z MCI). Celem oceny poziomu nasilenia objawów depresyjnych zastosowano skróconą 15-punktową Geriatryczną Skalę Oceny Depresji. Wszystkie osoby badane zostały poddane przesiewowej ocenie funkcjonowania poznawczego za pomocą Krótkiej Skali Oceny Stanu Psychicznego oraz Addenbrooke's Cognitive Examination-III. Do oceny poszczególnych domen poznawczych wykorzystano: Test Piętnastu Słów Reya, Test Fluencji Słownej, Test Rysowania Zegara, Test Powtarzania Cyfr oraz Test Łączenia Punktów.

**Wyniki:** Wykazano, że niezależnie związane z MCI są wiek (OR=1,09; 95% CI: 1,05–1,13) oraz poziom wykształcenia (OR=0,75; 95% CI: 0,69-0,81) w całej grupie wiekowej. W podziale na grupy w zależności od wieku okazało się, że w młodszej grupie MCI istotne okazały się wiek, poziom wykształcenia oraz depresja, a w starszej grupie MCI wiek oraz poziom wykształcenia.

**Wnioski:** Identyfikacja dysfunkcji poznawczych oraz czynników związanych z ich występowaniem stanowi istotny element procesu diagnostyczno-terapeutycznego.

**SŁOWA KLUCZOWE:** MCI, łagodne zaburzenia poznawcze, starzenie się

## ABSTRACT

**Introduction:** Cognitive limitations are a serious health and social problem, which concerns elderly people. Effective prevention and treatment of cognitive dysfunction is one of the challenges of modern medicine. There is not enough consistent data in the literature to indicate to indicate the relationship between various clinical and demographic factors with cognitive functioning in different age ranges.

**The aim:** To analyze clinical and demographic predictors of mild cognitive impairment by age group.

**Material and methods:** The analysis included 817 participants (669 with normal cognitive function and 148 people with MCI). The evaluation of the level of depressive symptoms was measured by the Short Form Geriatric Depression Scale. All participants were screened for cognitive functioning using the Mini-Mental State Examination and Addenbrooke's Cognitive Examination-III. Different cognitive domains were evaluated with different neuropsychological tools: the Rey Auditory Verbal Learning test, Clock Drawing test, Verbal Fluency test, Digit Span Test and Trail Making test.

**Results:** It has been shown that independently associated with MCI ware age (OR = 1.09, 95% CI: 1.05-1.13) and level of education (OR = 0.75, 95% CI: 0.69-0.81). Depending on the age, it turned out that in the younger MCI group, age, education and depression were significant, and the age and level of education were significant in the older MCI group.

**Conclusions:** The identification of cognitive dysfunctions is an important element of the diagnostic and therapeutic process.

**KEY WORDS:** MCI, mild cognitive impairment, aging

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## WSTĘP

Częstym problemem wieku podeszłego jest osłabienie sprawności funkcji poznawczych z czym wiąże się utrata zdolności do wykonywania codziennych zadań. Funkcje poznawcze definiowane są jako wyższe czynności umysłowe obejmujące takie procesy, jak: spostrzeganie, przyswajanie nowych informacji, zdolności wzrokowo-przestrzenne, uwaga, myślenie, funkcje językowe, pamięć

oraz funkcje wykonawcze. Normalny proces starzenia się wiąże się z osłabieniem pewnych zdolności poznawczych, takich jak: szybkość przetwarzania informacji, pamięć, sprawność językowa, zdolności wzrokowo-przestrzenne oraz funkcje wykonawcze. Związane z wiekiem osłabienie funkcjonowania poznawczego nie jest jeszcze dobrze poznane, jednak badania wskazują na zmiany objętości zarówno istoty szarej jak i białej mózgowia oraz zmian w poziomie neuroprzekaźników, które mogą przyczyniać się do obserwowanych deficytów poznawczych [1]. Warto przy tym podkreślić, że nie istnieje ustalony wzorzec stopnia nasilenia oraz zakresu dysfunkcji poznawczych, który odpowiadałby fizjologicznemu starzeniu się. Powszechnie przyjmuje się, że stanem pośrednim między zmianami funkcji poznawczych w przebiegu normalnego starzenia się a otępieniem jest obecność łagodnych zaburzeń poznawczych (MCI – *Mild Cognitive Impairment*). Kryteria MCI po raz pierwszy zostały opisane przez Petersena et al. jako izolowane zaburzenia pamięci (amnestyczny MCI), które mogą poprzedzać otępienie. Kryteria te obejmowały subiektywne skargi pacjenta na osłabienie funkcji poznawczych, obecność dysfunkcji poznawczych potwierdzoną w obiektywnym badaniu psychometrycznym, brak zmian w poziomie codziennego funkcjonowania oraz brak otępienia [2]. Później klasyczna koncepcja została rozbudowana i wyróżniono następujące podtypy MCI:

a. amnestyczny MCI: związany z zaburzeniem pojedynczej funkcji poznawczej, pamięci (aMCI – *amnestic*),
b. wybiórczy MCI: z izolowanym zaburzeniem poznawczym, innym niż pamięć (snmMCI – *single non memory MCI*),
c. uogólniony MCI: z zaburzeniem wielu funkcji poznawczych, w tym pamięci (mdMCI+ – *multiple domain amnestic MCI*) oraz
d. uogólniony MCI: z zaburzeniem wielu funkcji poznawczych, innych niż pamięć (mdMCI – *multiple domains non amnestic MCI*) [3]. Częstość występowania MCI szacowana jest na 5–37% w różnych regionach geograficznych i etnicznych [4].

W populacji polskiej częstość występowania MCI szacuje się na 9,3% [5]. Osłabienie funkcji poznawczych powoduje z czasem spadek jakości funkcjonowania człowieka, a w konsekwencji może prowadzić do otępienia, powodując ostatecznie deterioracją funkcjonowania poznawczego oraz stopniową utratę samodzielności. Spadek sprawności funkcjonalnej ogranicza zdolność do wykonywania czynności niezbędnych w codziennym życiu, prowadzi do utraty niezależności, a także do niepełnosprawności i śmierci [6]. Wskazuje się, że progresja do otępienia u chorych z MCI wynosi 21,9%, natomiast roczny współczynnik konwersji wynosi około 7% [7]. W rozważaniach na temat czynników ryzyka rozwoju MCI podkreśla się cukrzycę [8] oraz depresję [9]. Obecności wariantu ε4 genu APOE, nieprawidłowe wartości biomarkerów w płynie mózgowo-rdzeniowym, zmniejszona objętość hipokampa i kory śródwęchowej, depresja, cukrzyca, nadciśnienie, podeszły wiek, płeć żeńska, gorszy wynik w badaniu neuropsychologicznym zwiększa ryzyko progresji z MCI do otępienia w przebiegu choroby Alzheimera (AD – *Alzheimer's disease*) [10]. MCI stanowi heterogeniczne zaburzenie zarówno pod względem klinicznym, jak i etiologicznym [3,11]. Wśród czynników etiologicznych MCI wymienia się choroby neurodegeneracyjne, niedokrwienie mózgu, zaburzenia psychiczne i inne [3, 11]. W badaniu Solé-Padullésa et al. [12] dotyczącym związku rezerw poznawczych z anatomicznym i czynnościowym stanem mózgowia wykazano, że istnieje odwrotna zależność między zdrowym i patologicznym starzeniem się mózgu a rezerwami poznawczymi. W grupie osób zdrowych, większe rezerwy związane były z większą objętością mózgowia i mniejszą aktywnością tkanki nerwowej podczas wykonywania zadań poznawczych. Autorzy sugerowali, że powodem tego było efektywniejsze działanie sieci nerwowych w tej grupie. Natomiast w grupie osób z rozpoznaniem MCI lub AD, wyższy poziom rezerw poznawczych wiązał się z mniejszą objętością mózgowia i większą aktywnością tkanki nerwowej podczas wykonywania zadań poznawczych, co wskazywało na bardziej zaawansowaną neuropatologię. Z kolei badania biochemicze biomarkerów tau (t-tau) i amyloidu-β42 w płynie mózgowo-rdzeniowym osób z MCI przeprowadzone przez Rolstad et al. [13] wykazały, że u osób z wyższym poziomem edukacji, czyli rezerw poznawczych, koncentracja t-tau była mniejsza niż u osób z wykształceniem niższym. Wynik ten sugeruje, że wyższy poziom edukacji może stanowić czynnik ochronny przed tauopatią. Hipoteza rezerw poznawczych uzyskała także potwierdzenie w epidemiologicznym badaniu Afgin et al. [14]. W grupie mężczyzn, wyższy poziom edukacji wiązał się z rzadszym rozpoznaniem MCI. W badaniu Fritsch et al. [15] wykazano odwrotną zależność między liczbą lat edukacji a stopniem obniżenia funkcjonowania poznawczego mierzonego skalą Mini–Mental State Examination, MMSE [16]. W grupie osób z MCI i dłuższym okresem edukacji, także Vadikolias et al.. [17] wykazali wolniejszy przebieg pogarszania się funkcji poznawczych obejmujących werbalne i niewerbalne zadania podczas roku obserwacji. Z kolei Wilson et al. [18] przedstawili wyniki mówiące, że wyższy poziom przedchorobowych umiejętności werbalnych w postaci funkcji leksji (czytania) był związany z szybszą deterioracją poznawczą w chorobie Alzheimera. Natomiast Zahodne i wsp [19] w trwającym 11 lat badaniu longitudinalnym wykazali, że wyższy poziom edukacji był związany z lepszymi wynikami w zadaniach poznawczych, równocześnie nie był on związany z procesem pogarszania się funkcjonowania mentalnego z biegiem czasu. W dyskusji otrzymanych wyników autorzy tego doniesienia powołują się na hipotezę pasywnego związku rezerw poznawczych z procesem starzenia się.

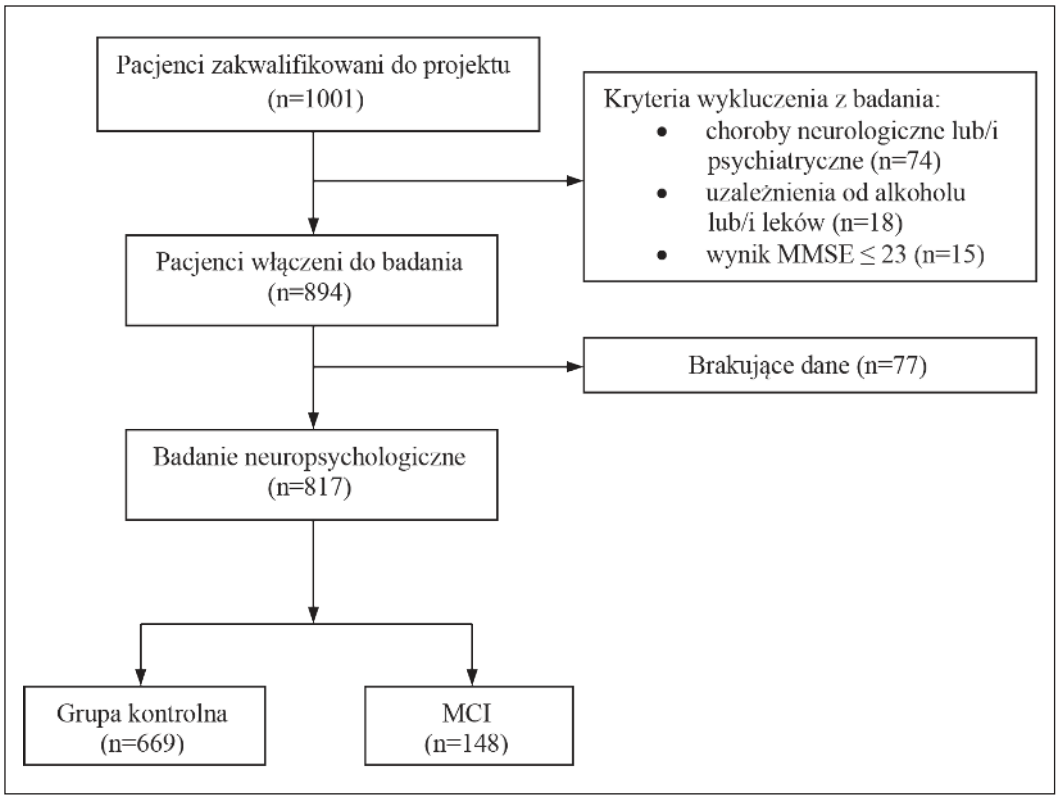
W rozważaniach na temat czynników klinicznych związanych z osłabieniem funkcjonowania poznawczego warto zaznaczyć także obecność zaburzeń nastroju. Uważa się, że depresja wieku podeszłego (LDD – *late-life depression*) jest najpowszechniej występującym problemem natury psychicznej dotykającym ludzi w okresie późnej dorosłości [20]. W literaturze przedmiotu nie ma jednak spójności co do tego, jak duży odsetek starszych osób zmaga się z objawami depresji: niektórzy autorzy szacują tę wartość na około 7% [21], inni podają, że aż 65% osób po 65. roku życia doświad-

**Tabela 1.** Charakterystyka zmiennych demograficznych i klinicznych w grupie MCI oraz w grupie kontrolnej.

| Zmienne | Grupa | | |
|---|---|---|---|
| | MCI (n=148) | Kontrolna (n=669) | *p* |
| **Demograficzne** | | | |
| Wiek (lata)[2] | 71,93 ± 6,51 | 68,91 ± 4,91 | < 0,001 |
| Kobiety[1] | 99 (67) | 482 (72) | 0,141 |
| Poziom wykształcenia (lata)[2] | 12,12 ± 3,41 | 15,04 ± 3,13 | < 0,001 |
| **Kliniczne** | | | |
| BMI (kg/m$^2$)[2] | 28,34 ± 3,99 | 28,38 ± 5,38 | 0,937 |
| Leki[2] | 4,76 ± 2,95 | 4,51 ± 3,05 | 0,411 |
| GDS[2] | 2,91 ± 3,03 | 2,06 ± 2,41 | < 0,001 |
| Nadciśnienie[1] | 97 (66) | 416 (63) | 0,474 |
| Choroba niedokrwienna serca[1] | 19 (12) | 81 (13) | 0,709 |
| Niewydolność serca[1] | 10 (7) | 26 (4) | 0,102 |
| Cukrzyca[1] | 23 (16) | 92 (14) | 0,305 |
| Choroby tarczycy[1] | 43 (29) | 219 (33) | 0,453 |
| Choroby płuc[1] | 15 (10) | 61 (9) | 0,876 |
| Choroby wątroby[1] | 18 (12) | 51 (8) | 0,092 |
| Choroby nerek[1] | 23 (16) | 83 (13) | 0,428 |
| **Testy neuropsychologiczne** | | | |
| MMSE[2] | 26,99 ± 1,41 | 28,84 ± 1,05 | < 0,001 |
| ACE-III[2] | 82,44 ± 6,49 | 94,58 ± 3,21 | < 0,001 |
| AVLT – 30 min odroczenie[2] | 6,25 ± 2,84 | 10,24 ± 2,53 | < 0,001 |
| Fluencja kategorialna[2] | 14,43 ± 4,38 | 19,83 ± 4,15 | < 0,001 |
| Fluencja literowa[2] | 10,67 ± 4,22 | 14,76 ± 4,31 | < 0,001 |
| Test Rysowania Zegara[2] | 4,12 ± 1,06 | 4,78 ± 0,53 | < 0,001 |
| Test Łączenia Punktów cz. A (s)[2] | 63,23 ± 26,25 | 44,86 ± 15,49 | < 0,001 |
| Test Łączenia Punktów cz. B (s)[2] | 162,52 ± 69,35 | 93,19 ± 33,95 | < 0,001 |
| Powtarzanie cyfr wprost[2] | 4,95 ± 0,93 | 5,46 ± 0,96 | < 0,001 |
| Powtarzanie cyfr wspak[2] | 3,17 ± 0,88 | 3,91 ± 0,87 | < 0,001 |

n - liczebność;
[1][%] - procent z ogółu;
[2]M ± - średnia i odchylenie standardowe;
MCI – *mild cognitive impairment*;
MMSE – *Mini–Mental State Examination*;
ACE-III – *Addenbrooke's Cognitive Examination-III*;
AVLT – *The Rey Auditory Verbal Learning Test*.

cza objawów obniżonego nastroju i innych symptomów zespołu depresyjnego [22]. Co istotne, objawy te nie pozostają bez wpływu na pozostałe obszary ich zdrowia, związane zarówno z dobrostanem fizycznym, jak i psychicznym [23], a co więcej – stanowią częstą przyczynę śmierci. Uważa się, że większość osób w wieku podeszłym, które popełniły samobójstwo cierpiało z powodu objawów depresji [24, 25]. Stąd niezwykle ważnym wydaje się być podejmowanie badań nad uwarunkowaniami oraz konsekwencjami depresji pojawiającej się w tym właśnie okresie życia. Istotnym problemem, na który napotykają uczeni zainteresowani tą problematyką oraz klinicyści pracujący z pacjentami geriatrycznymi, jest trudność z różnicowaniem objawów depresji od objawów zespołu otępiennego. Wynika to m.in. z tego, że w obrazie klinicznym LDD często pojawiają się takie symptomy, jak np. spowolnienie psychoruchowe czy tendencja do unikania odpowiadania na pytania zawarte w testach mierzących sprawność poszczególnych funkcji poznawczych, co przekłada się na niską wartość uzyskiwanych w nich wyników [26]. Wchodzą one w skład tzw. syndromu *pseudodemencji*, który może w swym obrazie bardzo przypominać otępienie [27]. Współwystępowanie i wzajemna zależność




**Ryc. 1.** Schemat rekrutacji pacjentów do badania.

symptomów depresji i zaburzeń funkcji poznawczych jest zresztą bardzo interesującym tematem dla licznych badaczy. Gao wraz z zespołem dokonali przeglądu badań mających na celu sprawdzenie, czy obecność objawów depresyjnych zwiększa ryzyko wystąpienia MCI bądź otępienia. Według wyników ich analizy, pacjenci depresyjni – w porównaniu do zdrowych badanych – w znaczącej części przypadków znajdują się w grupie podwyższonego ryzyka rozwoju demencji bądź innych, znaczących klinicznie zaburzeń funkcji poznawczych [9]. Z kolei z metaanalizy dokonanej przez Raimundo Mourao et al. wynika, że doświadczanie objawów depresji przez osoby z rozpoznanym MCI zwiększa ryzyko, że w przyszłości rozwinie się u nich zespół otępienny. Autorzy sugerują, że symptomy depresyjne rozumieć można zatem nie tylko jako odpowiedź emocjonalną danej osoby na uświadomienie sobie przez nią stopniowej utraty sprawności poznawczej, ale jako marker dysfunkcji poznawczych [28]. Na podstawie wyników kolejnej metaanalizy wykazano, że deficyty w obszarze funkcji poznawczych, a szczególnie funkcji wykonawczych, pamięci i uwagi, są często obecne w trakcie trwania epizodu depresyjnego, a część z nich (dotyczy to funkcji wykonawczych i uwagi) pozostaje, pomimo ustąpienia innych objawów zespołu depresyjnego. W oparciu o taką obserwację autorzy wysnuli wniosek, że obniżenie sprawności funkcji poznawczych powinno się uznawać za rdzenną cechę zaburzenia depresyjnego, nie mniej istotną niż np. obniżenie nastroju [29].

Niewątpliwie identyfikacja MCI stanowi wyzwanie kliniczne, a właściwa ocena stanu funkcjonowania poznawczego ma kluczowe znaczenie dla dalszego procesu diagnostyczno-terapeutycznego. Wobec dużych rozbieżności wyników badań dotyczących predyktorów MCI autorzy niniejszej pracy postawili za cel analizę zależności między czynnikami demograficznymi i klinicznymi a występowaniem łagodnych zaburzeń poznawczych w populacji osób po 60. roku życia w różnych grupach wiekowych, którzy uczestniczyli w krakowskim projekcie geriatrycznym.

## MATERIAŁ I METODY

Badani rekrutowani do badania byli uczestnikami projektu pt.: „Realizacja Projektu Diagnostyki, Profilaktyki Geriatrycznej z wykorzystaniem elementów Teleopieki sposobem lepszego dostosowania systemu opieki zdrowotnej do potrzeb szybko rosnącej populacji osób powyżej 60 roku życia" dofinansowanego przez Norweski Mechanizm Finansowy na lata 2009–2014 i Mechanizm Finansowy Europejskiego Obszaru Gospodarczego na lata 2009–2014 realizowanego przez Nową Rehabilitację Sp. z o.o. w Centrum Medyczno-Rehabilitacyjnym w Krakowie. Wszyscy uczestnicy wyrazili zgodę na udział w badaniu. Łącznie do badania włączono 1001 osób. Kryterium włączającym do badania był wiek powyżej 60 lat. Kryteriami wyłączenia z niniejszej analizy były: obecność chorób neurologicznych i/lub psychiatrycznych, uzależnienie od alkoholu i/lub leków, upośledzenie ogólnej sprawności poznawczej (osoby, które uzyskały 23 punkty lub mniej w Krótkiej Skali Oceny Stanu Psychicznego – (MMSE – *Mini–Mental State Examination*)). Po uwzględnieniu braków danych grupę badaną stanowiło

**Tabela 2.** Analiza regresji logistycznej zmiennych związanych z MCI.

| | | MCI | |
|---|---|---|---|
| **Zmienne** | **Wald $\chi^2$ test** | **OR (95% CI)** | **p** |
| *Model 1: Cała grupa wiekowa (n=817)* | | | |
| Wiek (lata) | 24,21 | 1,09 (1,05–1,13) | < 0,001 |
| Poziom wykształcenia (lata) | 67,97 | 0,75 (0,69–0,81) | < 0,001 |
| Chi-kwadrat ( $\chi^2$) | | 123,03 | |
| p | | < 0,001 | |
| *Model 2: Młodsza grupa wiekowa (n=675)* | | | |
| Wiek (lata) | 5,22 | 1,09 (1,02–1,17) | < 0,05 |
| Poziom wykształcenia (lata) | 50,62 | 0,73 (0,67–0,79) | < 0,001 |
| Geriatryczna Skala Oceny Depresji[2] | 3,93 | 1,09 (1,01–1,18) | < 0,05 |
| Chi-kwadrat ( $\chi^2$) | | 81,35 | |
| p | | < 0,001 | |
| *Model 3: Starsza grupa wiekowa (n=142)* | | | |
| Wiek (lata) | 7,01 | 1,18 (1,05–1,34) | < 0,01 |
| Poziom wykształcenia (lata) | 12,72 | 0,79 (0,71–0,91) | < 0,001 |
| Chi-kwadrat ( $\chi^2$) | | 24,13 | |
| p | | < 0,001 | |

MCI – *mild cognitive impairment.*

817 osób (Ryc. 1). Dane kliniczne i demograficzne zebrano podczas wywiadu oraz na podstawie dokumentacji medycznej przedstawionej przez badanego.

Rozpoznania kliniczne zostały ustalone na konsylium przez interdyscyplinarny zespół składający się ze specjalistów z zakresu geriatrii, neurologii, chorób wewnętrznych, kardiologii, neuropsychologii, psychologii oraz fizjoterapii. Ocenę poziomu niezależności w zakresie podstawowych czynności codziennego życia (ADL – *Activities of Daily Living,*) [30] oraz złożonych czynności codziennego życia (IADL – *Instrumental Activities of Daily Living*) [31] wykorzystywano jako miarę stanu funkcjonalnego każdego badanego. Wskaźnik masy ciała (*body mass index, BMI*) obliczono według wzoru: BMI= masa ciała [kg]/(wzrost [m])2.

W celu oceny poziomu nasilenia objawów depresyjnych zastosowano skróconą 15-punktową Geriatryczną Skalę Oceny Depresji (GDS-SF – *Geriatric Depression Scale- Short Form*). Skala jest stosowana jako przesiewowe narzędzie umożliwiające dokonanie oceny nasilenia symptomów depresji u osób w podeszłym wieku [32]. Punktacja przedstawia się następująco: wynik od 0 do 5 punktów oznacza brak objawów depresji, z kolei wynik od 6 do 15 punktów wskazuje na obecność objawów depresyjnych.

MCI zdiagnozowano zgodnie z kryteriami wyszczególnionymi przez Winblad et al. [11], które są następujące: i) nie stwierdza się otępienia, (ii) stwierdza się osłabienie funkcji poznawczych oceniane obiektywnie (za pomocą odpowiednich narzędzi) lub subiektywnie (zgłaszane przez pacjenta lub osoby z jego otoczenia) połączone z obiektywnymi deficytami funkcjonowania poznawczego, (iii) zachowana jest zdolność do wykonywania czynności życia codziennego, a wykonywanie złożonych czynności instrumentalnych jest albo nienaruszone albo minimalnie osłabione. Obiektywne deficyty funkcjonowania poznawczego zdefiniowano jako wynik 1,5 SD lub więcej poniżej średniej w całej grupie badanej. Z grupy 817 badanych 148 osób spełniało kryteria MCI.

Wszystkie osoby badane zostały poddane przesiewowej ocenie funkcjonowania poznawczego za pomocą MMSE [16], oraz *Addenbrooke's Cognitive Examination*-III (ACE--III) [33]. Do oceny pamięci epizodycznej wykorzystano Test Piętnastu Słów Reya (*AVLT – Auditory Verbal Learning Test*) [34]. Do oceny sprawności językowej wykorzystano Test Fluencji Słownej (VFT – *Verbal Fluency Tests*) [35]. Do oceny funkcji wzrokowo-przestrzennych wykorzystano Test Rysowania Zegara (CDT – *Clock Drawing Tes,*) [36]. Test Powtarzania Cyfr Wprost i Wspak (DST –*Digit Span Test,*) użyto do oceny uwagi i pamięci operacyjnej [35]. Test Łączenia Punktów (TMT – *Trail Making Test*) zastosowano do oceny funkcji wykonawczych [37].

## ANALIZA STATYSTYCZNA

W analizie wykorzystano elementy statystyki opisowej. Wyniki zostały przedstawione jako wartości średnie dla grup z odchyleniem standardowym SD lub jako wartości procentowe. W celu oceny normalności rozkładu analizowanych zmiennych zastosowano test Shapiro-Wilka. W porównaniach międzygrupowych zastosowano test t-Studenta, a w przypadku niespełnienia założenia normalności test U Manna-Withney'a. Dla porównania dwóch zmiennych kategorialnych wybrano test chi-kwadrat. W drugim etapie

przeprowadzono analizę regresji logistycznej wieloczynnikowej, obejmującej zarówno parametry demograficzne, jak i kliniczne w celu określenia związku analizowanych czynników z dysfunkcjami poznawczymi. Zmienną zależną był status poznawczy, a jako zmienne niezależne wprowadzano czynniki, które były istotne w modelach regresji jednoczynnikowej. Jako istotne przyjęto wyniki dla których p <0,05. Analizę statystyczną przeprowadzono za pomocą Statistica 13 PL.

## WYNIKI

W pierwszym etapie analizy porównano pod względem czynników demograficznych i klinicznych grupę MCI i grupę o prawidłowym funkcjonowaniu poznawczym. Grupa MCI różniła się od grupy kontrolnej pod względem wieku (p <0,001), poziomu wykształcenia (p <0,001) i poziomu nasilenia objawów depresyjnych (p <0,001). Osoby z MCI były starsze, mniej wykształcone i miały wyższy poziom objawów depresyjnych. Co interesujące, nie zaobserwowano różnic międzygrupowych w zakresie występowania chorób przewlekłych (Tab. 1). W drugiej części przeprowadzono analizę regresji logistycznej w trzech grupach wiekowych (cała grupa MCI, MCI≤74. roku życia, MCI≥75. roku życia). Przeprowadzona analiza wykazała, że niezależnie związane z MCI są wiek (OR=1,09; 95% CI: 1,05–1,13) oraz poziom wykształcenia (OR=0,75; 95% CI: 0,69-0,81) w całej grupie wiekowej. Każdy rok życia powyżej 60. roku życia zwiększa szansę MCI o 9%, natomiast każdy ukończony rok edukacji zmniejsza szansę MCI o 25%. Model wielokrotny był istotnie różny w porównaniu do modelu tylko z wyrazem wolnym ($\chi^2$=123,03; p<0,001). W grupie młodszej MCI wykazano, że wiek (OR=1,09; 95% CI: 1,02–1,17), poziom wykształcenia (OR=0,73; 95% CI: 0,67–0,79) oraz poziom nasilenia objawów depresyjnych (OR=1,09; 95% CI: 1,01–1,18) są niezależnie związane z MCI. W młodszej grupie MCI każdy rok życia powyżej 60. roku życia zwiększa szansę MCI o 9%, każdy ukończony rok edukacji zmniejsza szansę MCI o 27%, z kolei każdy punkt na skali GDS zwiększa szansę MCI o 9%. Model wielokrotny był istotnie różny w porównaniu do modelu tylko z wyrazem wolnym ($\chi^2$=81,35; p<0,001). W najstarszej grupie MCI, zarówno wiek (OR=1,18; 95% CI: 1,05–1,34), jak i poziom wykształcenia (OR=0,79; 95% CI: 0,71–0,91) okazały się niezależnie związane z MCI. Każdy rok życia zwiększa szansę MCI o 18%, a każdy rok edukacji zmniejsza szansę MCI o 21%. Model wielokrotny był istotnie różny w porównaniu do modelu tylko z wyrazem wolnym ($\chi^2$=24,13,03; p<0,001). Wyniki przeprowadzonych analiz przedstawiono w tabeli 2.

## DYSKUSJA

W świetle przeprowadzonych badań oraz wniosków sformułowanych przez innych autorów, można stwierdzić, że starszy wiek i niższy poziom wykształcenia są niezależnie związane z MCI [39, 40]. Dotychczasowe badania dotyczące metod obrazowania [12], badań biochemicznych [13] oraz analiz epidemiologicznych [14] dowodzą, że hipoteza rezerw poznawczych, rozumianych jako poziom wykształcenia, może mieć znaczenie w rozumieniu funkcjonowania poznawczego osób z MCI. Potencjalny związek tych rezerw w przebiegu choroby u osób z MCI jest tematem ważnym i wartym analizy. W doniesieniach dotyczących postępu zaburzeń poznawczych u osób z chorobą Alzheimera i wyższym poziomem edukacji można znaleźć sprzeczne wyniki – od wolniejszego przebiegu deterioracji [15], braku pogorszenia [40], po szybsze pogorszenie [18, 19, 41]. W grupie osób z MCI i dłuższym okresem edukacji, Vadikolias i in. [17] wykazali wolniejszy przebieg pogarszania się funkcji poznawczych obejmujących werbalne i niewerbalne zadania podczas roku obserwacji. Analogicznie, pozytywny wpływ liczby lat edukacji znalazł potwierdzenie w badaniu Fritsch et al. [15]. Badania te wykazują korzystny wpływ rezerw poznawczych na sprawność poznawczą i pozostaje w zgodzie z wynikami otrzymanymi w niniejszym badaniu, że każdy ukończony rok edukacji zmniejszał ryzyko MCI. Wyniki te potwierdzają hipotezę rezerw poznawczych, które mogą mieć wpływ nie tylko na początek wystąpienia objawów, ale i na tempo pogarszania się funkcjonowania poznawczego.

Co interesujące, wyniki przeprowadzonego badania pokazały, że objawy depresyjne zwiększały szansę wystąpienia MCI jedynie w młodszej grupie osób. Związek między poziomem nasilenia objawów depresyjnych a zaburzeniami poznawczymi ma złożony charakter. W literaturze nie ma zgodności w kwestii ustalenia związku między depresją – MCI – a otępieniem [42]. Niektórzy badacze są zdania, że depresja stanowi istotni czynnik ryzyka MCI oraz otępienia [9]. Inne badania sugerują, że obecność depresji może także zwiększać ryzyko progresji u chorych z MCI do otępienia [28]. Co więcej, udowodniono, że w zaburzeniach depresyjnych obserwuje się osłabienie funkcji poznawczych, szczególnie funkcji wykonawczych [29, 43]. Nasuwa się pytanie, czy objawy depresyjne mogą stanowić wczesną manifestację, a nie czynnik ryzyka otępienia? Jak trafnie podkreślili Panza i współpracownicy [44] występowanie depresji wieku podeszłego, MCI i otępienia może stanowić kliniczne kontinuum. Kontynuując powyższe rozważania, można przyjąć za innymi autorami, że depresja jest zarówno czynnikiem ryzyka, objawem prodromalnym, jak również chorobą współwystępującą z otępieniem [45]. W niniejszym badaniu w grupie osób młodszych poziom nasilenia objawów depresyjnych był niezależnie związany z MCI. Być może objawy depresyjne w tej grupie były efektem zauważania przez pacjentów obniżania się ich sprawności poznawczej, więc elementem reaktywnym względem trudności poznawczych.

Warto podkreślić, że pojawienie się depresji po raz pierwszy w wieku podeszłym może stanowić prodromalny objaw AD, natomiast nawracająca depresja może stanowić zwiększone ryzyko otępienia [46]. Drugą z przywołanych zależności tłumaczy się między innymi koncepcją neuroprogresji depresji, która mówi o tym, że wraz z czasem trwania i rozwojem choroby dochodzi do postępujących nieprawidłowości neurobiologicznych. Zmiany te zostają zapisane na poziomie

epigenetycznym, mogą być trwałe i stanowić swoisty ślad pamięciowy, który wzmaga podatność jednostki na doświadczenie kolejnych epizodów depresji [47]. Co więcej, epizody te są w coraz większym stopniu niezależne od pojawiających się stresorów, wiążą się za to z narastającymi zaburzeniami funkcjonowania poznawczego oraz ze zmianami strukturalnymi mózgu [48, 49]. Najczęściej obserwuje się zmniejszenie objętości hipokampa [50, 51], poza tym badacze zwracają uwagę na zmiany w obrębie ciała migdałowatego, kory oczodołowo-czołowej, przedniego zakrętu obręczy, zwojów podstawy i przysadki mózgowej [51]. W piśmennictwie znaleźć można także doniesienia mówiące wprost o tym, że liczba przebytych epizodów depresji wiąże się z ryzykiem rozwoju otępienia. Przykładowo Kessing i Andersen [52] przedstawili dane, z których wynika, że przebycie 4 epizodów depresji wiąże się z dwukrotnie większym ryzykiem rozwoju otępienia w ciągu życia, a każdy kolejny nawrót choroby jeszcze to ryzyko zwiększa. Ciekawym zagadnieniem, które warto by uwzględnić w dalszych badaniach wydaje się być zatem porównanie sprawności funkcji poznawczych u pacjentów z wieloletnim rozpoznaniem choroby afektywnej i tych, których w momencie badania można by uznać za depresyjnych, ale nie posiadających doświadczenia depresji w swojej dotychczasowej biografii.

Niniejsze badanie zawiera pewne ograniczenia, dlatego należy je ostrożnie interpretować. Przekrojowy charakter badania powstrzymuje od wyciągania wniosków na temat potencjalnych czynników ryzyka MCI.

## WNIOSKI

Wyniki naszych badań pokazały, że zaburzenia depresyjne, jak i niższe wykształcenie wiążą się z obniżoną sprawnością funkcji poznawczych. Charakter związku między depresją a zaburzeniami poznawczymi w wieku podeszłym jest niewątpliwie złożonym zagadnieniem i wymaga dalszych badań prospektywnych. Stale rosnąca liczba osób w wieku senioralnym skłania do poszukiwania czynników ryzyka łagodnych zaburzeń funkcji poznawczych.

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**ORCID numbers:**
*Anna Rajtar-Zembaty - 0000-0002-1938-0555*
*Jakub Rajtar-Zembaty - 0000-0002-3853-568X*
*Katarzyna Olszewska - 0000-0001-6348-2527*

**Konflikt interesów**
*Autorzy deklarują brak konfliktu interesów.*

**AUTOR KORESPONDUJĄCY**
**Anna Rajtar-Zembaty**
Zakład Psychologii Lekarskiej
Katedra Psychiatrii
Mikołaja Kopernika 21A, 31-501 Kraków, Polska
e-mail: anna.maria.rajtar@gmail.com

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ORIGINAL ARTICLE
PRACA ORYGINALNA

# EFFECTS OF DIABETES MELLITUS ON REPARATIVE OSTEOGENESIS

**Oksana K. Melekhovets[1], Vira D. Tovazhnyanska[2], Iryna I. Yakovtsova[2]**
[1]SUMY STATE UNIVERSITY, SUMY, UKRAINE
[2]KHARKIV MEDICAL ACADEMY OF POSTGRADUATE EDUCATION, KHARKIV, UKRAINE

## ABSTRACT

**Introduction:** Chronic hyperglycemia as the main link in DM pathogenesis leads to systemic vessels and nerves lesion with chronic bone complications development consequently.
**The aim:** To evaluate influence of hyperglycemia on reparative osteogenesis after perforated tibial fracture in rats.
**Materials and methods:** A total of 30 white adult rats were subdivided into two groups: 15 healthy rats in Group 1 (control) and 15 rats with alloxan induced hyperglycemia in Group 2 (investigated) and were carried out of experiment on the 10th, 20th and 30th day after the fracture. Hyperglycemia in rats was verificated as the postprandial glycemic rate ≥ 8,0 mmol/l. Tibia diaphysis fracture was modeled by a cylindrical defect with a diameter of 2 mm with portable frezer. Morphological evaluation. A complex morphological studies included histological, morphometric and immunohistochemical examination.
**Results:** This is confirmed by an increase in MMP-9 expression in connective tissue, a decrease in TGF-β expression in all phases, an increase in the expression of CD3 and CD20 and a marked decrease in the expression of all vascular markers. During hyperglycemia, incomplete blood supply to the tissues occurs, necrosis of bone and soft tissues develop in the area of the fracture, the reparative reaction slows down considerably and manifests itself in the development of fibrous and, less commonly, cartilage tissue.
**Conclusions:** In hyperglycemia rats, there was a delay in the callus formation, a decrease in proliferation and ossification, and a slowdown in the processes of angiogenesis.

**KEY WORDS:** hyperglycemia, reparative osteogenesis, diabetes mellitus, perforated tibial

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## INTRODUCTION

International Diabetic Federation (IDF) notes that about 425 million individuals suffered from diabetes mellitus (DM) in 2017 and this amount will rise to 629 million in 2045 [1]. Chronic hyperglycemia as the main link in DM pathogenesis leads to systemic vessels and nerves lesion with chronic bone complications development consequently.

Complex general and local biological and biochemical changes occur in bone tissue restoration process in DM. They depend on the bone's blood supply, patient's age, general condition of body, and quality and type of treatment [2]. Bone's fracture is always accompanied by soft tissue damage.

Tissue regeneration is determined by genetic and epigenetic factors. The epigenetic factor consists of many components; hormonal status is one of the key ones. The slowing down of bone reparative processes during diabetes mellitus is caused by many mechanisms. In particular, glycosylation end products formation causes big effect on bone strength [3]. Also, diabetic polyneuropathy can lead to increased bone resorption, and micro- and macroangiopathy - disrupt the blood flow to the bones.

From literature data it is known that wound healing disorders in the first phase of inflammation cause impaired fibroblast proliferation and collagen synthesis. Delayed wound healing in diabetic patients may be due to a defect in the inflammatory response [4, 5]. Insulin deficiency has a great effect in the inflammation phase and less effect on collagen synthesis, as confirmed by the results of studies on tissue cell cultures. In vitro studies, decrease in calcification level and ossification of the newly formed tissue and disruption of cartilage formation under conditions of hormone deficiency were found. A special role in bone wound healing disorders has bone callus vascularization. Adequate microcirculation, through enhanced oxygenation, ensures the normal functioning of osteoblasts [6, 7]. Despite the prevalence of diabetes, the question of hyperglycemia effect on reparative osteogenesis at all its stages remains un-studied. The literature data are numerous and contradictory.

## THE AIM

The aim of our study was to evaluate influence of hyperglycemia on reparative osteogenesis after perforated tibial fracture in rats.

## MATERIALS AND METHODS

We conducted an experimental study on white rats, to study the effect of hyperglycemia at the stage of reparative osteogenesis after perforated tibial fracture. To study the histological features, 2 groups of rats weighing from 70 to 200 g were formed.

Group 1 - control: 15 healthy adult rats.

Group 2 - investigated: 15 rats with hyperglycemia, which was induced by alloxan. Hyperglycemia in rats was verificated as the postprandial glycemic rate ≥ 8,0 mmol /l. On day 7 of hyperglycemia, we modeled a fracture at the level of the lower third of tibia diaphysis by forming a cylindrical defect with a diameter of 2 mm by portable frezer.

Experimental animals were carried out of experiment on 1, 2 and 3 phases of osteogenesis, namely on the 10th, 20th and 30th day after the fracture (5 animals from each group at one time-point).

All animal manipulations, as well as their withdrawal from the experiment, required to regulatory documents (European Convention for the Protection of Vertebrate Animals (Strasbourg, 03.18.1986), Directive of the Council of the European Economic Society for the Protection of Vertebrate Animals (Strasbourg, 24.11.1986), the Law of Ukraine "On Medicines", 1996, Articles 7, 8, 12, the leadership of the PIT GSP (in 2008), GLP (2002), in accordance with the requirements and standards, the standard clause on issues Ethics of the Ministry of Health of Ukraine No. 690 of September 23, 2009).

For histological examination, one piece of soft tissue and bone was taken in the fracture zone. After cutting, it was fixed in a 10% formalin solution and underwent a decalcification procedure. For decalcification we used concentrated formic acid diluted with an equal amount of 70% alcohol. Then it was carried out on alcohols of increasing concentration and filled with paraffin. After serial sections 5–6 × 10–6 m thick were made, which were stained by hematoxylin and eosin using histological method. These microscopic preparations were used for a general assessment of tissues condition, microscopic examination of bone tissue, and morphometric research.

The study of morphometric parameters included the measurement of periosteum width, cell density in inner layer of periosteum at 1 $mm^2$, osteocytes density at 1 $mm^2$. Morphological evaluation also included immunohistochemical methods. We investigated immunohistochemical markers expression: Ki-67 to assess the proliferative activity of cells; MMP-9 - to determine the processes of collagen formation, TGF-β - to assess the ossification of soft callus; CD31, VEGF, CD34, eNOS and iNOS were studied to assess angiogenesis and the degree of vascularization; the composition of immunocompetent cells was assessed using CD3 (T-lymphocyte marker), CD20 - B-lymphocytes.

Demasking heat treatment was performed by boiling sections method in citrate buffer (pH 6.0). For the visualization of primary antibodies we used Mouse/Rabbit-PolyVue HRP/DAB DetectionSystems detection system (DiagnosticBioSystems, USA). DAB (diaminobenzidine) was used as the chromogen.

To assess immunohistochemical label level, a semi-quantitative scale was used: + - weak, ++ - moderate, +++ - strong reaction.

A complex of morphological studies was carried out on an Olympus BH-2 microscope (Japan) using a Baumer / optronic Type camera: CX05c and Olympus DP-Soft software (Version 3: 1) following by statistical analysis with Microsoft Excel 2010.

## RESULTS AND DISCUSSION

In the control group, a complete reparative bone regeneration had occurred with the formation of full bone structure, ensuring restoration of bone's anatomical shape and function, as evidenced by morphometric and immunohistochemical research methods.

In the first phase, surrounding tissues and bone tissue disintegration, an increase of periosteum, periosteum cells and osteocytes proliferation, which is necessary for transition to the second phase, was detected. Also we found large-focal lymphoid infiltration and newly formed small-caliber vessels. The activity of eNOS expression depends on the level of calcium in the cytosol of endotheliocytes, which, in our opinion, also indirectly argues in favor of normal bone healing. Expressed eNOS expression was determined, and iNOS expressed moderately.

In the second phase, tissue organization, lymphocytic infiltration, edema and cell proliferation were observed. It was especially seen in connective and cartilage tissues, which was confirmed by an increase of MMP-9 and Ki-67 expression. At the same time, the expression of TGF-β was moderate, as was the expression of all vascular endothelium markers (Fig.1).

In the third phase, massive bone marrows merged into a compact substance with wide bone canaliculi of primary osteons. In rats, a clear cortical layer was determined, the periosteum was clearly differentiated. We observed subsidence of inflammatory process, as well as the processes of angiogenesis. The calcified structures were clearly oriented, the areas of excessive regenerate bedding were in the process of resorption, which was confirmed by strong expression of TGF-β.

In the study of hyperglycemia group in the first phase, extensive zones of hemorrhages were observed in fracture zone and surrounding soft tissues, sometimes with the accumulation of hemosiderin granules. In many small and medium vessels were determined near-wall thrombi and focal congestion. The periosteum fibrous layer was markedly loosened. In the periosteum was found uneven plethora. When compared with the control group, its width was significantly increased ($p = 0.03$), due to edema and wrinkling of the structure. As in the control, near the fracture site in a compact substance, lacunae with resorption foci and rare osteons were found, but their number is lower than in the control (Fig. 2).

In osteons, numerous osteocytes were observed, their number tended to decrease. Bone cells and the inner layer of the periosteum proliferated, which was confirmed by moderate expression of Ki-67, in some fields of view the expression of this marker was weak. The proliferation index was $2.8 \pm 0.1$ ($p = 7.9892E-11$), and it was significantly reduced compared with the control group.

During immunohistochemical study with TGF-β, its expression was not observed. In soft tissues, virtually diffuse lymphoid infiltration was detected, which was confirmed by strong expression of CD3 and CD20 (Fig. 3).

MMP-9 expression, in contrast, was moderate, both in connective tissue and in cartilage, which was not observed

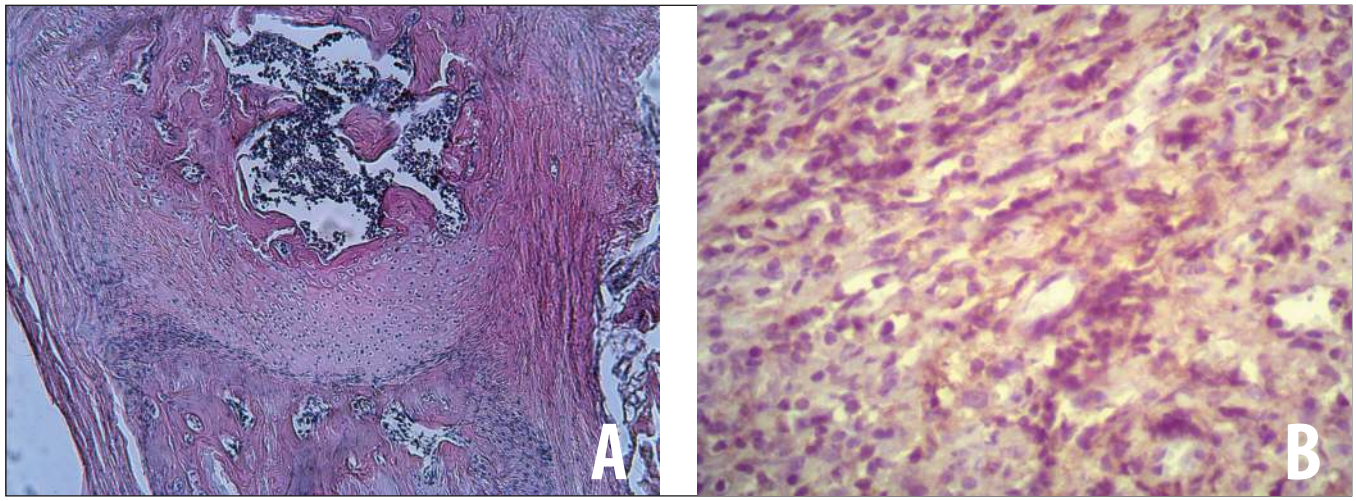


**Fig. 1.** A. The osteons structure in bone near the fracture site in control group rat in the first phase of reparative osteogenesis. Stained with hematoxylin and eosin, x100
B. Weak expression of TGF-β of rat bone in the control group in control group rat in the first phase of reparative osteogenesis. Indirect immunoperoxidase method using TGF-β, x400

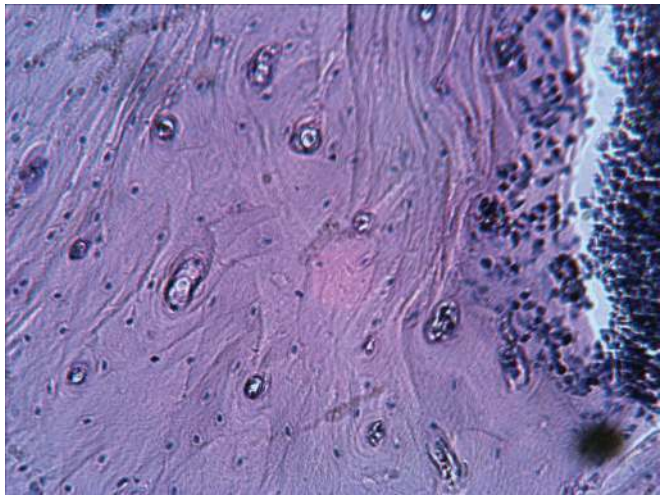

**Fig. 2.** The structure of rare osteons in bone near the fracture site in hyperglycemia group in the first phase of reparative osteogenesis. Stained with hematoxylin and eosin, x100

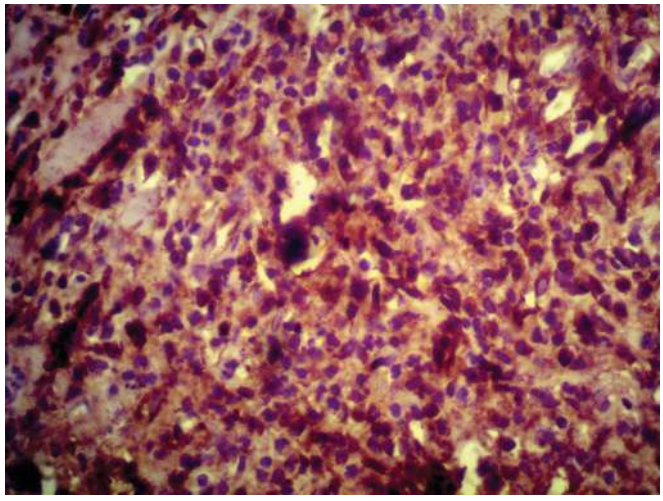

**Fig. 3.** Srong CD20 expression in soft tissues near fracture site in hyperglycemia group in the first phase of reparative osteogenesis. Indirect immunoperoxidase method using CD20, x400

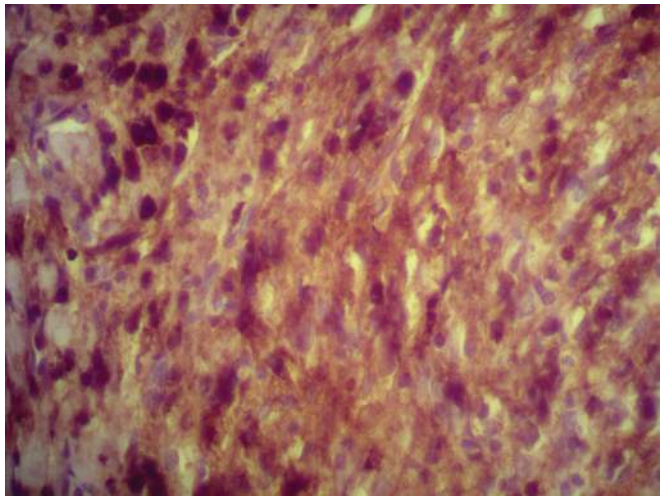

**Fig. 4.** Strong MMP-9 expression in hyperglycemia group in the third phase of reparative osteogenesis. Indirect immunoperoxidase method using MMP-9, x400

in the control group. When assessing vessel formation, weak expression of CD34 was detected, VEGF marker was found in small areas and also expressed weakly, while expression of CD31 was not detected at all. ENOS expression was reduced, however, iNOS expressed moderately.

In the second phase of reparative regeneration, beginning of soft bone callus formation was observed. Unlike healthy rats, osteoid tissue was formed in 40.0% (n = 2) of observations, and in 60.0% (n = 3) there was a fibrous structure of osteoid tissue and cartilage patches. The border between the fibrous layer of periosteum and connective tissue of paraosteum looked blurred. The periosteum was significantly ($p = 0.04$) wider than in the control group. As in the first phase in hyperglycemia rats, it was observed edematous. The cell density of periosteum inner layer tended to decrease, while the density of osteocytes was significantly reduced ($p = 0.06$) when compared with the control group. Lacunas with optically empty resorption

zones were observed in several fields of view in a compact bone substance. Outside the fracture, formed and, in some places, collapsing osteons with cells resembling osteocytes were detected.

Comparing to healthy rats, cell proliferation of periosteum and osteogenic tissue was less observed. The proliferation index was significantly reduced comparing with the control (p = 1.4082E-08). Lymphocytic infiltration was lower than in the first phase, however, it still remained large-focal with a tendency to merge foci. Active expression of CD3 and CD20 was observed.

During evaluating of angiogenesis, we observed mild CD34 expression and weak VEGF expression. IHC studies with CD31 also showed weak expression. At the same time, strong expression of iNOS was determined, and the expression of eNOS decreased.

In the third phase, in microscopic preparations of hyperglycemia rats, the onset of solid callus formation was observed. In the space between fragments, a small mesh of bone trabeculae was found, mainly from lamellar bone tissue. The width of the periosteum averaged 149.5 ± 3.2 μm. Periosteum inner layer cell density and the number of osteocytes tended to decrease, when compared with the control group, but when compared with rats of the same group, the second phase, on the contrary, tended to increase. The index was also significantly lower than in healthy rats (p = 7.0767E-07). Expression of MMP-9 was moderately active in cartilage and connective tissue (Fig. 4).

IHC studies with TGF-β showed moderate expression in several fields of view. In hyperglycemia group inflammatory process subsided, but infiltration still remained focal with a tendency for lymphocyte accumulation to be perivascular.

Immunohistochemistry method showed strong CD34 expression in the vascular endothelium. When IHC assay with VEGF, expression of this marker remained moderate, as in the second phase, CD31 expressed weakly. In IHC studies with eNOS and iNOS markers, their expression level was about the same.

## CONCLUSIONS

The results demonstrated that in hyperglycemic rats, there was a delay in the callus formation, a decrease in proliferation and ossification, and a slowdown in the processes of angiogenesis. This is confirmed by an increase in MMP-9 expression in connective tissue, a decrease in TGF-β expression in all phases, an increase in the expression of CD3 and CD20 and a marked decrease in the expression of all vascular markers. Due to hyperglycemia, incomplete blood supply to the tissues occurs, necrosis of bone and soft tissues develop in the area of the fracture, the reparative reaction slows down considerably and manifests itself in the development of fibrous and, less commonly, cartilage tissue.

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**Authors' contributions:**
*According to the order of the Authorship.*



**ORCID numbers:**
*Oksana K. Melekhovets - 0000-0001-9031-7009*
*Vira D. Tovazhnyanska - 0000-0002-4340-9186*
*Iryna I. Yakovtsova - 0000-0002-1027-9215*



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## CORRESPONDING AUTHOR

**Oksana K. Melekhovets**
Sumy State University
1 Sanatorna Str., 40018, Sumy, Ukraine
tel: +380667122929
e-mail: melekhovets.oksana@gmail.com



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ORIGINAL ARTICLE
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# ADD-ON GRADE-RANKING SCALE FOR ASSESSING THROMBOTIC RISK IN PATIENTS WITH ISCHEMIC HEART DISEASE AND PERCUTANEOUS CORONARY ANGIOPLASTY

**Nadezhda V. Storozhuk[1], Aleksey B. Panasenko[2], Boris G. Storozhuk[1], Tatiana V. Dovgalyuk[3]**
[1]NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE
[2]VINNYTSIA MYKHAILO KOTSIUBYNSKYI STATE PEDAGOGICAL UNIVERSITY, VINNYTSIA, UKRAINE
[3]INSTITUTE OF REHABILITATION OF THE DISABLED OF NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE

## ABSTRACT

**Introduction:** The anticipation of the development of thrombotic complications in coronary angioplasty patients helps to prevent this dangerous complication. Development of the available informative scales on the basis of mathematical methods taking into account the main clinical and biochemical parameters significantly simplifies the classification of patients in terms of thrombotic risk.

**The aim** of the paper is to concentrate information on the state of hemostasis in the studied category of patients using the method of the main components and to obtain a matrix with minimal loss of information, which is convenient for analysis and the creation of a grade-ranking scale.

**Materials and methods:** Data of 70 patients with coronary heart disease and percutaneous coronary angioplasty were analyzed. The level of soluble fibrin, fibrinogen, D-dimer, protein C, and ratios rf/dd×100 were determined, and also the presence of diabetes mellitus and restenosis in the history was considered.

**Results:** As a result of a stepwise study using the method of the main components, in the first stage two most singular matrices were obtained that describe 70% of the entire data variance (one of them is the component rf+dd, and the second one is fg+pc), which led to the first indicator of the level of thrombotic risk. At the second stage, the level of thrombotic risk was clarified, taking into consideration the presence of diabetes and history of restenosis, and it is recommended to use a second indicator for its determination (rf/dd×100).

**Conclusions:** The presented grade-ranking scale scale allows the anticipation of the development of thrombotic complications in the studied category of patients with high probability.

**KEY WORDS:** hemostasis, thrombotic risk, coronary angioplasty, method of main components

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## INTRODUCTION

For clinical and biochemical studies of hemostasis, a significant array of investigated parameters and indicators is characteristic, which is caused by the desire to improve the information component in relation to external and internal factors that affect the condition of the coagulating blood system. In the meantime, large masses of initial clinical data cause considerable difficulty in their processing and interpretation, since, on the one hand, they are directed to the completeness and depth of the research, and, on the other hand, erode the existing interrelationships between the results of the study. The mentioned problem is solved by methods of compaction of information using the method of the main components, as one of the methods of factor analysis, which allows obtaining a convenient matrix analysis with a minimum loss of information [1].

## THE AIM

To obtain the integral biochemical and clinical parameters characterizing the state of hemostasis in patients with ischemic heart disease (IHD) and performed percutaneous coronary angioplasty for the development of an add-on grade-ranking scale for assessing the thrombotic risk, i.e. finding algorithms for the classification of patients depending on the assessment of the formidability and risk of thrombotic complications (average, high, very high).

## MATERIALS AND METHODS

The data of 70 patients, determined by random sampling, who underwent necessary biochemical and clinical examination underwent surgery and percutaneous coronary angioplasty, are included in the matrix. To biochemical laboratory parameters belong the data of soluble fibrin (rf) (mkg/ml) as a measure of «pre-thrombosis»; fibrinogen (fg) (mg/ml) as the main protein of the coagulation system; protein C (pc) (in % relative to normal index) as a natural anticoagulant; D-dimer (dd) (ng/ml) as a «post-thrombosis» indicator, which characterizes the presence of thrombus and fibrinolytic activity; to the clinical data – the presence of type II diabetes mellitus (DM)

and restenosis (R) in the medical history [2, 3, 4, 5]. The latter was taken into account in connection with a number of scientific studies that indicate that the presence of these clinical factors may significantly affect the development of thrombogenesis [6, 7].

Methodologically, the research was carried out in three stages.

In the first stage, using the method of the main components to the initial biochemical data, the percentage of the total dispersion described by each component was analyzed. After the analysis it was decided to leave only the first two main components. Subsequently, by expert evaluation, groups of patients with the average, high and very high risk of stent thrombosis were pre-allocated and the values of the first and second main components for each of the selected groups of patients were determined.

The measure of thrombotic risk was determined by the remoteness of the biochemical parameters from the normal values. To determine the measure of this distance in the space determined by the first two main components, the Minkowski metric with weighted coefficients [8][1] was used.

After performing the inverse transformation by the ratios for calculating the values of the main components, the formulas for assessing the degree of thrombotic risk in terms of absolute values of the four indices: rf, fg, dd i pc were established. Also, the value of the grade index $B_1$ (which is equal to «1» for an average risk level, «2» – for high, «3» – for very high) was determined.

In the second and third stages, the grade scale was specified by an additional indicator, namely: the presence of diabetes mellitus and/or restenosis. For these patients, the values of score points $B_2$ and $B_3$ were obtained.

Eventually, the final indicator was determined by the formula:

$P = \max\{B_1, \alpha B_2, \beta \cdot B_3\}$

where α = 1, if the patient is diagnosed with diabetes mellitus (0 – otherwise), β = 1, if the patient is diagnosed with restenosis (0 – otherwise), with:

P = 1 – average thrombotic risk;

P = 2 – high thrombotic risk;

P = 3 – very high thrombotic risk.

## RESULTS AND DISCUSSION

Table I presents the correlation data of selected indicators. Before applying the method of the main components, we perform data transformation, centering them relatively to «0» and making the standard deviation equal to «1». The latter is carried out according to the formula:

$$z = \frac{x - \mu}{\sigma}$$

where μ is the mean value of the parameter x,

σ is its standard deviation.

As an example, we will take the indictors of two random patients after the conversion (Table II).

Let X be a matrix with 70 lines and 4 columns with the obtained data. To determine the main components, we diagonize the matrix of covariates $X^T X$ (Table III). We obtain the two largest singular values of the matrix X, which describe 70% of the entire data variance: $\sigma_1 = 11{,}24$, $\sigma_2 = 8{,}34$. The proper vectors corresponding to these singular values are as follows:

$\boldsymbol{\nu}_1 = (0{,}61; 0{,}39; 0{,}63; -0{,}27)$

$\boldsymbol{\nu}_2 = (0{,}11; 0{,}51; -0{,}07; 0{,}84)$

The value of the i-th main component is calculated by the formula:

$$C_i = \frac{rf - \mu_1}{\sigma_1} x_{1(i)} + \frac{fg - \mu_2}{\sigma_2} x_{2(i)} + \frac{dd - \mu_3}{\sigma_3} x_{3(i)} + \frac{pc - \mu_4}{\sigma_4} x_{4(i)},$$

where rf, fg, dd, pc – are respectively the values of soluble fibrin, fibrinogen, D-dimer and protein C;

$\mu_1, \mu_2, \mu_3, \mu_4$ – mean values according to these indicators;

$\sigma_1, \sigma_2, \sigma_3, \sigma_4$ – their root mean square deviations;

$x_{1(i)}, x_{2(i)}, x_{3(i)}, x_{4(i)}$ – coordinates of the *i*-th of the proper vector $\nu_i$.

The projection of data on a plane, which is determined by the proper vectors of two components with the boundary of the area of the middle level of thrombotic risk, is presented in Fig. 1.

Let us analyze the obtained results. All the indicators significantly affect the value of the first main component, but above all – it is equally soluble fibrin and D-dimer. The incremental value of this component indicates that the values of soluble fibrin and D-dimer significantly differ from the norm, and the compensatory mechanism as an anticoagulant of protein C is insufficient, and patients with this value of the first main component should be classified as having high or very high thrombotic risk.

The value of the second main component depends significantly on the protein C and fibrinogen, while the levels of soluble fibrin and D-dimer do not actually affect their values. The high value of this indicator with a low first major component in a number of patients may indicate an elevated protein C level, which is positive, taking into account the prediction of possible thrombotic complications. Instead, the low value of this component (less than -1) indicates low protein C content, and patients with this value can not be classified as an intermediate level of thrombotic risk.

Let us add the extent of distance from this area, on which we will evaluate the level of thrombotic risk. For convenience, we use the Minkowski distance with weighted coefficients. We calculate the distance to the centre of the median risk area, which we defined as (-1; 0,5), and weighted the coefficients are to be assigned 2 and 1, based on the expert estimates (the area highlighted in Figure 1 is twice elongated along the second component than the first one).

Thus, for each point (*x; y*) we attribute the number of its distance from the centre of the region with an average thrombotic risk, which is calculated by the formula:

$R = 2|x + 1| + |y - 0{,}5|$

[1] – the mathematical part of the work was performed with the help of consulting company «Nestlogic Inc» (www.nestlogic.com).

**Table I.** Correlation matrix of the studied indicators.

| № | Indicator | Soluble fibrin (rf) | Fibrinogen (fg) | D-dimer (dd) | Protein C (pc) |
|---|---|---|---|---|---|
| 1 | rf | | 0,26 | 0,57 | -0,11 |
| 2 | fg | 0,26 | 1 | 0,24 | -0,02 |
| 3 | dd | 0,57 | 0,24 | 1 | -0,22 |
| 4 | pc | -0,11 | -0,02 | -0,22 | 1 |

**Table II.** The value of standard indicators of the studied patients (№№ 8, 28) after the conversion.

| № | № of the patient | Biochemical indicators | | | | Value of biochemical indicators after data centering | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | rf | fg | dd | pc | rf | fg | dd | pc |
| 1 | 8 | 14,5 | 5,6 | 151 | 97 | 2,75 | 0,87 | 3,33 | 0,18 |
| 2 | 28 | 3,1 | 3,6 | 20 | 86 | -047 | -0,50 | -0,62 | -0,47 |

**Table III.** Coordinate indices of the vectors of the main components.

| № | № of the component | % described dispersion | Singular value | Proper vectors |
|---|---|---|---|---|
| 1 | 1st | 45,1 | 11,24 | (0,61; 0,39; 0,63; -0,27) |
| 2 | 2nd | 24,9 | 8,34 | (0,11; 0,51; -0,07; 0,85) |
| 3 | 3rd | 19,7 | 7,43 | (-0,39; 0,76; -0,28;-0,43) |
| 4 | 4th | 10,3 | 5,38 | (0,68; -0,01; -0,72; -0,15) |

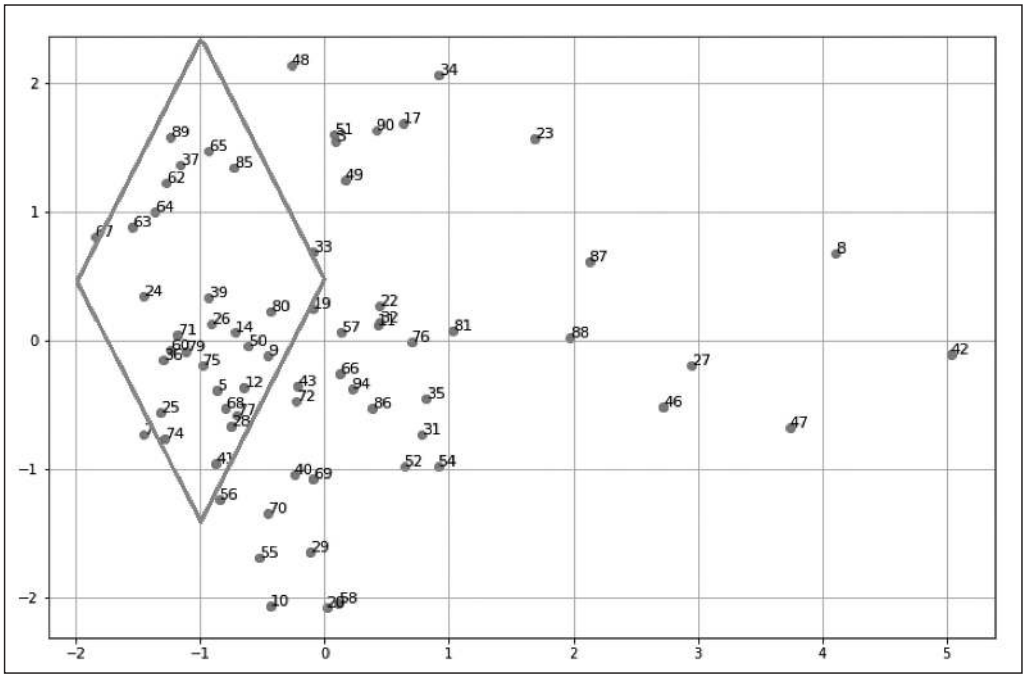

**Fig. 1.** Projection of data on the plane by the first two main components with the boundary of the site which corresponds to the average thrombotic risk.

The resulting number below will be called the first indicator of thrombotic risk.

For instance, the value of the first two components for patient №3 is 0,09 and 1,55, respectively. Therefore, the value of the first indicator of thrombotic risk for this patient will be equal to:

$R = 2|0{,}09 + 1| + |1{,}55 - 0{,}5| = 3{,}23$

At the same time, for example, for patient №25 the value of the first two main components is equal to -1,32 and -0,56, so the value of the first index of thrombotic risk is equal to:

$R = 2|-1{,}32 + 1| + |-0{,}56 - 0{,}5| = 1{,}7$

The classification of patients in accordance with the level of thrombotic risk according to the value of the first indicator $R$ will be carried out according to the following scheme:

- if $0 \le R < 2{,}5$ – average thrombotic risk;
- if $2.5 \le R < 4{,}5$ – high thrombotic risk;
- if $R \ge 4{,}5$ – very high thrombotic risk.

We perform a reverse transformation, which allows us to determine the level of thrombotic risk without calculating the values of the main components. To do

this, we use the mean values of each of the indicators, the standard deviation, and the coordinates of the main component vectors, which are presented in Table III. We substitute these values for the formula for calculating the first main component and, after simplifications, we obtain:

$C_1 \approx 0{,}17 \cdot rf + 0{,}27 \cdot fg + 0{,}019 \cdot dd - 0{,}015 \cdot pc - 1{,}259$

Hereupon, we calculate the value of the first summand in the formula for deriving the first indicator of the level of thrombotic risk:

$2|C_1 + 1| = |0{,}34 \cdot rf + 0{,}54 \cdot fg + 0{,}04 \cdot dd - 0{,}0318 \cdot pc - 0{,}518|$

If this value appears to be higher than 4,5, then the value of the second component can not be calculated, since unequivocally the patient must be classified into a category with a very high thrombotic risk.

By analogy we calculate the value of the second main component:

$C_2 \approx 0{,}031 \cdot rf + 0{,}352 \cdot fg - 0{,}0021 \cdot dd + 0{,}05 \cdot pc - 6{,}3$

$|C_2 - 0{,}5| = |0{,}031 \cdot rf + 0{,}352 \cdot fg - 0{,}0021 \cdot dd + 0{,}05 \cdot pc - 6{,}8|$

Thus, the value of the first indicator of thrombotic risk can be calculated by the formula:

$R = 2|C_1 + 1| + |C_2 - 0{,}5| = |0{,}34 \cdot rf + 0{,}54 \cdot fg + 0{,}04 \cdot dd - 0{,}0318 \cdot pc - 0{,}518| + |0{,}031 \cdot rf + 0{,}352 \cdot fg - 0{,}0021 \cdot dd + 0{,}05 \cdot pc - 6{,}8|$

We define a relatively convenient scale for assessing thrombotic risk based on the performed research. For this purpose, we will carry out the normalization of the first indicator of thrombotic risk, dividing the two parts of the last equality with a factor of 0,0318 (with the change in pc in the first clause will be = 1) and we will make certain roundings. We get the following modified indicator:

$R' = |10 \cdot rf + 20 \cdot fg + 1{,}25 \cdot dd - pc - 20| + |10 \cdot fg + 1{,}5 \cdot pc - 215|$ (1)

After calculations we get a modified scale in which:

- if $0 \le R' < 80$ – the average thrombotic risk ($B_1 = 1$);
- if $80 \le R' < 140$ – high thrombotic risk ($B_1 = 2$);
- if $R' \ge 140$ is a very high thrombotic risk ($B_1 = 3$).

When comparing the values of the first indicator of thrombotic risk and its modification, the compliance is 92,9%, that is, the prognostic value is practically unchanged.

Thus, the first stage is reduced to calculating the value of R' by the formula (1) and finding the obtained value of the ball $B_1$.

At the second stage, the level of thrombotic risk was determined, taking into account the presence of diabetes mellitus (DM) and diagnosed restenosis. Let us analyze more detailed indicators of patients with diabetes and restenosis. Of the 70 patients who reached the final sample, 18 had diabetes mellitus and 23 patients were with history of restenosis, herewith eight patients were diagnosed with DM and restenosis.

Since the rank correlation coefficient, determined by us earlier in the general group among other indicators, is significantly higher than with rf and is positive (r = 0,28), and in the group with diabetes – with dd, which has a negative value (r = -0,51), then with the aim of identifying stronger correlation bonds it is possible to add another integral index, namely: ratio rf/dd×100. Given that rf is an indicator of «prethrombosis» and dd is «postthrombosis», the indicated ratio of these indices may demonstrate the state of the coagulating and antigreshing hemostasis units.

The obtained data testify that in the group of patients with diabetes mellitus, a rather high direct correlation between the ratio rf/dd and the diagnosed restenosis (r = 0,67) compared with the general group (r = 0,35) was distinguished. Consequently, the ratio of rf/dd can be taken as an additional integral indicator that would characterize the degree of thrombotic risk for patients with diabetes mellitus.

Analyzing the results, obtained in the patients in this sample, who were diagnosed with restenosis (n = 23) and those without restenosis (n = 47) for 18 months, it was found that for patients with restenosis, the mean ratio of rf/dd×100 is 21,5 with a standard deviation of 11,5, and for patients without restenosis the mean value is 14,3 with a standard deviation of 12,6.

Thus, when the actual standard deviation is virtually unchanged, there is a significant difference between the mean values of rf/dd×100 in these groups.

Summarizing the aforementioned, it is possible to conclude that when a patient is diagnosed with diabetes, the second indicator of thrombotic risk should be recommended, namely: rf/dd×100. At the same time, according to our estimates:

- if the indicator R" > 8, , then the patient should be classified into a group with an average thrombotic risk (then $B_2 = 1$);
- If R' is in the range of 8 to 16, then the patient should be classified into a group with a high thrombotic risk ($B_2 = 2$);
- if R" <16, , then the patient should be classified into a group with a very high thrombotic risk ($B_2 = 3$).

If the patient is diagnosed with restenosis, then, again, it is recommended to determine the second indicator of thrombotic risk and obtain the value of $B_2$ on the same scale.

As noted, the final indicator is determined by the formula:

$P = \max(B1, \alpha \times B2, \beta \times B3)$

where $\alpha = 1$, if the patient is diagnosed with diabetes mellitus (0 – otherwise), $\beta = 1$, if the patient is diagnosed with restenosis (0 – otherwise).

Table IV gives examples of the final grade scale for the assessment of thrombotic risk.

The verification of the developed grade-ranking scale of the results of the 18-month inspection showed that in 73,9% of cases it corresponds to very high risk (patients with restenosis) and in 26,1% of cases it corresponds to high thrombotic risk, in patients who also had restenosis. According to the results of the grade-ranking scale, none of the 23 patients with restenosis fell into the average-level category.

Hence, the presented grade-ranking scale scale allows a high probability to predict the development of thrombotic complications in patients with percutaneous coronary angioplasty.

**Table IV.** Results of evaluation of thrombotic risk level on the example of patients №8 and №28

| № | № of the patient | rf mkg/ml | fg mg/ml | dd ng/ml | pc % | DM | R | Risk assessment | | | G/r scale |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 1 stage | 2 stage | 3 stage | |
| 1 | 8 | 14,5 | 5,6 | 151 | 97 | - | + | 3 | 3 | 2 | 3 |
| 2 | 28 | 3,1 | 3,6 | 20 | 86 | - | - | 1 | 0 | 0 | 1 |

Note: DM – diabetes; R – restenosis; G/r scale – grade-ranking scale.

## CONCLUSIONS

1. The application of the method of the main components allows obtaining the value of individual and accumulated contributions of the studied hemostasis to total dispersion, giving rank evaluation of the influence of the initial parameters on the formation of the main components and the percentage explained by the latest information.
2. Consideration of the four indicators that characterize hemostasis in patients with coronary angioplasty (rf, fg, dd, pc), rf/dd×100 and binary index (DM, history of restenosis) makes it possible to classify patients with the help of developed grade-ranking scale of thrombotic risk.

Prospects for further research. Further introduction of informative biochemical markers for thrombogenesis and the use of available mathematical methods of compaction of information will further improve the process of predicting the level of thrombotic risk.

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**Authors' contributions:**
*According to the order of the Authorship.*

**ORCID numbers:**
*Nadezhda V. Storozhuk - 0000-0003-4424-4990*
*Aleksey B. Panasenko - 0000-0003-1403-2241*
*Boris G. Storozhuk - 0000-0002-9590-2159*
*Tatiana V. Dovgalyuk - 0000-0003-1614-9021*

**Conflict of interest:**
*The Authors declare no conflict of interest.*

## CORRESPONDING AUTHOR

**Tatiana V. Dovgalyuk**
Cosmonauts ave. 26, sq. 22, 21021 Vinnitsa, Ukraine
tel: +380500636522
e-mail: postboxt05@gmail.com

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# ELECTROMYOGRAPHIC CHARACTERISTICS OF CHEWING MUSCLES OF INDIVIDUALS WITH PATHOLOGICAL ABRASION OF HARD DENTAL TISSUES

**Aleksey V. Bida[1], Volodymyr I. Struk[2], Vitaliy I. Bida[1], Serhii M. Hermanchuk[1]**
[1]SHUPYK NATIONAL MEDICAL ACADEMY OF POSTGRADUATE EDUCATION, KYIV, UKRAINE
[2]PUBLIC MEDICAL ESTABLISHMENT "MUNICIPAL STOMATOLOGICAL POLYCLINIC", CHERNIVTSI, UKRAINE

## ABSTRACT

**Introduction:** Pathological abrasion of hard dental tissues is accompanied by both morphological and functional disorders of the dentofacial system. Among the functional changes, changes in the bioelectrical activity of the masticatory muscles are primarily considered.

**The aim** was to study the functional state of the masticatory muscles in patients with pathological abrasion of hard dental tissues of varying degrees of severity compared with the norm.

**Materials and methods:** Electromyographic studies were conducted in 89 patients aged 18 to 59. 70 patients had pathological abrasion of hard dental tissues of various degrees and 17 patients had intact dentitions and physiological forms of occlusion.

**Results:** The results of electromyographic studies showed an extension of the chewing period, a reduced chewing rhythm, a deterioration of chewing efficacy in case of the pathological abrasion of teeth, compared with the norm, which increased in dynamics. The correlation between excitatory and inhibitory processes, however, sharply deteriorated with an increase in the duration of activity due to the reduction of the relative bioelectric rest period. The magnitude of the biopotential amplitude decreased relative to the norm with a serious violation of the coordination of masticatory muscles in general.

**Conclusions:** The results of electromyographic studies of the masticatory muscles make it possible to determine the degree of functional changes in the neuromuscular system of the dentofacial system of patients with pathological abrasion of hard tissues of varying severity, compared with the norm. This indicates a decrease in chewing efficacy and the progression of morphological disorders that increase in dynamics.

**KEY WORDS:** pathological abrasion of teeth, electromyography, masticatory muscles

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## INTRODUCTION

According to the law of interdependence of morphology and function, any structural changes at different levels of system organization of living organisms are accompanied by functional disorders, and vice versa [1]. Pathological abrasion of hard dental tissues refers to diseases that are accompanied by serious morphological and functional disorders. The prevalence of pathological abrasion of hard dental tissues varies from 4% to 57% at young age, reaches 91% in older people and is accompanied by both morphological and functional disorders of the dentofacial system. [2, 3]. Functional disorders in the form of changes in the bioelectrical activity of the masticatory muscles and biodynamic equilibrium are in direct dependence on the clinical form and severity of pathological abrasion of teeth [4, 5].

The study of electromyographic characteristics of the masticatory muscles allows us to determine the degree of functional changes in the pathological conditions of the chewing system [6, 7] and subsequently to control the degree of functional rehabilitation of patients after prosthetics, which determines the relevance of our research.

## THE AIM

The aim was to study the electromyographic characteristics of the masticatory muscles in patients with pathological abrasion of hard dental tissues of varying degrees of severity.

## MATERIALS AND METHODS

To reach the aim, we have clinically examined and conducted electromyographic studies of masticatory muscles (m. Masseter) in 89 patients aged 18 to 59 with pathological abrasion of hard dental tissues, including the control group of the same age period in the number of 17 patients with physiological forms of abrasion of teeth within the enamel with intact dentitions and physiological forms of occlusion.

All studies were conducted in accordance with the Council of Europe Convention on Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (ETS No. 164) dated 04.04.1997, and the Helsinki Declaration of the World Medical Association (2008). Each patient signed an informed consent to participate in the study.

Depending on the degree of pathological abrasion, the examined individuals were divided into the following clinical groups: Group I – 35 patients with pathological abrasion of 1 degree (up to 1/3 of the crown height); Group II – 37 patients with a lesion depth of 2 degree (from 1/3 to 2/3 of the crown height). Group III included 17 patients with physiological forms of abrasion within the enamel.

Patients with a lesion depth of the third degree (from 2/3 of the crown height to the gum level) were not included in the study because in most cases the clinical picture was accompanied by a significant loss of the anatomical shape of the teeth, sometimes a complete loss of the tooth crown, defects of the dentition of a significant size complicated by dentofacial deformations with the loss of antagonist teeth and the impossibility of full chewing, which made it impossible in principle to conduct functional tests "maximum compression of dentition in the position of central occlusion" and "volitional chewing".

The functional state of the masticatory muscles by the method of functional electromyography was determined in patients from the I, II clinical groups and the III control group. It consisted in recording the bioelectric potentials of the muscles before the beginning of the prosthesis.

The electromyographic study was performed using a computer neuroelectromyograph M-Test, produced by the association "DX-Systems" (Ukraine) and a computer system for the analysis of electromyographic records. The method of conducting the study included fixing on the motor points of the right and left masticatory muscles (m. Masseter) of the skin silver electrodes in diameter of 5 mm with a constant interelectrode distance of 15 mm, to which a gel was applied for electrophysiological studies. Daily bread quota in at the amount of 1 $cm^3$ and weight of 1.5 gr. was used as food stimulus. Electromyograms were recorded in the following sequence: calibration signal – relative physiological resting position – volitional three-second compression of the jaws – relative physiological resting position – volitional chewing – swallowing.

Bioelectric activity of the masticatory muscles during electromyographic studies was evaluated qualitatively and quantitatively. In particular, the nature of the inclusion of motor units in the process of functioning of the masticatory muscles, the lack of activity in the state of relative physiological rest and the nature of the alternation of periods of bioelectric activity and rest in the process of chewing were determined. During quantitative processing of electromyograms, the following indicators were taken into account: the amplitude of compression and chewing (μV); the bioelectrical activity time (ms); the resting phase duration (ms) and the coefficient "K". The frequency indicator of biopotential oscillations (F in Hz) was also of interest.

## RESULTS AND DISCUSSION

Analysing the degree of functional disorders of the masticatory muscles caused by pathological abrasion and the change in the anatomical shape of the teeth, we certainly based on the physiological norm. The results of conducted electromyographic studies in the control group showed that the maximal three-second volitional jaw compression was normally characterized by the instantaneous inclusion of motor units, which was expressed in the structure of the record by high-amplitude oscillations of biopotentials of approximately the same magnitude. Muscle relaxation was

**Table I.** Electromyographic indicators of the masticatory muscles of the study groups at maximum compression of the jaws and volitional chewing

| Studied Electromyographic Indicator | Masticatory Muscle | Average Indicators of Group III (Control Croup) (n=17) | Patients with pathological abrasion of hard dental tissues | | | |
|---|---|---|---|---|---|---|
| | | | Group I (n=35) | Probability of Differences with Control Group (P) | Group II (n=37) | Probability of Differences with Group I (P) |
| Average Compression Amplitude (μV) | right | 756±21,9 | 511±9,5 | <0,01 | 443±8,8 | <0,01 |
| | left | 782±29,4 | 522±11,0 | <0,01 | 451±7,9 | <0,01 |
| Average Chewing Amplitude (μV) | right | 815±15,5 | 548±8,2 | <0,01 | 531±9,3 | <0,01 |
| | left | 804±19,3 | 561±10,4 | <0,01 | 519±10,1 | <0,01 |
| Oscillation Frequency while Compression (Hz) | right | 290±10,5 | 323±4,4 | <0,01 | 350±3,6 | <0,01 |
| | left | 283±8,4 | 320±4,1 | <0,01 | 345±4,1 | <0,01 |
| Oscillation Frequency while Chewing(Hz) | right | 280±7,9 | 295±3,8 | <0,01 | 300±3,2 | <0,01 |
| | left | 277±9,3 | 297±3,1 | <0,01 | 306±3,3 | <0,01 |
| Active Phase Duration (Ms.) | right | 298±14,8 | 430±5,4 | <0,01 | 471±6,6 | <0,01 |
| | left | 301±14,1 | 421±5,6 | <0,01 | 480±6,1 | <0,01 |
| Resting Phase Duration (Ms.) | right | 280±15,4 | 239±5,3 | <0,01 | 221±6,1 | <0,01 |
| | left | 172±12,9 | 241±6,3 | <0,01 | 218±5,1 | <0,01 |
| "K" | right | 1,04±0,04 | 1,59±0,03 | <0,05 | 1,72±0,03 | <0,05 |
| | left | 1,05±0,04 | 1,55±0,02 | <0,05 | 1,79±0,04 | <0,05 |

represented by a rapid transition to a state of rest. Volitional chewing was characterized by a clear division of the structure of records, that is, expressed by alternating "firings" of bioelectric activity with rest periods. The amplitude of oscillations of biopotentials, appearing at the beginning of the "firing", rises to its middle and gradually decreases in the end. One of the main features of volitional chewing in patients of the control group was a change in chewing sides in the process of one chewing test. This happened reflexively and indicated a high degree of coordination activity of the masticatory muscles. When conducting a test with a volitional chewing, periods of activity alternated with periods of rest. At first high-amplitude oscillations were observed, which at the end of the chewing became less pronounced.

In patients of Groups I and II, there was an extension of the chewing period, a decrease in the chewing rhythm and a deterioration of chewing efficacy. Particularly noticeable changes took place within individual dynamic cycles: the correlation between excitatory and inhibitory processes sharply deteriorated with an increase in the duration of activity by reducing the period of relative bioelectric rest, and the magnitude of the biopotential amplitude decreased relative to the norm.

To establish the degree of functional disorders of the masticatory muscles of patients with pathological abrasion of hard dental tissues of varying degrees of severity, a quantitative analysis of the obtained electromyographic indicators was carried out. The results are shown in Table I.

As can be seen from Table I in patients of the control group, high-amplitude oscillations of biopotentials of approximately the same magnitude were observed during the test of a three-second voluntary compression of the jaws on the electromyograph. The average compression amplitude was 756 ± 21.9 and 782 ± 29.4 μV, respectively for the right and left masticatory muscles. In case of pathological abrasion of hard dental tissues, a significantly lower difference of indicators was observed 511 ± 9.5 μV and 522 ± 11.0 μV respectively for the right and left masticatory muscle of group I and 443 ± 8.8 μV and 451 ± 7.9 μV respectively for the right and left masticatory muscle of group II.

The average amplitude of biopotentials during chewing was 815 ± 15.5 μV and 804 ± 19.3 μV respectively for the right and left masticatory muscle. In individuals of the control group with intact dentitions, the period of bioelectric activity was approximately equal to the rest period, which was reflected in the K values – 1.04 ± 0.04 and 1.05 ± 0.04, respectively for the right and left masticatory muscles.

The conducted studies have shown that much more pronounced functional changes in the activity of the masticatory muscles take place in people of the II group – decrease in the activity of the average amplitude of their biopotentials, both during the compression test and during the volitional chewing test. When conducting a maximum compression test, different amplitudes of biopotentials were determined as for the right and left masticatory muscles, there was a loss of individual biopotentials, a significant decrease in the accuracy of the electromyographic records, the absence of a clear alternation of the activity and rest phases, which affected the coefficient "K", and which indicates pronounced functional changes in the activity of the dentition.

The analysis of the indicators obtained from individuals in group II shows that these patients chewed food for much longer period of time, the duration of the bioelectric activity phase of the masticatory muscle during the volitional chewing test was significantly higher than the rest duration, and the amplitude of bioelectric indicators was uneven in relation to the right and left sides of chewing. During the volitional compression test, loss of biopotentials was often observed, which was confirmed by a statistically significant difference in the rates among all groups of patients. The indicators' values of the coefficient "K" significantly exceeded the indicators of the control group, which showed a significant negative dynamics of functional bioelectric activity – 1.72 ± 0.03 and 1.79 ± 0.04 for the right and left masticatory muscles, respectively, against 1.04 ± 0.04 and 1.05 ± 0.04 respectively for the right and left masticatory muscle in patients of the control group.

## CONCLUSIONS

The results of electromyographic studies of masticatory muscles make it possible to determine the degree of functional changes in their activity in patients with pathological abrasion of hard dental tissues of varying severity. In particular, in patients with pathological abrasion of the two study groups, compared with the norm, there is a prolongation of the chewing period, a change in the chewing rhythm and a decrease in chewing efficacy, the correlation between the excitatory and inhibitory processes is sharply deteriorating, the bioelectric activity period increases due to the reduction of the relative bioelectric rest period, the masticatory muscles of both sides generally function irrationally. The obtained results confirm the relationship between the degree of pathological abrasion of hard dental tissues and the degree of functional disorders of the masticatory muscles.

**Prospects for further research.** The prospect of further research is the need for further in-depth study of the functional changes in the masticatory muscles against the background of the pathological abrasion of hard dental tissues in order to find the best ways to rehabilitate such patients.

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**Authors' contributions:**
*According to the order of the Authorship.*

**ORCID numbers:**
*Aleksey V. Bida - 0000-0003-1764-9669*
*Volodymyr I. Struk - 0000-0002-1127-1485*
*Vitaliy I. Bida - 0000-0002-1786-2032*
*Serhii M. Hermanchuk - 0000-0002-9927-564X*

**Conflict of interest:**
*The Authors declare no conflict of interest.*

**CORRESPONDING AUTHOR**
**Serhii M. Hermanchuk**
Chekhov street 24, apartment 21, 08200 Irpen, Kyiv region, Ukraine
tel: +380506059241
e-mail: shermanchuk@ukr.net

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# MINIMALLY INVASIVE AND TRADITIONAL OPERATIVE TECHNIQUES IN SURGICAL TREATMENT OF ACUTE COMPLICATED PANCREATITIS

**Victor P. Andriuschenko, Dmytro V. Andriuschenko, Oleg T. Girniak**
LVIV DANYLO HALYTSKY NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

## ABSTRACT

**Introduction:** The issue of surgical treatment of acute pancreatitis, in particular the choice of operative technique, is becoming increasingly relevant.

**The aim:** To work out surgical approach in patients with acute complicated pancreatitis (ACP) using minimally invasive and traditional operative techniques.

**Materials and methods:** 170 patients underwent surgery for ACP. The main group (109 subjects) had minimally invasive techniques (MIT) dominated, the comparative group (61 subjects) – traditional operations.

**Results:** MIT performed "as final" in 62 (69%), "stage" – in 16 (18%) and "stabilizing patient condition" – in 12 (13%) of observations. The number of combined interventions predominated in the main group – 26% and 12% ($\chi^2$=4.002; p=0.04), traditional in comparative groups – 67% and 17% cases ($\chi^2$=40.291; p<0.0001). Primary laparotomy operations were used in 41 (67%) patients from comparative and 19 (17%) patients from the main group ($\chi^2$=40.291; p<0.0001). The extent of traditional operations in the main group consisted predominantly of necrosequestrectomy with Beger closed drainage – in 26 (55%) and 15 (31%) observations, respectively ($\chi^2$=5.018; p=0.02). Necrosequestrectomy with subsequent stage lavage performed in common purulent-necrotic lesions were comparable in both groups – in 11 (23%) and 13 (26%) observations ($\chi^2$=0.0013; p>0.05).

**Conclusions:** The worked out surgical treatment approach in ACP with individual and combined use of MIT and traditional operations resulted in decreased rates of postoperative complications from 13.1% to 8.3% and mortality from 14.8% to 9.2%.

**KEY WORDS:** Acute Complicated Pancreatitis, Operative Techniques

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## INTRODUCTION

Acute pancreatitis (AP) is one of the most complex, prognostically unfavorable and often life-threatening acute diseases of the abdominal cavity [1, 2, 3]. The issue of treating these categories of patients is extrapolated not only to the purely medical aspects, but also to the equally important socio-economic context due to the dominance of male patients of working age [4, 5].

Surgical approach is one of the mainstream in addressing AP issue with the definition, in particular, of the potential and significance of minimally invasive intervention techniques and feasibility of their both individual and combined use with open traditional operations [6,7, 8].

## THE AIM

To work out the surgical treatment approach in patients with acute complicated pancreatitis through clarification of possibilities of using minimally invasive and traditional operative techniques.

## MATERIAL AND METHODS

The comprehensive examination was performed with 170 patients hospitalized to the Municipal Pancreatic Centre based on the Department of General Surgery at the Lviv Danylo Halytsky National Medical University with a confirmed ACP diagnosis (based on clinical, laboratory-biochemical, radiological and instrumental findings). In accordance with the previously formulated approach [9] this category of patients included individuals with present local complications of the disease, as well as manifestations of transient or prolonged organ failure. In accordance with Atlanta classification, 2012 [7], the following types of pancreatic fluid collections (FC) were identified as local complications. 1. Acute peripancreatic fluid collection (APFC) with aseptic content with no signs of necrosis. 2. Acute necrotictic collection (ANC), both with fluid and fragments of necrotic tissues content due to glandular parenchyma and/or parapancreatic fat necrosis. 3.Post-necrotic pancreatic/retropancreatic fluid collection (PNFC) containing a fluid component in the form of pus and necrotic tissue/detritus and predominantly infected.

The age of hospitalized patients ranged from 22 to 74 years, of whom 36 (33%) female and 73 (67%) – male patients. The entire cohort of patients was divided into two groups. The first one, main group, included 109 patients, in relation to whom the principle of surgical treatment was implemented with the priority use of minimally invasive techniques (MIT). The second, comparative group included 61 patients, in respect of whom mainly traditional surgical interventions were used. Clinical, laboratory, biochemical,

**Table I.** Minimally invasive and open surgical operations.

| Group of patients | Type of surgical interventions | | | |
|---|---|---|---|---|
| | traditional n (%) | minimally invasive n (%) | combined n (%) | Total n (%) |
| main | 19 (17 %) | 62 (57 %) | 28 (26 %) | 109 (100 %) |
| comparative | 41 (67 %) | 13 (21 %) | 7 (12 %) | 61 (100 %) |

**Table II.** Types of open surgical interventions.

| Type of surgery | Group of patients | |
|---|---|---|
| | main n (%) | comparative n (%) |
| NSE* + closed drainage | 26 (55 %) | 15 (31 %) |
| NSE + semiopen drainage | 4 (9 %) | 21 (43 %) |
| NSE + programmed relaparotomy | 11 (23 %) | 13 (26 %) |
| Lumbotomy lavage | 6 (13 %) | - |
| Total | 47 (100 %) | 49 (100 %) |

Note: NSE*– necrosequestrectomy

additional – radiological (X-ray, ultrasonographic, computer-tomographic), intraluminal (esophagogastroduodenoscopic), instrumental (video-laparoscopic), bacteriological and pathomorphological methods were used. The obtained study results were worked out using variation statistics methods with Student's and $\chi^2$ tests.

ACP severity analysis according to Atlanta Classification (2012) in the main and comparative groups allowed stating that the number of patients with severe ACP in the main group was 26 (24%), in comparative group – 11 (18%), with moderate severity – 83 (76%) and 50 (82%) patients, respectively. The proportion of those hospitalized with severe ACP in both groups did not differ significantly ($\chi^2$=3.16; p>0.05). Thus, the isolated groups were comparable both in the nature of pathology and severity of the clinical course of disease as well.

## RESULTS AND DISCUSSION

All hospitalized patients were subjected to surgical treatment using various interventional techniques. Thus, the main group had mostly MIT used in the form of ultrasonographic puncture, puncture-drainage and video-laparoscopic techniques ranging as "final", "stage" and "stabilizing patient condition". In particular, "final" techniques were used in 62 (69%), "stage" – in 16 (18%) and "stabilizing patient condition" – in 12 (13%) of observations.

The total number of surgical operations in both groups did not differ significantly – 109 and 67 interventions, respectively ($\chi^2$= 0.651; p> 0.05). However, the structure of operative techniques was different (Table I). Thus, the proportion of combined (minimally invasive and traditional) interventional techniques in the main group of patients was significantly higher –26% and 12% of observations, respectively ($\chi^2$= 4.002; p=0.04), while traditional surgical interventions prevailed in comparison group – 67% and 17%, respectively ($\chi^2$= 40.291; p <0.0001).

Thus, 29 patients (26%) with acute peripancreatic PC (APFC) had puncture and 17 patients (16%) with acute necrotic PC (ANC) had puncture-drainage ultrasonographic techniques used. Diagnostic and therapeutic video-laparoscopy was performed in 16 clinical observations (15%) with unlimited fluid collection in the form of enzymatic peritonitis/pancreatogenic ascites. These MITs allowed achieving the final positive therapeutic outcome.

Consequently, 62 patients (57%) after using MITs in the form of puncture and puncture-drainage intervention ultrasonography and video-laparoscopy resulted in favourable clinical course of the disease with no need for an open surgical operation.

In 6 observations (6%) with post-necrotic PC (PNFC), despite the use of interventional sonography, ultrasonographic monitoring verified the formation of limited fluid paracolon translucency in descending colon projection – four clinical cases and ascending – two clinical cases. These localized purulonecrotic affected areas were treated and drained from small precision lumbotomic incisions followed by patients recovery.

10 patients (9%), after puncture-draining sonography with central localization of purulonecrotic-affected area, due to its insufficient clinical efficacy, had surgical intervention performed with a small laparotomy access with lavage of clearly marked devitated tissues with no need for subsequent repeated stages of operations.

Thus, 16 patients (15%) due to MITs had the purulonecrotic areas limited, which created conditions for lavage and drainage followed by traditional stage of operation using small incisions.

The interventional drainage ultrasonography was performed in 12 observations (11%) with severe ACP with purulonecrotic local complications against the background of unstable hemodynamics and manifestations of multiple organ failure (MOF). This intervention, along with intensive infusion drug therapy in a resuscitation and anesthetic

department setting for two or three days, allowed achieving optimum stabilization in patients' condition, levelling MOF signs and performing traditional open surgery under significantly better conditions.

The implementation of developed approaches using MITs allowed reducing the number of indications for open interventions. For example, if in the comparative group primary laparotomy operations were used in 41 patients (67%), then, in the main group of 19 patients (17%), that is two-fold less ($\chi^2$=40.291; p <0.0001). In addition, 28 patients (26%) of the main group had traditional operations performed as combined following the minimally invasive stage (15%) and stabilizing patient condition (11%) interventions.

A fundamentally important technical element of laparotomy surgical intervention was the choice of optimal operative access, which would provide proper exploitation with the creation of conditions for a complete and adequate exploitation of both gland, and all probable affected areas of the retroperitoneal fat as well. Thus, the main group had an arcuate hypochondriac (subcostal) access dominated (26; 55%) – $\chi^2$=14.287; p=0.0002, while the comparative group had supramedian laparotomy used more often (37; 76%) – $\chi^2$=38,43; p<0,0001.

The scope of operations in the main group vs comparison group (Table II) consisted mainly of necrosequestrectomy with Beger's closed through cleaning/through aspiration drainage in 26 (55%) and 15 (31%) observations ($\chi^2$=5,018; p=0,02), since MIT resulted in the formation of limited purulonecrotic lesions, lavage of which using this method was effective. The semi-open approach using tube and rubber drains or Penrose drain prevailed in the comparative group – 21 (43%) and 4 (9%) clinical cases, respectively ($\chi^2$=12,965; p=0,0003). Necrosequestrectomy with subsequent staging lavage through programmed relaparotomy performed in generalized (more than two sites) purulonecrotic lesions were comparable in the main and comparative groups – 11 (23%) and 13 (26%) observations, respectively ($\chi^2$=0,0013; p>0,05).

Analysis of the main clinical and statistical success rate of treatment in the main and comparative groups showed that the frequency of postoperative complications in these patients was 8.3% and 13.1%, respectively, and postoperative mortality decreased due to the developed surgical approach from 14.8% to 9.2% .

The matter of adequate surgical approach in ACP continue to be the subject of numerous discussions [7,10,11]. This concerns, above all, the controversy of views regarding potential, significance and feasibility of using minimally invasive interventional techniques [12,13]. Along with the arguments in favour of using traditional operations in terms of their efficacy, rationale for more extensive MITs application [4,5,10] is equally convincing. Assessing own experience with such interventions in AP, some researchers report a reduction in the number of complications up to 5%, number of open surgical interventions up to 3%, and mortality rate up to 20% [5]. Other publications indicate that, in general, minimally invasive operative techniques are effective in 60-84% of cases with morbidity rate of up to 90% and mortality – up to 24% [12]. However, these techniques associated with the need for multiple CTs with patient's radiation exposure and higher cost of treatment [8,11]. Consequently, no unambiguous recommendations for using particular operative technique in specific clinical situations are clearly in evidence. The worked out approach defines MIT niche with the effective use in individual applications and combined with traditional interventions.

## CONCLUSIONS

1. Surgical treatment of ACP patients using the developed surgical approaches based on both minimally invasive (interventional sonography, video laparoscopy) and traditional intervention techniques as well, provides for a significant increase in the proportion of non-invasive techniques, both in individual applications and combined with open surgeries.
2. Laparotomy is effective in limited purulonecrotic glandular lesions and/or parapancreatic/paracolon fat with inflammation site lavage and Beger's closed drainage, and with generalized processes – necrosequestrectomy with subsequent stage lavage through programmed relaparotomy.
3. Developed surgical approach with individual and combined MIT and traditional open surgical interventions reduces the postoperative complications and mortality rates.

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**Authors' contributions:**
*According to the order of the Authorship.*

**ORCID numbers:**
*Victor P. Andriuschenko - 0000-0003-1848-7358*
*Dmytro V. Andriuschenko - 0000-0003-1046-7889*
*Oleg T. Girniak - 0000-0002-6355-5703*

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**CORRESPONDING AUTHOR**
**Victor P. Andriuschenko**
5 Lychakivska str., apt. 44, Lviv 79008, Ukraine
tel: +380677266279
e-mail: avp.victor@gmail.com

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# WPŁYW WYBRANYCH TRENDÓW DIETETYCZNYCH NA SPOSÓB ODŻYWIANIA MŁODZIEŻY LICEALNEJ

# INFLUENCE OF DIETARY TRENDS ON THE NUTRITION OF THE YOUTH

**Anita Bielawska[1], Katarzyna Tomczyk[1,2], Beata Łabuz-Roszak[1]**

[1]KATEDRA I ZAKŁAD PODSTAWOWYCH NAUK MEDYCZNYCH, WYDZIAŁ ZDROWIA PUBLICZNEGO W BYTOMIU, ŚLĄSKI UNIWERSYTET MEDYCZNY W KATOWICACH, BYTOM, POLSKA

[2]STUDIUM DOKTORANCKIE WYDZIAŁU ZDROWIA PUBLICZNEGO W BYTOMIU, KATEDRA I ZAKŁAD ZDROWIA ŚRODOWISKOWEGO, ŚLĄSKI UNIWERSYTET MEDYCZNY W KATOWICACH, BYTOM, POLSKA

## STRESZCZENIE

**Wstęp:** Trendy dietetyczne, takie jak spożywanie produktów bez laktozy i glutenu oraz stosowanie alternatywnych diet odchudzających, zyskują coraz większą popularność, w szczególności wśród osób młodych. Determinują je wybory żywieniowe, istotne z punktu widzenia zdrowia człowieka. Diety alternatywne wciąż są postrzegane jako skuteczne metody odchudzania. Stosowanie diet niekonwencjonalnych może prowadzić do niedoborów niezbędnych składników odżywczych, wzrostu ryzyka rozwoju przewlekłych chorób niezakaźnych i ukształtowania nieprawidłowych nawyków żywieniowych. Dieta zbilansowana w odróżnieniu od diety alternatywnej uwzględnia zasady racjonalnego żywienia oraz zalecenia żywieniowe Instytutu Żywności i Żywienia (IŻŻ).

**Cel pracy:** Zbadanie wpływu popularnych trendów dietetycznych na sposób odżywiania młodzieży licealnej.

**Materiał i metody:** Przedmiotem badań była młodzież w wieku od 17 do 21 lat uczęszczająca do szkół licealnych na terenie Rudy Śląskiej (262 uczniów w tym: 157 kobiet i 105 mężczyzn). Badanie zostało zrealizowane za pomocą autorskiego kwestionariusza ankiety. Udział w badaniu był anonimowy i dobrowolny.

**Wyniki:** U ponad połowy badanych młodych kobiet (54,8%) i mężczyzn (52,4%) odnotowano niedowagę (BMI<18 kg/m$^2$). Na diecie niezbilansowanej przynajmniej raz w życiu było 33,6% badanych. Licealiści znali produkty bezglutenowe i bezlaktozowe, ale trendy dietetyczne, takie jak: spożywanie produktów bezglutenowych i bezlaktozowych, nie wpływały na ich sposób odżywiania. Podstawowym źródłem wiedzy żywieniowej wśród ankietowanych byli znajomi i przyjaciele (78,2%).

**Wnioski:** Wyniki przeprowadzonych badań podkreślają konieczność wdrożenia odpowiednich programów edukacyjnych na temat zasad prawidłowego żywienia. Wzrost świadomości młodzieży w tym zakresie może przyczynić się do obniżenia zainteresowania wciąż popularnymi dietami alternatywnymi wśród osób młodych i podejmowania przez nich właściwych zachowań zdrowotnych.

**SŁOWA KLUCZOWE:** młodzież licealna, odżywianie, diety alternatywne, trendy dietetyczne

## ABSTRACT

**Introduction:** Dietary trends such as consumption of lactose-free and gluten-free products or the use of alternative slimming diets are gaining increasing popularity, especially among young people. They determine their dietary choices, which are important from the point of view of human health. Unconventional diets are still considered as effective weight loss methods. The use of alternative diets may cause shortages of an essential nutrients, increase the risk of chronic non-communicable diseases and lead to the formation of incorrect eating habits. Balanced diet, in contrast to the alternative diet, takes into account the principles of rational nutrition and nutritional recommendations of the Institute of Food and Nutrition (IŻŻ).

**The aim:** To investigate the influence of popular dietary trends on nutrition of high school adolescences.

**Material and methods:** Subjects were adolescences in the age of 17-21 years attending high schools in Ruda Slaska (262 students, including 157 women and 105 men). Self-constructed questionnaire was applied in the study. Participation in the study was anonymous and voluntary.

**Results:** In more than a half of young women (54,8%) and men (52,4%) the body mass deficiency was revealed (BMI<18 kg/m$^2$). 33,6% of the respondents were on the non-balanced diets at least once in their lives. High school students knew gluten-free and lactose-free products but dietary trends, such as the consumption of gluten-free and lactose-free products, did not affect their diet. The main source of nutritional knowledge among respondents were their friends (78,2%).

**Conclusions:** The results of the conducted research indicate the need to implement educational programs on the principles of proper nutrition. The increasing awareness of the youth in this regard may contribute to reducing the interest in still popular alternative diets among young people and taking appropriate health behaviors by them.

**KEY WORDS:** high school students, nutrition, alternative diet, dietary trends

## WSTĘP

Tematyka zdrowego odżywiania staje się coraz bardziej popularna, zarówno wśród dorosłych, jak i wśród młodzieży. Coraz częściej jest przewodnim tematem programów telewizyjnych, audycji radiowych, artykułów popularno-naukowych, doniesień naukowych, a także pseudonaukowych. W mediach i internecie często podawane są sprzeczne informacje na ten temat [1]. Media determinują wybory żywieniowe młodych ludzi. To one kształtują wizerunek współczesnego człowieka, popularyzując szczupłą i wysportowaną sylwetkę. Wywołują u odbiorców chęć dążenia do ideału. W związku z powyższym mogą wpływać na zdrowie człowieka i jego sposób odżywiania, kreując obowiązujące trendy dietetyczne, takie jak spożywanie produktów bez laktozy i glutenu oraz stosowanie alternatywnych diet odchudzających [2, 3].

Pomimo panującej mody na świadome odżywianie, wciąż króluje opinia o istnieniu diety cud [5]. Osoby dążące do redukcji masy ciała często wybierają jedną z powszechnie dostępnych diet, takich jak: wysokobiałkowa, niskokaloryczna, wysokotłuszczowa, jednoskładnikowa [4]. Nie są świadome konsekwencji zdrowotnych ich stosowania. Korzystanie z diet niekonwencjonalnych może prowadzić do niedoborów makro- i mikroskładników, niezbędnych do prawidłowego funkcjonowania organizmu człowieka, rozwoju przewlekłych chorób niezakaźnych i ukształtowania nieprawidłowych nawyków żywieniowych [5]. Rodząca się moda na spożywanie produktów bezglutenowych i bezlaktozowych może być powodem nieracjonalnej diety ludzi zdrowych. Diety eliminacyjne są formą leczenia nietolerancji pokarmowych. Ich stosowanie jest konieczne w żywieniu dzieci i dorosłych nietolerujących glutenu, który zawarty jest w zbożach (np. jęczmień, pszenica) i nietolerancji składników mleka [6].

Prawidłowo zbilansowany jadłospis opiera się na zaleceniach żywieniowych Instytutu Żywności i Żywienia. Dostarcza do organizmu wszystkich składników odżywczych i mineralnych niezbędnych do utrzymania zdrowia i zapewnienia prawidłowego rozwoju somatycznego, fizycznego i psychicznego człowieka [7]. Propagowanie zdrowych zasad żywienia wśród młodzieży jest niezwykle ważne. Młode osoby łatwiej ulegają wpływowi środków masowego przekazu i opinii rówieśników [8].

## STOSOWANIE DIET ELIMINACYJNYCH

Dieta bezglutenowa to jedna z najbardziej popularnych diet ostatnich lat. Obserwowany trend jest szczególnie niebezpieczny, gdyż samodzielne wykluczenie glutenu może uniemożliwić późniejszą diagnostykę zaburzeń związanych z jego spożywaniem [9].

Najczęściej kojarzoną formą nieprawidłowej reakcji na gluten jest celiakia. Celiakia jest chorobą ogólnoustrojową, autoimmunologiczną, wywołaną nietolerancją glutenu (gliadyna z pszenicy, sekalina z żyta, awenina z owsa i hordeina z białka jęczmienia) [10]. Szkodliwe działanie glutenu może doprowadzić do wygładzenia błony śluzowej jelita i zaniku kosmków jelitowych, co będzie upośledzać wchłanianie w przewodzie pokarmowym. Może to doprowadzić do niedożywienia, a w konsekwencji do nieprawidłowego rozwoju organizmu. Szacuje się, że w Europie jedno na tysiąc dzieci choruje na celiakię, z czego 30% stanowi postać klasyczna (inaczej zwaną aktywną lub jawną) [11]. Z uwagi na nasilenie objawów oprócz postaci klasycznej wyróżniamy również postać niemą i latentną. Do charakterystycznych objawów zaliczamy: biegunki (tłuszczowe lub wodniste), bóle brzucha, wzdęcia, czasem utratę masy ciała i łaknienia. Dieta eliminacyjna (stosowana przez całe życie) jest jedyną skuteczną metodą leczenia celiakii, polegającą na wykluczenie produktów zawierających w swoim składzie gluten [12, 13]. Aż u 85% pacjentów obserwuje się ustanie niepożądanych zmian chorobowych dzięki stosowaniu diety [14].

## NIETOLERANCJA LAKTOZY – CHARAKTERYSTYKA

Alergia pokarmowa na białko oraz nietolerancja laktozy są głównymi przesłankami do stosowania diety eliminacyjnej, polegającej na usunięciu z jadłospisu produktów mlecznych lub ograniczeniu ich spożycia [6]. Obecnie modne produkty bez laktozy coraz częściej są stosowane przez osoby zdrowe.

Nietolerancja laktozy charakteryzuje się niedoborem enzymu laktazy, co prowadzi do jej późniejszej nietolerancji. Głównymi przyczynami nietolerancji może być tzw. hipolaktazja – czyli niedobór enzymu laktazy i alaktazja – wrodzony niedobór laktazy.U niektórych osób z genotypem C/C w zakresie genu promotorowego (genu kodującego laktazę), aktywność laktazy będzie ulegać stopniowej redukcji, co może skutkować wystąpieniem objawów nietolerancji laktozy. Drugorzędowy niedobór laktazy może wystąpić również w wyniku choroby, która prowadzi do uszkodzenia jelit (np. ostre zapalenie jelit) [15]. Młodzież i osoby dorosłe z hipolaktazją mogą odznaczać się aktywnością laktazy na poziomie zaledwie od 5 do 10% swej aktywności z okresu niemowlęctwa [16]. Klinicznymi objawami nietolerancji laktozy jest jeden lub więcej objawów, takich jak: ból brzucha, nudności, biegunka, wzdęcia po spożyciu produktów z laktozą, występującymi specyficznie w zależności od możliwości hydrolizy tego disacharydu [17]. Wcześnie stosowana dieta bez laktozy może zmniejszać wchłanianie wapnia i w aspekcie długoterminowym może powodować zmniejszenie mineralizacji kości i w konsekwencji osteoporozy [18].

## NAJCZĘŚCIEJ STOSOWANE DIETY ALTERNATYWNE

Najczęściej stosowanymi dietami odchudzającymi są diety wysokobiałkowe i o obniżonej kaloryczności. Pomimo skuteczności tych diet w redukcji masy ciała, są one przedmiotem dyskusji wielu specjalistów ze względu na konsekwencje zdrowotne ich stosowania (uszkodzenia nerek, osteoporoza i inne) [4,19]. W świetle polskich badań, w których sprawdzano długość efektów prowadzenia diet odchudzających po 5 latach 30% respondentów utrzymało obniżoną masę ciała, a po 10 latach – 10% [20].

### DIETA WYSOKOBIAŁKOWA

Dieta wysokobiałkowa, którą m.in. jest dieta dr Pierre'a Dukana, w swojej pierwszej fazie zaleca: produkty nabiałowe o obniżonej zawartości tłuszczu, mięso, jaja oraz niektóre podroby. Znikoma zawartość owoców i warzyw, a tym samym błonnika, jest często przyczyną zaparć. W drugiej fazie diety do produktów z pierwszej fazy zostają włączone wybrane rodzaje warzyw, co w dalszym ciągu nie pokrywa zapotrzebowania na błonnik. Faza trzecia, tzw. stabilizacji zawiera również w ograniczonej ilości produkty zbożowe, a jeden z dziesięciu dni powinien być tylko „białkowy". W końcowej fazie należy przejść do racjonalnego odżywiania z zachowaniem cotygodniowej kuracji uderzeniowej (białkowej) [21, 22]. Oprócz szybkich efektów utraty masy ciała, można też zauważyć niekorzystne konsekwencje stosowania tej diety. Zwiększona praca nerek (filtracja) powoduje dodatkowe wypłukanie wapnia, co w konsekwencji może prowadzić do osteoporozy. Dodatni bilans azotowy, zwiększone wytwarzanie mocznika i amoniaku, dostarczanie większych ilości fosforanów dodatkowo obciąża wątrobę i nerki [23, 24].

### DIETA NISKOKALORYCZNA

Typowymi założeniami diety niskokalorycznej (ok. 1000 kcal/dzień) jest redukcja spożywanych tłuszczy oraz węglowodanów posiadających wysoki indeks glikemiczny (IG). Dodatkowo należy znacznie zwiększyć podaż warzyw i wody [5, 25]. Warto zaznaczyć, iż długotrwałe stosowanie diet niskokalorycznych będzie skutkowało niedoborami witamin i składników mineralnych [26]. W początkowej fazie kuracji uzyskiwane są największe efekty, co jest wynikiem zużycia zapasów glikogenu ze względu na niską podaż węglowodanów [4, 19].

## CEL PRACY

Celem pracy było zbadanie wpływu popularnych trendów dietetycznych na sposób odżywiania młodzieży licealnej.

## MATERIAŁ I METODY

Badaniem objęto 262 uczniów w wieku od 17 do 21 lat, uczęszczających do losowo wybranych szkół licealnych znajdujących się na terenie miasta Ruda Śląska. Kobiety stanowiły 59,9% (N=157) badanej grupy licealistów, a mężczyźni stanowili 40,1% (N=105). Udział uczniów w badaniu był dobrowolny i anonimowy.

Badanie zostało zrealizowane za pomocą autorskiego kwestionariusza skonstruowanego na podstawie dostępnego piśmiennictwa. Pytania w nim zawarte pozwoliły ocenić wpływ obecnie panujących trendów dietetycznych na sposób odżywiania młodzieży.

Obliczenia statystyczne wykonano przy użyciu programu Statistica 10.0, Stat Soft Polska. Wynik uznano za istotny statystycznie, jeżeli uzyskany poziom istotności *p* był mniejszy lub równy 0,05. Do zbadania zależności pomiędzy zmiennymi jakościowymi zastosowano test niezależności $\chi^2$. Celem doboru odpowiednich metod statystycznych dokonano weryfikacji zgodności rozkładu zmiennych z rozkładem normalnym z użyciem testu Kołmogorova-Smirnova. W zależności od typu rozkładu, istotność różnic średnich sprawdzano testem t-Studenta, U Manna-Whitney'a lub Kruskala-Wallisa.

## WYNIKI

Stan odżywienia ankietowanych oszacowano za pomocą wskaźnika masy ciała (BMI). Wyniki przedstawiono w tabeli I.

Jak wykazano, 88 osób (33,6%) przebywało kiedykolwiek w przeszłości lub w trakcie badania na diecie. W tej grupie znalazło się 61 kobiet (38,9% wszystkich badanych kobiet) oraz 27 mężczyzn (25,7% wszystkich badanych mężczyzn). Do najczęściej stosowanych przez licealistów diet należały: dieta niskokaloryczna, dieta wysokobiałkowa, dieta racjonalna, dieta wegetariańska, ograniczenie spożywania słodyczy (cukru), dieta bez laktozy i glutenu oraz diety zalecane przez dietetyka. Nie wykazano, aby młodzież istotnie statystycznie częściej stosowała diety niskokaloryczne lub wysokobiałkowe w porównaniu do innych diet alternatywnych ($p>0,05$).

Kolejne pytanie dotyczyło znajomości i spożywania produktów bezglutenowych. Jedynie jedna osoba (0,4%) stwierdziła, że zna i spożywa takie produkty, bo choruje na celiakię. Kolejne 39 osób (14,9%) znało i spożywało produkty bezglutenowe, bo słyszało, że są zdrowe. Najwięcej, bo aż 151 licealistów (57,6%) znało, ale nie spożywało produktów bezglutenowych. Pozostałe 71 osób (27,1%) nie znało i nie spożywało produktów bezglutenowych (Tab. II).

Następnie badanych licealistów zapytano, czy znają i spożywają produkty bez laktozy. 9 osób (3,4%) stwierdziło, że zna i spożywa produkty bez laktozy, ponieważ choruje na nietolerancję laktozy. 44 osoby (16,8%) znały i spożywały produkty bez laktozy, bo słyszały, że są zdrowe. Najwięcej, bo aż 148 licealistów (56,5%) znało, ale nie spożywało produktów bez laktozy. Pozostałe 61 osób (23,3%) nie znało oraz nie spożywało produktów bez laktozy (Tab. II).

Zaobserwowano istotne statystycznie różnice w udzielanych przez respondentów odpowiedziach na pytanie dotyczące znajomości i spożywania produktów bezglutenowych i bezlaktozowych ($p<0,001$). Uzyskane wyniki wykazały, że licealiści wprawdzie znają tego typu produkty, ale ich nie spożywają.

Codzienną aktywność fizyczną deklarowało zaledwie 106 uczniów (40,3%). Najwięcej badanych osób (N=120; 45,8%) deklarowało umiarkowaną lub intensywną aktywność fizyczną przez 30 minut, ale jedynie kilka razy w tygodniu. Pozostałe 36 osób (13,6%) w ogóle nie ćwiczyło. Nie wykazano statystycznie istotnej zależności pomiędzy BMI młodzieży licealnej a ich poziomem aktywności fizycznej. Źródła wiedzy żywieniowej ankietowanych przedstawiono w tabeli III.

## DYSKUSJA

Obecnie niezwykle modne stają się produkty bezglutenowe i bezlaktozowe. Moda na tego typu żywność sprawiła, że coraz

**Tabela I.** Stan odżywienia badanych osób (wg wskaźnika BMI).

| Stan odżywienia wg BMI | Niedowaga (BMI≤18,5 kg/m²) N(%) | Prawidłowa masa ciała (BMI = 18,6-24,9 kg/m²) N(%) | Nadwaga (BMI≥25 oraz <30 kg/m² ) N(%) | Otyłość (BMI≥30 kg/m²) N(%) |
|---|---|---|---|---|
| Kobiety | 86 (54,8%) | 56 (35,7%) | 10 (6,3%) | 5 (3,2%) |
| Mężczyźni | 55 (52,4%) | 29 (27,6%) | 18 (17,1%) | 3 (2,9%) |

**Tabela II.** Znajomość i spożywanie produktów bezglutenowych i bezlaktozowych.

| Produkty | Odpowiedzi | N | Odsetek [%] | p |
|---|---|---|---|---|
| Produkty bezglutenowe | Znam i spożywam, bo choruję na celiakię | 1 | 0,4% | p<0,001 (B vs C) |
| | Znam i spożywam, bo słyszałem/am, że to zdrowe | 39 | 14,9% | |
| | Znam, ale nie spożywam | 151 | 57,6% | |
| | Nie znam i nie spożywam | 71 | 27,1% | |
| Produkty bez laktozy | Znam i spożywam, bo stwierdzono u mnie nietolerancję laktozy | 9 | 3,4% | p<0,001 (B *vs.* C) |
| | Znam i spożywam, bo słyszałem/am, że to zdrowe | 44 | 16,8% | |
| | Znam, ale nie spożywam | 148 | 56,5% | |
| | Nie znam i nie spożywam | 61 | 23,3% | |

**Tabela III.** Źródła aktualnej wiedzy żywieniowej młodzieży licealnej

| Źródła aktualnej wiedzy żywieniowej | N | % |
|---|---|---|
| Książki, podręczniki, artykuły naukowe | 91 | 34,7% |
| Ulotki, broszury | 58 | 22,1% |
| Czasopisma, gazety | 104 | 39,7% |
| Zajęcia w szkole | 115 | 43,9% |
| Znajomi, przyjaciele | 205 | 78,2% |
| Blogi internetowe | 150 | 57,3% |
| Forum internetowe | 156 | 59,5% |
| Profile na „Facebooku" | 131 | 50% |
| Znane osoby, celebryci | 81 | 30,9% |
| Trener | 99 | 37,8% |
| Dietetyk | 66 | 25, 2% |
| Na siłowni | 121 | 46,2% |

częściej sięgają po nią osoby zdrowe [27]. Diety eliminacyjne polegają na redukcji z jadłospisu chorego nietolerowanych składników pokarmowych. Ich stosowanie jest niezbędne w leczeniu objawów alergii. Diety eliminacyjne muszą być tak skomponowane, aby uwzględnione w nich pokarmy dostarczały składników odżywczych i witamin niezbędnych do prawidłowego funkcjonowania organizmu [6, 14].

Nie ma wskazań dotyczących stosowania diety bezglutenowej u osób „tolerujących" gluten. Podążanie za „bezglutenową modą" jest błędem w szczególności popełnianym wśród osób, które nie potrafią prawidłowo skomponować swojego jadłospisu. Dieta bezglutenowa dla ludzi zdrowych może być nieracjonalna [28, 29]. Dopuszcza się jednak rozsądną eliminację glutenu w diecie osób zdrowych, o ile nie wpływa to negatywnie na całościowy charakter ich sposobu odżywiania [30]. W niniejszej pracy wykazano, że ponad połowa licealistów (57,6%) znała produkty bezglutenowe, ale ich nie spożywała.

Podobne wyniki uzyskano w zakresie znajomości i spożywania produktów bez laktozy. W przypadku i tych produktów nieobojętne pozostają media [2]. Całkowite ich wyeliminowanie z jadłospisu wiąże się z ryzykiem niedoboru witaminy D, wapnia i ryboflawiny. Dlatego stosowanie diety ubogiej w laktozę powinno być rekomendowane jedynie w przypadku zdiagnozowanej nietolerancji [27]. Najwięcej uczniów z województwa śląskiego (56,5%) znało, ale nie spożywało produktów bez laktozy. 9 osób (3,4%) spośród wszystkich badanych uczniów stwierdziło, że zna i spożywa tego typu produkty, ponieważ choruje na nietolerancję laktozy. Nietolerancja na składniki mleka jest głównym wskazaniem do jego eliminacji z diety [27].

Młodzież, pod wpływem kreowanych przez massmedia wizerunków, podejmuje niewłaściwe wybory żywieniowe

[31]. Nastolatkowie często postrzegają swoją masę ciała, jako zbyt dużą [32]. Brak akceptacji swojego wyglądu oraz błędna ocena swojej wagi stanowi przyczynę decyzji o odchudzaniu w okresie nastoletnim i stosowaniu różnorodnych diet [33, 34]. W przeprowadzonym badaniu wykazano, że 33,6% wszystkich ankietowanych uczniów stosowało lub stosuje obecnie dietę wysokobiałkową lub niskokaloryczną. W tej grupie znalazło się 38,9% kobiet oraz 25,7% mężczyzn. Jest to w szczególności niepokojące zjawisko zaobserwowane w badanej populacji, gdyż u ponad połowy kobiet (54,8%) i mężczyzn (52,8%) odnotowano niedowagę. Do najczęściej stosowanych przez licealistów diet, oprócz niskokalorycznych i wysokobiałkowych, należały: dieta racjonalna, dieta wegetariańska, ograniczenie spożywania słodyczy (cukru) oraz diety zalecane przez dietetyka. Natomiast w badaniu autorstwa Kolarzyk i wsp., zrealizowanym wśród uczniów krakowskich szkół ponadpodstawowych (N=878), diety odchudzające stosowane były przez 8,4–20,5% ankietowanych. Respondenci korzystali z takich diet niekonwencjonalnych, jak: dr. Atkinsa, South Beach czy niskowęglowodanowa, jogurtowa, proteinowa oraz diety owocowe lub owocowo-warzywne. Były one stosowane częściej przez dziewczęta (20,57%) niż chłopców (8,44%) [33]. Według badań przeprowadzonych przez Wojtyłę-Buciora (N=999), 42% licealistów odchudzało się pomimo prawidłowej masy ciała, a 46% zamierzało schudnąć [34]. Na szczególną uwagę zasługuje fakt, że masa ciała osób odchudzających się w 80% przypadków była w normie. Niepokojącym jest stwierdzenie rodziców badanej młodzieży z powiatu kaliskiego, według których w ciągu ostatnich dwóch lat odchudzało się co czwarte dziecko. Badanie potwierdziło częstsze zainteresowanie dietami odchudzającymi wśród dziewcząt niż chłopców. Wykazano też, że w rodzinach, w których matki odchudzały się, dziewczęta częściej stosowały diety redukcyjne, w porównaniu do rodzin, w których matki nie stosowały takich praktyk [35, 36]. Podstawową formą leczenia otyłości i nadwagi jest prawidłowo skomponowana dieta redukcyjna, która zakłada spadek masy ciała. Źle zbilansowany jadłospis może prowadzić do negatywnych efektów zdrowotnych [37]. Dlatego ważne jest, aby kuracja odchudzająca przebiegała pod nadzorem dietetyka i zakładała dążenie do zmiany nawyków żywieniowych [5].

W badaniu własnym wykazano, że podstawowym źródłem wiedzy żywieniowej uczniów z Rudy Śląskiej są znajomi i przyjaciele (78,2%), fora internetowe (59,5%), blogi (57,3%) i profile społecznościowe (50%). Wykazano, że młodzież nie korzysta z wiarygodnych źródeł dotyczących prawidłowych zasad żywienia, co może stanowić jedną z ważnych przyczyn podejmowania przez nią błędnych decyzji żywieniowych. Według badania Kolarzyk E. i wsp. wiedzę na temat diet młodzież czerpała głównie z internetu (49,19%), dalej od znajomych (14,72%), a następnie z prasy (14,24%) oraz innych źródeł (14,08%) [33]. W badaniu Kowalcze przeprowadzonym wśród młodzieży gimnazjalnej zamieszkałej w Warszawie, dziewczęta głównie czerpały wiedzę żywieniową od rodziców (85%) i nauczycieli (74%), a następnie z telewizji. Chłopcy, podobnie jak dziewczęta, wskazywali na rodziców (71%), nauczycieli (78%) i telewizję, jako główne źródła wiedzy żywieniowej (74%) [38]. Korzystanie z nierzetelnych informacji naukowych w zakresie prawidłowych zasad żywienia przez uczniów może zwiększać ryzyko podejmowania przez nich zachowań antyzdrowotnych [8].

Wyniki przytoczonych badań podkreślają konieczność wdrożenia odpowiednich programów edukacyjnych dotyczących zasad prawidłowego żywienia. Wzrost świadomości młodzieży w tym zakresie może przyczynić się do obniżenia zainteresowania wciąż popularnymi dietami alternatywnymi wśród osób młodych i podejmowania przez nie właściwych zachowań zdrowotnych.

## PODSUMOWANIE

1. Licealiści znali produkty bezglutenowe i bezlaktozowe, ale trendy dietetyczne, takie jak: spożywanie produktów bezglutenowych i bezlaktozowych, nie wpływały na ich sposób odżywiania.
2. Nie wykazano, aby młodzież istotnie statystycznie częściej stosowała diety niskokaloryczne lub wysokobiałkowe w porównaniu do innych diet alternatywnych. Niepokojący jest jednak fakt, że młode osoby korzystały z diet niekonwencjonalnych, które mogą stanowić zagrożenie dla ich zdrowia.
3. Stwierdzono niedowagę u ponad połowy badanej populacji.
4. Głównym źródłem aktualnej wiedzy licealistów na temat zasad prawidłowego żywienia byli znajomi i przyjaciele, drugie miejsce zajęły źródła internetowe.

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**Konflikt interesów:**
*Autorzy deklarują brak konfliktu interesów*



**ORCID:**
*Katarzyna Tomczyk - 0000-0002-1978-4920*
*Beata Łabuz-Roszak - 0000-0002-9835-8240*

## AUTOR KORESPONDUJĄCY

**Beata Łabuz-Roszak**
Katedra i Zakład Podstawowych Nauk Medycznych
Wydział Zdrowia Publicznego Śląskiego Uniwersytetu Medycznego
ul. Piekarska 18, 41-902 Bytom, Polska
tel: +48 605097110
e-mail: broszak@sum.edu.pl



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**Załącznik – Autorska ankieta**

1. Data urodzenia ……..
2. Płeć……..
3. Wzrost…….
4. Masa ciała……...
5. Czy kiedykolwiek stosowałaś/stosowałeś lub obecnie stosujesz jakąkolwiek dietę?
……..

Jeśli tak, to podaj jaką……..

6. Jaka jest Twoja aktywność fizyczna (zaznacz prawidłową odpowiedź):

a. ćwiczę umiarkowanie lub intensywnie minimum 60 min codziennie
b. ćwiczę umiarkowanie lub intensywnie minimum 30 min codziennie
c. ćwiczę umiarkowanie lub intensywnie minimum 30 min kilka razy w tygodniu
d. nie ćwiczę w ogóle

7. Czy znasz i spożywasz produkty bezglutenowe (zaznacz właściwą odpowiedź):

a. znam i spożywam, bo choruję na celiakię
b. znam i spożywam, bo słyszałam/słyszałem, że to zdrowe
c. znam, ale nie pożywam
d. nie znam i nie spożywam

8. Czy znasz i spożywasz produkty bezlaktozowe (zaznacz właściwą odpowiedź):

e. Znam i spożywam, bo stwierdzono u mnie nietolerancję laktozy
f. Znam i spożywam, bo słyszałam/słyszałem, że to zdrowe
g. Znam, ale nie pożywam
h. Nie znam i nie spożywam

9. Jakie są źródła Twojej aktualnej wiedzy żywieniowej (można zaznaczyć kilka)?

| **Źródło wiedzy** | **Korzystam** | **Nie korzystam** |
|---|---|---|
| Książki / Podręczniki /Artykuły naukowe | | |
| Ulotki/Broszury | | |
| Czasopisma /Gazety | | |
| Zajęcia w szkole | | |
| Znajomi /Przyjaciele | | |
| Blogi internetowe | | |
| Forum internetowe | | |
| Profile na „Fecebooku" | | |
| Znane osoby / Celebryci | | |
| Trener | | |
| Dietetyk | | |
| Na siłowni (i innych miejscach gdzie ćwiczę) | | |

ORIGINAL ARTICLE
PRACA ORYGINALNA

# FEATURES OF SUBJECTIVE PERCEPTION OF SOCIAL SUPPORT BY PATIENTS WITH ENDOGENOUS MENTAL DISORDERS

**Anna O. Kaminska, Nataliia G. Pshuk, Liudmila V. Stukan**
NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE

## ABSTRACT

**Introduction:** Previous research shows that the role of perceived social support, defined as individuals' confidence of the availability of adequate support when needed, is considered as a protective external resource to promote better adaptation in psychiatric patients.

**The aim** of our study was to reveal the features of patients with endogenous mental disorders regarding their ability to perceive social support.

**Materials and methods:** A total of 168 patients with schizophrenia (F.20) and 75 patients with affective disorders (F30.F.33) were involved into this study under informed consent conditions. Control group included 55 mentally healthy respondents. Perceived social support was measured using Multidimensional Scale of Perceived Social Support (MSPSS) by Zimet (1998).

**Results:** Family, friends and significant others become main donors of social support for patients with endogenous mental disorders. Meanwhile, perceived social support in patients with schizophrenia is mostly coming from family. In patients with affective disorders, indicators of perceived social support from friends and significant others are significantly higher compared to patients with schizophrenia ($P < 0.001$). Revealed features can be used while developing appropriate psychoeducational programs for patients with endogenous mental disorders.

**Conclusions:** On the basis of revealed data, the key features of ability to perceive social support in patients with endogenous mental disorders, depending on the duration of the disease, were determined. It has been revealed that ability to perceive social support in patients with endogenous mental disorders decreases with prolongation of duration of the disease.

**KEY WORDS:** endogenous mental disorders, perceived social support, social support donors

Wiad Lek 2019, 72, 9 cz II, 1747-1751

## INTRODUCTION

Cooperation with the social environment of patients with mental disorders is a major aspect of psychiatric care, and social support is one of the central aspects of the multidisciplinary team work. [1]. Social support is a form of help to buffer certain stress factors and excessive subjective requirements imposed by social environment towards an individual.

There are "instrumental" (tangible, immediate financial assistance) and emotional (that promotes self-affirmation of the subject) types of support. Three main characteristics of social support are: 1) type of support, including its amount and how satisfying it is; 2) sources of support - specialists, family, friends, organizations; 3) functions of support - emotional and instrumental [2]. In addition, support can be direct, aimed at the patient or family caregivers, or indirect - through the activation of patients' social networks and their closest environment [3]. One of the important types of support is inclusion of both patients and their family caregivers into group forms of psychosocial therapy. Such groups in process of working on one or another module often maintain formed connections and practically turn into therapeutic communities. In practice, the whole range of forms and methods of social support is used. At the same time, it can be both general and aimed at help to resolve certain specific tasks [4]. Ability to perceive social support is an integral indicator, that shows the individual ability to identify persons' most priority relationships with the representatives of society (family, friends, significant others) [5]. One of the important factors influencing the overall effectiveness of treatment for schizophrenia and affective disorders is family support resource, which can help the patient to rebuild relationships with others, expand social contacts, use appropriate social skills, and form a self-service system [6].

## THE AIM

The aim of our study was to reveal the features of patients with endogenous mental disorders (EMD) regarding their ability to perceive social support.

## MATERIALS AND METHODS

Under informed consent conditions, 168 patients with schizophrenia (F.20) and 75 patients with affective disorders (F30.F.33) were surveyed. The main criteria for inclusion of patients into the study were: presence of general diagnostic criteria for schizophrenia and affective disorders according to ICD-10 (1994). Additional criteria

for inclusion of patients into the study were: presence of episodic manifestations of psychosis with progressive development of "negative" symptoms during the intervals in between psychotic episodes; state of remission in patients with schizophrenia and intermissions in patients with affective disorders; presence of an own or parental family; informed consent of a wife, husband or other family caregiver to participate in the study. The exclusion criteria were: domination of behavioral inadequacy in the clinical picture; presence of acute productive symptoms or presence of an acute manic or depressive condition; presence of signs of schizophrenic defect.

Among the surveyed patients with schizophrenia, 77 patients were diagnosed with an episodic type of progression with an increasing defect and 91 – with continuous type of progression. Surveyed patients were aged from 23 to 45 years (mean age 34.1 ± 0.8 years). Duration of observation of these patients corresponded to the requirements of ICD-10 and was at least a year, mean 2.7 ± 1.1 years. According to the total duration of the disease patients were divided into groups as follows - in 57 patients duration was up to 4 years (main group of patients with schizophrenia 1 - 1MGSch), in 58 patients - 4-8 years (main group of patients with schizophrenia 2 - 2MGSch) and in 53 patients - more than 8 years (main group of patients with schizophrenia 3 - 3MGSch). The average age of the disease manifestation was 25.3 ± 2.9 years. Patients with affective disorders (AD) accounted 30.9% (75 persons) of the total number of patients surveyed (MGAD – main group of patients with affective disorders). Among them 44 patients suffered from bipolar disorder and 31 persons were diagnosed with recurrent depressive disorder. Patients were aged 29 to 56 years (mean age 38.6 +0.3 years). Total duration of the disease was from 3 to 17 years.

The control group (CG) included 55 people who never sought for help from physicians for mental illness. The respondents from main and control groups were representative according to the basic socio-demographic characteristics. The study of perception of social support was conducted using the MSPSS scale by Zimet [7].

## RESULTS AND DISCUSSION

In overcoming stress and problem situations, the social support process plays a key role, due to its main components: social networks, coping strategy "search for social support" and the ability of a person to perceive social support. Due to social networks, sense of mutual trust, reliability in relationships and commitment are created, which provide awareness of the fact that, despite the circumstances, support for the sick person will still be ensured. Therefore, we considered it expedient to study the ability to perceive social support for EMD patients (schizophrenia and affective disorders). This is especially significant for patients who are outside of the psychiatric hospital. It is precisely because of the ability to accept or not to accept social support, social and communicative activity of the personality is formed, and features of emotional and behavioral reaction in frustration conditions are determined. In a situation where disease, on the one hand, completely changes personality structure and leads to suppression of emotional sphere, and on the other hand, complicates process of adequate interpersonal communication in family as well as in society in general, it is through psychological resources that an adaptive or non-adaptive behavioral style is formed, based, first of all, on processes of empathy, affiliation, psychological protection, locus of control, self-esteem and ability to perceive social support [8].

As shown in Table I, the patients surveyed, both in general and in certain spheres, had significantly lower subjective levels of perceived social support, compared to healthy individuals.

Indicators for the general assessment of patients with schizophrenia regarding the subjective perception of social support were 5.9 ± 2.0 points (or 49.2% of maximum expressiveness), while in patients with affective disorders - 8.7 ± 2.6 points (72.5% of maximum degree of expressiveness). Meanwhile, by all subscales, higher rates were recorded in patients with affective disorders ($P < 0.05$).

For the "family" subscale, only 47 (27.9%) patients of MGSch showed 100.0% of expressiveness of perceived social support; 54 patients (32.1%) - 75.0% expressiveness of this feature; 29 (17.3%) patients - 50% and 10 (5.9%) - 25% of expressiveness, while in MGAD 26 patients (34.6%) showed a 100% degree of perception of this feature, 30 (40.0%) - 75.0% expressiveness of the feature; 11 (14.6%) - 50.0% and 8 (10.6%) - 25.0% expressiveness for perceived social support.

Disturbed interpersonal relationships in a family where schizophrenic patient lives, inhibited desire of family members to provide support to the patient, and this lifestyle have led to disintegration and breaks in family relationships. Family members' counteraction towards behavioral changes, negative emotional responses to any event, caused negative and aggressive manifestations in patients with schizophrenia, increased emotional instability, aggressiveness and irritability. Social support of family did not meet the needs of patients and did not coincide with their intentions, desires, and as a result, patients denied support of family members, became non-complient, and the relationships became even more negatively emotionally colored. Meanwhile, patients with affective disorders, by contrast, believed that family was trying to help by counseling in any situation, supported their sympathies and desires, and only in their own families, patients could discuss their problems and get meaningful advice when making any decisions.

Only 33 (19.6%) patients from MGSch showed 100% degree of expressiveness of perceived social support according to "friends" subscale; 49 (29,1%) patients - 75% expressiveness of the sign; 35 (20.8%) patients - 50% expressiveness of the sign and 51 (30.4%) - 25% expressiveness of the sign.

As for MGAD, 26 patients (34.6%) showed a 100.0% degree of perceived social support, 31 (41.3%) patients - 75.0%; 16 (21.3%) patients and 2 patients (2.6%) showed respectively 50.0% and 25.0% expressiveness of perceived social support from others.

Study of the "friends" social network in the dynamics (anamnestically) convincingly shows that this network for patients

**Table I.** Results of the study of perceived social support in patients with endogenous mental disorders ( M±m)

| Subscales | MGSch (n=168) | MGAD (n=75) | CG (n=55) |
|---|---|---|---|
| Family | 2,6±0,7** | 3,8±0,9** | 3,8±0,2** |
| Friends | 1,3±0,2** | 2,7±1,1** | 3,5±0,5** |
| Significant others | 2,0±0,1* | 2,2±0,6* | 3,2±0,8** |
| General scores | 5,9±2,0** | 8,7±2,6** | 10,2±1,1** |

Note: the differences are statistically significant for * (P<0,05); ** (P<0,001)

**Table II.** Ability to perceive social support in patients with schizophrenia depending on the duration of the disease (M±m)

| Subscales | 1MGSch (n=57) | 2MGSch (n=58) | 3MGSch (n=53) | CG (n=55) |
|---|---|---|---|---|
| Family | 3,1±0,2* | 2,8±0,5* | 2,3±1,6** | 3,8±0,2** |
| Friends | 2,0±1,3** | 1,4±,18* | 1,1±0,3* | 3,5±0,5** |
| Significant others | 2,4±0,1* | 2,1±0,9* | 1,7±0,2** | 3,2±0,8** |
| General scores | 7,5±1,8 * | 6,3±0,4* | 5,1±,05* | 10,2±1,1** |

Note: the differences are statistically significant for * (P<0,05); ** (P<0,001)

with schizophrenia is leveled and subsequently ceases to exist. An increase in the phenomena of emotional and voluntary loss with autism contributes to the formation of an inadequate social network, where casual acquaintances become partners and friends of patients. Meanwhile, patients with affective disorders create a different psychological position, where new expectations and positive thoughts occur after communicating with friends, with hopes for the future and confidence that friends are always ready to help.

According to the "significant others" subscale 37 (22.0%) patients from MGSch showed 100.0% perception of social support; 66 (39.3%) of patients - 75% expressiveness of the sign; 42 (25.0%) - 50% expressiveness of the sign and 23 patients (13.7%) - 25% expressiveness of the sign. Somewhat different results were found in patients with affective disorders. 21 patients (28.0%) found 100.0% of perception of social support, 24 (32.1%) - 75.0%, 17 patients (22.6%) - 50.0% and 13 (17.3%) showed a result of 25.0%. In general, we can state that patients with EMD show, mainly, average levels of perceived social support according to the "significant others" subscale. The "significant others" network for patients with schizophrenia and affective disorders, was the source of material benefits, through which patients could afford satisfying their own needs. Forced nature of communication with its members made patients carry activities that meet the interests of social network regardless of their own desires. The limited experience of independent problem solving, destruction of social networks, lack of effective social support and its misperception contributed to the development of non-constructive behavioral patterns (avoidance). The results for "family", "friends", "significant other" subscales from the respondents of the control group were evenly distributed. The total score in healthy individuals was 10.2 points (or 85.0%, of the maximum possible expressiveness).

According to the "family" subscale, in the control group individuals that we surveyed, the average score was 3.8 ± 0.2 points (31.6%); for "friends" subscale - 3,5 ± 0,5 points (29,2%); for "significant others" subscale - 3.2 ± 0.8 points (39.2%). For the "family" subscale, 22 (40.0%) persons of the control group showed 100% expressiveness regarding perceived social support; 17 (30.9%) - showed 75% expressiveness of this feature; 12 (21.8%) showed 50% expressiveness of the sign and 4 (7.2%) respondents - 25% expressiveness of the sign. For the "friends" subscale, 25 (45.4%) of the control group showed 100% expressiveness of perceived social support; 15 (27.2%) - 75% expressiveness of the sign; 9 (16.3%) persons showed 50% expressiveness of the sign and 6 persons (10.9%) - 25%. For the "significant others" subscale 19 (34.5%) healthy individuals in the control group showed 100% perception of social support; 24 (43.6%) persons - 75% expressiveness of the sign; 7 (12.7%) of respondents in the control group showed 50% expressiveness and 5 (9.0%) - 25%. Subjective assessment of perceived social support in the CG described positive interpersonal relationships with members of social networks and effective functioning of the two-sidedly oriented social support process. For respondents of the control group, family was a constant source of social support. Active participation in family life increased their self-esteem, contributed to awareness of responsibility and self-importance for the family. The "friends" and "significant others" social networks were important components of life for the control groups' individuals to the extent that they attached to the vital importance. Conducting multiple interactions with representatives of social networks allowed them to get additional information on the issues that they were most worried about and were of significant importance to them, made it easier to identify possible solutions. Summarizing the foregoing, we can conclude that subjective ability to perceive assistance from society becomes one of the most important characteristics of the social-supporting process in patients with schizophrenia and affective disorders and to a certain extent determines directions for promoting the effectiveness of treatment.

An intergroup analysis of social support perception in schizophrenic patients shows (Table II) that for any duration of disease family remains the leading social support donor for the patient. Of course, with the duration of the disease for more

**Table III.** Ability to perceive social support in patients with affective disorders (MGAD) depending on the duration of the disease (M±m)

| Subscales | 1MGAD (n=34) | 2 MGAD (n=22) | 3 MGAD (n=19) | CG (n=55) |
|---|---|---|---|---|
| Family | 3,3±0,2* | 2,8±0,1* | 2,5±1,1** | 3,8±0,2** |
| Friends | 2,8±0,3** | 2,6±1,1* | 2,1±0,3* | 3,5±0,5** |
| Significant others | 3,1±0,1* | 2,5±0,4* | 2,0±0,9** | 3,2±0,8** |
| General scores | 9,2±0,6 * | 7,9±1,6* | 6,6±2,3* | 10,2±1,1** |

Note: the differences are statistically significant for * (P<0,05); ** (P<0,001)

than 8 years (3MGSch), the rates (2.3 ± 1.6) are significantly (P <0.05) decreased compared to those found in 2MGSch and 1MGSch patients (2.8 ± 0.5 and 3.1 ± 0.2 respectively). Detected fluctuations of scores for "family" subscale in patients with schizophrenia can be considered in the context of personality changes, namely, an increase in emotional-volitional loss. As for the subscales scores in the middle of the group (1MGSch, 2 MGSch, 3 MGSch), the overall picture was somewhat ambiguous. Among social support donors, the first ranked position was taken by the "family", the second – by the "significant others" (Table II). It can be assumed that in the family micro-environment there is an artificial cultivation and idealization of certain individuals who are close to the family, which can not but touch personality of the patient, with formation of priorities in communication and possibly, rather material, than moral support.

As for the donors of social support, patients with schizophrenia give the least value to "friends" category (it's progressively decreasing with the extension of the duration of the illness (1MGSch - 2.0 ± 1.3, 2MGSch - 1.4 ± 18 and 3MGSch - 1.1 ± 0.3; P<0.05). In our opinion, the progression of the abulia phenomena, deformation of emotional components of personality in schizophrenia causes lack of need for the interpersonal relationships formation, as a social support factor.

According to the "family" and "significant others " subscales respectively 22 (38.6%) and 17 (29.3%) patients showed 100.0% of perceived social support in 1MGSch, 24 patients (42.1%) and 19 (32.7%) showed 75.0% perceptions of support; 11 (19.3%) and 21 (36.8%) - 50.0% of the maximum scores. According to the "friends" subscale in the same group of patients, 29 patients (50.8%) had 100.0% perception of friends as social support donors; 17 (29.8%) showed 75.0% of the maximum perception, and 11 (19.3%) identified 50.0% of the ability to perceive social support in prosocial networks. In 2MGSch, among donors of social support, the first ranked place is occupied by "family" subscale (2.8 ± 0.5 points), the second ranked place - "significant others" (2.1 ± 0.9) and the third ranked place is taken by "friends" subscale (1.4 ± 1.8 points). It can be assumed that with the duration of the disease from 4 to 8 years still, the main hope of patients is aimed at getting family support. 100.0% of perceived social support from family were shown by 12 patients (20.6%), 75.0% - by 21 (36.2%) patients, 13 patients (22.4%) showed 50.0% and 12 patients (20.6%) - 25% of perceived social support. According to the "significant other" construct, percentages were as follows: 100.0% of perceived social support was shown by 10 patients (17.2%), 75.0% - by 11 (18.9%), 25 (43.1%) patients had a 50.0% perceived support level and 12 (20.6%) patients - 25.0%. As social support donors according to the "friends" subscale 100.0% perception was found in 9 (15.5%) patients, in 15 patients (25.8%) - 75.0% of the maximum, in 12 (20.6%) - 50.0% and in 22 patients (37.9%) perceived social support was 25.0%.

Scores for perception of social support donors in 3MGSch revealed low ability of patients to accept help of prosocial networks, as evidenced by percentage rates. For the "family" subscale, the average scores were 2.3 ± 1.6 points, and were the lowest among all groups of surveyed patients, as well as scores for other subscales. In this group of patients, only 6 patients (11.3%) showed 100% perceived social support, 11 (20.7%) perceived 75.0% of the maximum, 23 (43.3% - 50.0% of the maximal expression and 13 patients (24.5%) showed 25.0%. According to the "friends" subscale (average scores 1.1 ± 0.3), the scores were the lowest. 100.0% of perceived social support has not been shown by any surveyed respondent; in 12 patients (22.6%) the scores were 75.0%, in 15 (28.3%) - 50.0% and 26 (49.1%) scores were 25.0% of the maximum possible. Accordingly, for the "significant other" construct, scores were in 3 patients (5.6%) - 100.0% of social support perception, 8 patients (15.1%) showed 75.0% of expression, 28 people (52.8% ) - 50.0% and 14 (26.4%) - 25.0% of the maximum possible expression.

According to the obtained data, in situation of present disease (AD), family remains the main source of material and moral assistance for patients, provides positive emotional support. It is in the family circle that patients are trying to find the foundation for their own self-realization. However, the overall duration of the disease significantly (P <0.001) affects relationship with all donors of social support. According to the total assessment, loss of social support capacity with the extension of the total duration of the disease is determined (Table III).

100.0% of social support perception in 1MGAD for the "family" and "significant others" subscales was revealed in 7 (20.6%) patients; 12 patients (35.3%) showed 75.0% of perceived support; 9 (26.5%) - 50.0% of the maximum, and 6 respondents (17.6%) showed 25.0% of the maximum possible expressiveness of the sign. In the same group of patients, 100.0% perceived support from friends and other significant people for the respondent's personality was found respectively in 8 (23.5%) and 6 patients (17.6%); 10 (29.4%) and 9 (26.5%) showed 75.0% of the maximum expressiveness, and 10 (29.4%) and 12 (35.3%) found 50.0% of the ability to receive support donation in prosocial networks according to the subscales "friends" and "significant others". And only 6 (17.6%) and 7 (20.65) patients showed 25.0% of possible perception of social support.

In 2MGAD and 3MGAD among social support donors, the first ranked place is taken by the "family" subscale, the second ranked place – by the "friends" subscale and the third ranked place is occupied by "significant other" subscale scores (Table III). It can be assumed that with the duration of the disease from 4 to 8 years still, the main hope of patients is aimed at getting family support. 100.0% of social support perception from family showed 11 (50.0%) patients in 2MGAD and 6 (31.6%) patients in 3MGAD; 75.0% - 7 (31.8%) and 9 patients (47.4%) respectively; meanwhile, 4 patients (18.2%) in 2MGAD and 4 patients (21.0%) in 3MGAD showed a 50.0% perception of social support. According to the "significant other" construct, percentages in 2MGAD were as follows: 100.0% of perceived social support were present in 10 patients (45.4%), 75.0% - in 7 (31.8%), 3 patients (13.6% ) had a perception rate of 50.0%, and 2 patients (9.1%) found 25.0% of social support perception.

As donors of social support according to the "friends" subscale 100.0% of expressiveness of perceived social support was detected in 12 patients (54.5%) in 2MGAD and 6 respondents (31.6%) in 3MGAD; 75.0% of perceived support showed 8 patients (36.3%) from 2MGAD and 9 patients (47.3%) from 3MGAD; 2 patients (9.1%) in 2MGAD and 4 (21.0%) patients in 3MGAD found 50.0%. It should be mentioned that according to the construct "friends" in groups of patients from 2MGAD and 3MGAD there were no respondents with scores of perceived social support of 25,0% from the maximum possible. However, overall, scores of patients in 2MGAD were significantly superior to those of 3MGAD (2.6 ± 1.1 versus 2.1 ± 0.3; P <0.001).

## CONCLUSIONS

Thus, the data we received as for the ability of patients with endogenous mental disorders to perceive social support showed the following: presence of a mentally sick person in family is a factor, that causes activation of prosocial networks to assist in formation of adaptation mechanisms. "Family", "friends" and "significant others" become donors of social support for patients with endogenous mental disorders. Meanwhile, the social network "family" in patients with schizophrenia is in most cases represented by parental family; the social network of "friends" is narrow, the reasons for which are mental state of patients, severity degree of obligatory symptoms of schizophrenic process (autism, apathy, ambivalence), a certain level of disintegrative behavior with emotional and volitional loss. In the social network of "significant others" in patients with schizophrenia, leading donors of social support are determined as wife (28.6%), mother (39.8%), father (20.2%), husband (11.3%). In patients with affective disorders, indicators of perceived social support from friends and significant others are significantly higher compared to patients with schizophrenia (P <0.001). Revealed features should be taken into consideration while performing the development of appropriate psychoeducational programs for patients with endogenous mental disorders.

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**Authors' contributions:**
*According to the order of the Authorship.*

**ORCID numbers:**
*Anna O. Kaminska - 0000-0003-3281-989X*
*Nataliia G. Pshuk - 0000-0001-9857-2565*
*Liudmila V. Stukan - 0000-0003-2054-1325*

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**CORRESPONDING AUTHOR**
**Anna Kaminska**
Shevchenka street, 71a, Vinnytsya, Ukraine
tel: +380979719887
e-mail: adonidisvernalis@gmail.com

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# USAGE OF HISTOLOGICAL METHODS IN DETERMINING THE PRESCRIPTION OF SPLEEN INJURIES IN FORENSIC MEDICAL PRACTICE

**Olena P. Babkina[1], Dmytro O. Matyukhin[2], Svitlana I. Danylchenko[3], Edouard A. Glazkov[2], Oleksiy O. Galmyz[4]**
[1]OO BOHOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE
[2]LUHANSK STATE MEDICAL UNIVERSITY, RUBIZHNE TOWN, LUHANSK REGION, UKRAINE
[3]PETRO MOHYLA BLACK SEA NATIONAL UNIVERSITY, MYKOLAIV, UKRAINE
[4]LUGANSK REGIONAL CLINICAL ONCOLOGIC DISPENSARY, KREMENNAIA, UKRAINE

## ABSTRACT

**Introduction:** The article presents data from literary sources and a statistical analysis of one's own research on the nature, mechanism and prescription of spleen injury in the case of mechanical trauma and the absence of alcohol intoxication.

**The aim:** To study the dynamics of changes in the histological parameters of the spleen injured tissues in case of mechanical trauma depending on the prescription of injury.

**Materials and methods:** The material of the study was the spleen tissue of 56 males and females aged from 20-60 who died at known and unknown time in the presence and absence of alcohol in the blood. We used histological, histochemical methods, and carried out a statistical analysis of the results.

**Results:** The obtained results showed that during the mechanical injury of spleen there often developed a capsule and a parenchyma with hematoma in the area of injury. Our records showed that during the first 6 hours after injury, there appeared a hematoma in the center of the injury. Hemolysis of the erythrocyte particles was observed in the center of the hematoma. There were isolated leukocytes and fibrin tissues closer to the edge of the hematoma.

**Conclusions:** The obtained results indicate that there are several histological changes in the damaged spleen tissues area which directly depend on the time which passed from the moment of injury.

**KEY WORDS:** forensic medical examination, trauma, prescription, spleen, histological parameters

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## INTRODUCTION

The study of the mechanism of development and the prescription of injury to the abdominal cavity, in particular the spleen, is thoroughly researched by specialists in various fields of medicine, as these issues are extremely relevant, both in terms of diagnosis and treatment of patients, and in the preventive aspect of injury [1]. The prescription of injuries determination in the deceased, the life expectancy of victims after injury, the mechanism and morphological characteristics of injuries of the abdominal cavity were not deliberately studied and systematized, despite the fact that these cases are encountered very often in forensic medical practice. In recent years, many domestic and foreign authors [2], studying the possibility of solving this problem, have begun paying serious attention to the study of various biological objects with the following laboratory methods: histological, histochemical, biochemical, immunological, etc. The comprehensive methods for assessing the prescription of injury, based on the consideration of the case circumstances, in combination with the results of the forensic examination of the corpse and laboratory data are prospective. From this point of view, histological research methods turned to be very informative, as they were most often used in forensic medical practice while determining the prescription of injuries. The dynamics of organ and tissue changes after injury, in particular of the skin, and less attention was paid to the study of internal organs [3]. Nowadays the spleen injury occurs quite often and among the injuries of the abdominal cavity occupies one of the leading places. According to the literature the frequency of the spleen injuries is from 15 to 33% [4].

Microscopic changes in the damaged zone of spleen from the view point of the prescription of their formation have not been studied in details. Moreover, the features of the spleen damaged in cases of combined injury with other organs [5] have not been described. One of the methods for determining the prescription of spleen injury is a histological method.

## THE AIM

The purpose of this work was to study the dynamics of changes in the histological parameters of the spleen injured tissues in case of mechanical trauma depending on the prescription of injury.

## MATERIALS AND METHODS

The material of the study was the spleen tissue of 56 males and females aged from 20 to 60 who died in the presence and absence of alcohol in the blood and were subjected to an autopsy in the anatomical department of the Forensic Medical Examination Bureau. The collection of tissues of traumatized organs was carried out in the morgue at air temperature from +16 to 25 C, relative humidity 40-60%. In the course of research, we used histological and histochemical methods to detect the dynamics of regeneration processes of histological changes in the spleen tissues, and carried out a statistical analysis of the results.

The work was carried out in accordance with the requirements of the "Instruction on conducting forensic medical examination" (Order of the Ministry of Health of Ukraine No. 6 dated January 17, 1995), in accordance with the requirements and norms, the standard provisions on ethics of the Ministry of Health of Ukraine No. 690 dated September 23, 2009, "The procedure for the removal of biological objects from the dead, whose bodies are subject to forensic examination and pathological anatomical investigation, for scientific purposes" (2018).

## RESULTS AND DISCUSSION

In literary sources there is a large amount of data [6], indicating the presence of specific features of the spleen damage depending on the type of traumatic action, the place of external force use, the anatomical structure of the organ, topography, the state of the surrounding organs, resulting in damage or the capsule rupture and tissue breakage in a linear, stellate or zigzag form, focal hematoma under the spleen capsule and in the cellular gates, tissue ruptures in the gate area and on the back of the spleen, breakages in the spleen connection, its partial or complete disruption in the gate with its shifting into the peritoneal.

The main mechanisms for the formation of spleen injuries are stroke, compression, shaking of the body, or their combination. Up to now, there was no single morphological classification of spleen injuries, nor a single approach to the expert assessment of spleen injuries, including the nature of injuries, their shape, orientation, localization, volume, and morphological manifestations of trauma. Some authors singled out subcapsular hematomas, capsule ruptures, parenchymal ruptures, central damage, and two-stage ruptures. Thus, M. A. Sapozhnikova [7] distinguishes among the traumatic spleen injuries surface ruptures or cracks of the capsule, crossover hematomas with the preservation of the capsule integrity, crossover hematomas and breaks in the capsule integrity, tears and smashing of the organ, damage to its vascular leg. The author points out that there are specific features of the spleen injury depending on the type of traumatic effect: the formation of capsule breaks in traffic injuries and falling from high altitude; subcapsular ruptures and hematomas as a result of the organ concussion with a significant blood flow to the pulp; crossover hematomas splitting the spleen and tearing off its legs which occurs in case of direct kicks in the abdomen.

The classification of morphological manifestations of blunt trauma of the spleen was developed according to other data. The classification includes the nature of lesions, their shape, and orientation of the organ, localization, volume and morphological manifestations of the spleen trauma: hematomas, breaks, destruction of the organ, full or partial tearing. It is necessary to pay attention to the classification of the spleen injuries with traumatic blunt objects developed by Yu. I. Sosedko [8] which includes description of signs and constituent elements of objects. The author classifies the nature of the damage as the classification signs, which includes: constituent elements in the form of hematomas, breaks, fractures, subcapsular lesions, complete separation of the organ or its partial destruction, damage of connection; orientation of damages in the direction. The spleen injury with a traumatic blunt object with a limited surface depends on the place of external force application, direction of blow and energy of traumatic action. However, in the above classification, authors indicated trauma from blunt objects, despite the fact that a combined injury and injuries from sharp objects and from firearms. Yu. I. Sosedko [8] considers setting the spleen injury prescription with the help of microscopy to be very questionable. In the author's opinion, it is especially difficult to diagnose the early terms of injury, where the main diagnostic feature is the cellular response of the spleen tissue, which is due to its anatomical structure, contains a significant number of cellular elements. An objective indicator of the spleen subcapsular hematoma prescription is a leukocyte reaction, which can be reliably determined in the damaged area 2-3 hours after injury. Granulocytes gradually formed a torus demarcationis, which was visible under a microscope 12 hours after injury. A torus demarcationis completed its formation in one day. Granulocytes decay in the spleen damage area began on the 2$^{nd}$-3$^{rd}$ day. 4-5 days after injury there occured a massive disintegration of granulocytes.

Attention should be also paid to the peculiarities of the formation and morphology of the subcapsular spleen ruptures, in particular the hematomas under the organ capsule or the depths of its parenchyma with a rupture or no apparent rupture of parenchyma, which begin to appear at the time of splitting the spleen capsule at the site of the hematoma and gradually accumulate in the distant periods after the trauma. This process often leads to diagnostic errors in medical practice. The spleen capsule is not damaged. Cases when hematoma under the capsule accumulates and at different time after the trauma leads to the break of capsules and bleeding into the abdominal cavity, are called two-stage or two-phase. Two-stage, or "delayed", spleen ruptures according to the literature develop from 3 to 30 days and make up 10 to 30% of all injuries. Statistical data show that 50% of ruptures occur during the first week, not earlier than on the 2nd day after injury, 25% occur during the 2nd week, and 10% can occur in a month. The mechanism of the subcapsular spleen ruptures formation, the time interval of their formation and rupture, is partially reflected in the works of a number of

authors [9]. The morphological features of the subcapsular damage depend on the nature and extent of damage to the spleen parenchyma in the first stage of the injury and the term of the second stage of the injury, namely the capsule rupture in the place of the capsule hematoma accumulation. Taking into account the peculiarities of spleen injuries morphology, their volume, depth of distribution, duration of trauma, the author identified several types of subcapsular rupture of this organ.

There also arises a question of spleen injury prescription, which, despite the large number of conducted studies, was not finally resolved. Rusakova T. I. [10] established the dynamics of the inflammatory and reparative process occuring in the area of spleen damage and revealed its basic laws. The author found out that in spleen injury with a fatal end at the place of accident, they histologically determined only hematomas with unchanged erythrocytes in areas of tissue destruction. 2 hours after the injury, they often revealed rupture of the capsule and parenchyma with bleeding in the form of hematoma in areas of pulp destruction. Ruptures were represented by clots of blood, consisting mainly of unchanged red blood cells, white blood cells, among which a moderate amount of unchanged granulocytes was determined. In some fields of view, under the microscope, there could be seen a few clusters of tender, loose grainy masses of fibrin. Approximately 7-8 hours after injury there was a small amount of granulocytes in a state of disintegration among unchanged granulocytes. Small clusters or structures like torus demarcationis were formed near the edges of the hematoma granulocytes

Sapozhnikova M. A. [7] defined the spleen injuries prescription taking into account blood changes in hematoma and the surrounding tissue reaction. It is not possible to use a ferous pigment, which is formed in a pulp, knowing that in the normal spleen there is a destruction of the formed blood elements that are deposited, with hemosiderin grains discharge. As a result of the studies, the author described a histological picture of the changes observed in the spleen and parenchyma hematomas area at different periods of trauma occurence. It was noted that erythrocytes with clearly visible boundaries accumulated initially under the capsule or in the pulp of the spleen. Perifocal edema and fulminate sinusoids of the pulp develop around the prevailing hematoma. On the 2$^{nd}$-3$^{rd}$ day, there occured plasma and fibrin separation from the formed blood elements where the signs of hemolysis beginning in the center of hematoma were observed. Impregnation the spleen pulp with blood did not damage its structure. The red blood cells destruction occured at the same time as in subcapsular hematoma. The first signs of hematoma organization began to appear before the 5$^{th}$ day after the injury, when the fibroblasts from the capillaries walls were proliferating.

The obtained results [11] showed that mechanical ruptures of the spleen often caused ruptures in capsules and parenchyma as well as hematomas in the injured area. According to our data, during the first 6 hours after injury, and a histological examination there appeared a hematoma in the center of the injury. It had the form of a cluster of orange erythrocytes with clear contours. Hemolysis of the erythrocyte particles was observed in the center of the hematoma. There were isolated leukocytes and fibrin tissues closer to the edge of the hematoma. It should be noted that there appeared a perifocal edema along the edge of the hematoma. Leukotases and perifocal clumps of leukocytes were observed in the vessels. In the vicinity of the vessels, in sinuses, and near damaged areas we revealed small clumps of leukocytes not connected with vessels (Fig. 1).

6-12 hours after injury, most of the erythrocytes in the center of the injury had fuzzy contours with their widespread hemolysis. Unaffected erythrocytes were sometimes found only along the edge of the hematoma. The number of granulocytes in the center of hematoma increased and their destruction began. Granulocytes continued to accumulate on the periphery of the hematoma; most of them were in decay. Fibers appeared in the form of clusters forming a torus demarcationis, which clearly separated the areas of the damaged parenchyma from intact. There were focal clusters of granulocytes in the perifocal zone in the sinuses.

During 12-24 hours after injury we observed hemolyzed red blood cells. The granulocytes were completely destroyed; the formed torus demarcationis was represented by destroyed granulocytes; macrophages were with intracellular contents of hemosiderin grains; fibrin strands were on the border of the hematoma with intact tissues; thrombi were found in the vessels. There was an anemia of red pulp (Fig. 2). 2-3 days later, there began a resorption of erythrocytes destruction products and the formation of siderophages. The gistio-fibroblast cells proliferation and platelets organization in vessels (fibroblasts appearance and blood vessels in the thrombus) started on the edge of the hematoma, on the border with intact tissue. The formation of a torus demarcationis continued in the form of fuzzy strains of the fibrin mass which grew in the histo-fibroblastic cells and formed soft calcium fibers, most of which were hemosiderophages. Perifocal proliferative and leukocyte responses decreasd and were practically not expressed. Extracellular hemosiderin was occasionally present in light yellow color (Fig. 3).

If the prescription of injury is 4-6 days, there is a prevalence of connective tissue elements (lymphocytes, histiocytes, plasma cells); there is a massive disintegration of granulocytes and signs of blood clots organization in the spleen vessels (Fig. 4). The hematoma was represented by erythrocytes, which were completely hemolyzed; there was a large amount of leukocyte nuclear detritus with the disturbed integrit; the fibrin fibers were densified and clearly distinguish hematoma from damaged tissues. Multiple strains of histio-fibroblast cellular elements (fibroblasts, fibrocytes) grew into hematoma from parenchyma. They can be arranged both in order and chaotically. Delicate collagen fibers began to form a capsule. It should be noted that during this period the number of siderophages is sharply increased, and when colored with medications, small seeds of hemosiderin of light brown color are observed (Fig. 5).

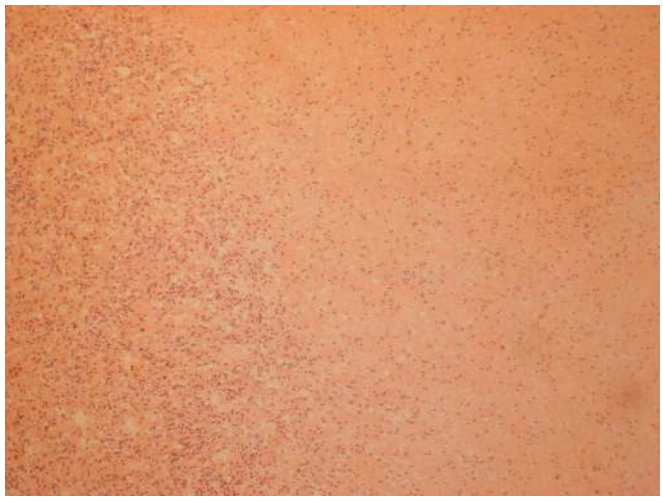

**Fig. 1.** Hematoma in the form of red blood cells accumulation, perifocal edema, small clumps of the leukocytes in the spleen in a woman, 24 years old, who died from a mechanical trauma. The prescription of injury is 6 hours. Colored with hematoxylin-eosin. ZB.: x100

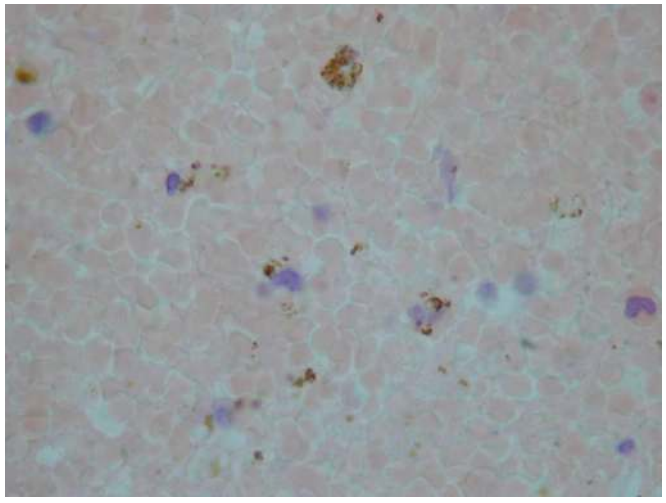

**Fig. 3.** Single hemosiderin granules in the spleen in a man, 60 years old, who died from a mechanical trauma. The prescription of injury is 30 hours. Colored with hematoxylin-eosin. ZB.: x 100

The capsule formation lasted up to 1-2 months from the moment of injury. It should be noted that in cases of two-stage spleen ruptures, we observed the formation of a subcapsular hematoma, which grew in its volume and resulted in the destruction of parenchyma. As a result of the aforementioned, the morphological picture could differ from the above, which should be taken into account when establishing the prescription of injury.

Thus, mechanism and prescription of spleen injury in the case of mechanical trauma and the absence of alcohol intoxication, microscopic changes in the damaged zone of spleen from the view point of the prescription of their formation have of combined not been studied in details authors.

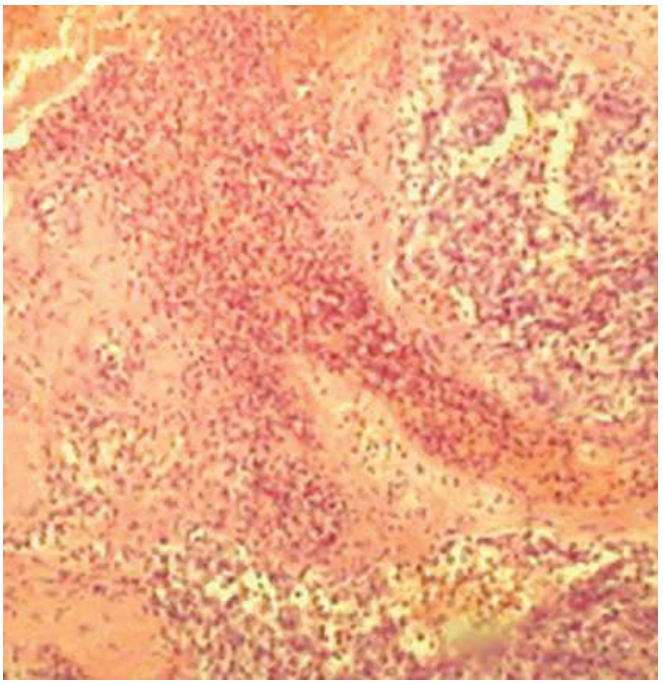

**Fig. 2.** Clear torus demarcationis, a large number of granulocytes in the stage of decay in the spleen of 40 year old man who died from a mechanical trauma. The prescription of the injury is 20 hours. Colored with hematoxylin-eosin. ZB.: x200

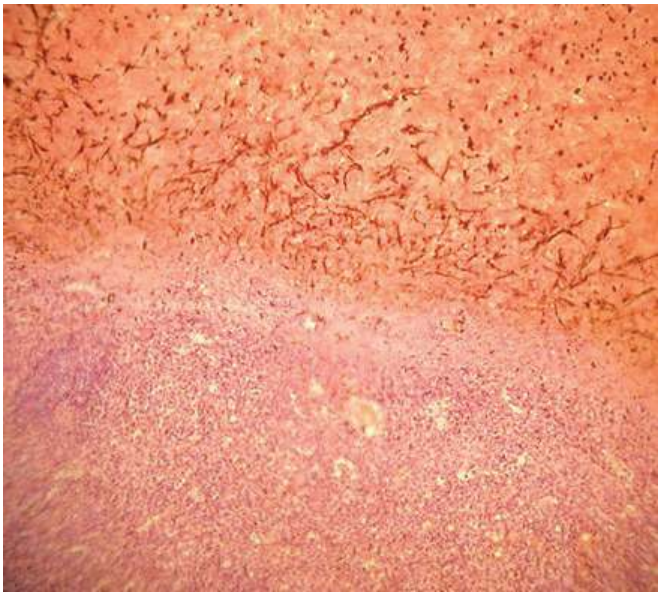

**Fig. 4.** Prevalence of connective tissue elements, the spleen granulocytes disintegration in a man, 54 years old, who died from mechanical injury. The prescription of the injury is 5 days. Colored with hematoxylin-eosin. ZB.: x 200

## CONCLUSIONS

Thus, the obtained results indicate that there are several histological changes in the damaged spleen tissues area which directly depend on the time which passed from the moment of injury. It is appropriate to use the histological method to determine the prescription of injury both in cases of isolated

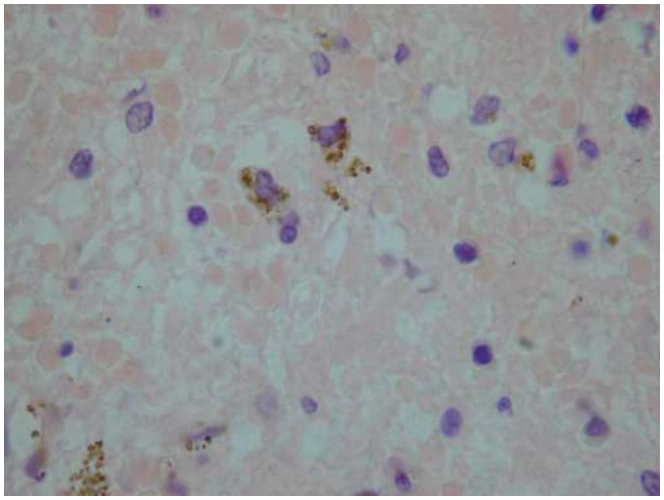

**Fig. 5.** Sideroblasts in the spleen tissues of a woman, 20 years old, who died from a mechanical trauma. The prescription of injury is 7 days. Colored with hematoxylin-eosin. ZB.: x200

spleen injury and in cases of combined injury of the abdominal organs as it enables establishing the prescription of injury more precisely.

**Prospects for further research:** Further research of spleen injuries, in particular the diagnosis of its mechanism, nature and time, is necessary for the development and application of such injuries prevention.

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**Authors' contributions:**
*According to the order of the Authorship.*

**ORCID numbers:**
*Olena P. Babkina - 0000-0001-8120-6526*
*Dmytro O. Matyukhin - 0000-0002-4429-4720*
*Svitlana I. Danylchenko - 0000-0001-5312-0231*
*Edouard A. Glazkov - 0000-0002-7087-8455*
*Oleksiy O. Galmyz - 0000-0001-7066-8100*

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**CORRESPONDING AUTHOR**
**Olena P. Babkina**
Department of Forensic Medicine and Medical Law
OO Bohomolets National Medical University
Kyiv, 01601, Ukraine
tel: +38 093 065 42 39
e-mail: hpbsme@gmail.com

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# APPLICATION OF ANTISEPTIC AND OSTEOPLASTIC DRUG FOR DESTRUCTIVE PERIODONTITIS TREATMENT

**Liliya I. Lyashenko, Larysa M. Lobach, Vladymyr N. Petrushanko, Zoryana Y. Nazarenko, Iryna M. Tkachenko**
UKRAINIAN MEDICAL STOMATOLOGICAL ACADEMY, POLTAVA, UKRAINE

## ABSTRACT

**Introduction:** Treatment of destructive forms of chronic periodontitis is extremely topical. Its relevance is associated with the features of treatment, which depends on the stage of the exacerbation process. The issue of the problem is also in the fact that the destructive seat of periodontitis is a source of chronic infection.

**The aim:** The task of the research was to evaluate the conservative treatment of chronic destructive forms of periodontitis with a dental kit "Cupratin", developed for professional usage in dental practice.

**Materials and methods:** "Cupratin" is a complex medicament based on suspensions of calcium hydroxide, copper-calcium hydroxide and powder, which contains hydroxide aluminosilicate and calcium sulphate, radiopaque filler. It has bactericidal and osteoplastic effect. The treatment involved 44 patients (44 teeth) in the age group of 37 to 50 years suffering from chronic granulating periodontitis without concomitant diseases.

Patients were divided into two groups: investigated and control. In the main group of patients, a suspension on the basis of copper-calcium was used for treatment (root canals were filled with "Cupratin" as a temporary filling material). Obturation of canals was preceded by chemical and mechanical treatment.

The medical material was in direct contact with periodontal tissues for 20-55 days.

Intraoral X-ray radiography was taken from the patients within the intervals of 3 and 6 months.

**Results and conclusions:** Positive results were obtained, which were characterized by the disappearance of subjective symptoms, intensive bone tissue reconstruction in the site of destruction and a decrease in the size of the destruction respectively.

**KEY WORDS:** Chronic destructive periodontitis, temporal obturation, osseous regeneration, bone mineralization

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## INTRODUCTION

Treatment of destructive forms of chronic periodontitis is extremely topical. Its actuality is associated with the features of treatment, which depends on the stage of the exacerbation of the process. The issue of the problem lies also in the fact that the destructive locus of periodontitis is a source of chronic infection [1, 2].

Among all diseases of the maxillofacial area, the number of chronic periodontitis varies from 15 to 30% according to various authors, [1, 7, 11]. In the last decade the number of patients with chronic inflammatory diseases of the maxillofacial area did not reduced despite the significant improvement in the quality of dental care.

Inflammatory locus in chronic periodontitis on the background of normal reactivity of the organism represents a protective reaction of the organism. Besides, the long-term existence of the focal point of chronic infection leads to a decrease in the level of nonspecific resistance of the organism during the violation of the functions of the immune system. As a result, this process leads to the development of complications [3, 9, 10].

The above-mentioned reasons explain the socio-medical significance of the problem of chronic periodontitis and the importance of the following research for new effective methods of its treatment [2, 4].

## THE AIM

Our aim was to improve the quality of chronic forms of periodontitis treatment in multi-root teeth during the remission stage by applying modern methods of antiseptic treatment, obturation of root canals in accordance with generally accepted requirements and activation of regenerative processes in the area of destruction of periapical tissues.

## MATERIALS AND METHODS

For the treatment of chronic granulating periodontitis a dental kit "Cupratin" was used for filling the root canals. Dental Kit "Cupratin" with a complex preparation, consists of:

- Suspension №1 based on calcium hydroxide;
- Suspension №2 based on copper-calcium hydroxide;
- Powder containing hydroxide, aluminosilicate and calcium sulfate, X-ray diffuser and technological additives.

Dental Kit "Cupratin" is a bactericidal system with highly active hydroxocuprat. High alkaline medium of suspensions (pH = 12-12,5) and high content of hydroxide and calcium oxide provides sterility and stimulates the formation of bone tissue.

Suspension №1 is a calcium hydroxide with distilled water. Calcium hydroxide stimulates the formation of mineralized tissue. The bactericidal action of highly dispersed

calcium hydroxide can be explained by alkaline proteolysis and saponification of proteins of organisms.

Suspension №2 is an equilibrated system of copper-calcium hydroxide with hydroxocuprat in water surrounding. The antibacterial activity of copper ions is much higher comparing to calcium hydroxide. The concentration of copper ions in the suspension is 2,0-3,0%.

44 patients of male and female sex from 37 to 50 years old without concomitant pathologies were examined. In 20 molars of the upper jaw and 24 molars of the mandible chronic granulating periodontitis at the remission stage without the presence of fistula was diagnosed.

All patients were examined according to the traditional schema. Additionally, an X-ray diagnosis of teeth was performed prior to treatment, immediately after treatment and in 3- and 6-months term with the dynamic monitoring.

Patients were divided into 2 groups depending on the treatment method used. Patients in the main group (24 persons) received a treatment method using the dental kit "Cupratin" and patients of the control group (20 people) used calcium-containing preparation "Calcisole-C".

For the treatment of periodontitis a traditional method of chemical and mechanical preparation was used. During the manipulation a system of nickel-titanium tools "Protaper" [5, 6] was used.

In the main group irrigation of root canals was performed with 3% solution of sodium hypochloride and 40% citric acid solution. A suslpension of calcium copper (№ 2) was also used. When processing canals with a suspension of copper-calcium hydroxide, hydroxocuprate ions are converted into a low-soluble copper hydroxide, which provides prolonged bactericidal, sterility and sealing of the canal and the apical part.

After medical treatment of infected canals they were obturated with paste which contained the powder with a suspension of calcium hydroxide (№ 1).

In the control group, the medical treatment of root canals was performed using 3% solution of sodium hypochloride and 40% solution of citric acid and temporary sealing of the root canals with "Calcisole-C".

After 6 months the root canals of teeth with chronic granulating periodontitis of both groups were obturated by cold lateral condensation gutta-percha method with the usage of "Viedent" siller (by Vladmiva).

## RESULTS AND DISCUSSION

We considered the area of the defeat decreased by 1/3 or more from the size of the previous center as a positive

**Table I.** Camparison of treatment efficiency indicators for patients of the main and groups

| Groups | Results | | | |
|---|---|---|---|---|
| | 3 months | | 6 months | |
| | Reduction of the lesion area | % person | Reduction of the lesion area | % person |
| Main (n = 24) | 1/2 | 92,0 ± 1,2 | 2/3 | 95,0 ± 1,3 |
| Control (n = 20) | 1/3 | 25,0 ± 0,7* | 1/2 | 73 ± 1,2** |

Note * p <0,001 - the reliability of the difference between the indicators of the main and control groups.
** p <0,05 - the reliability of the difference between the indicators of the main and control groups.

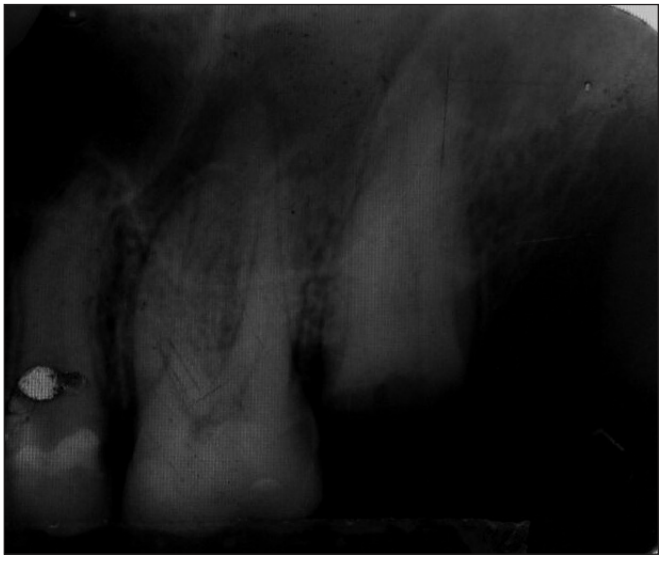

**Fig. 1**. Tooth 26 before treatment (control group).

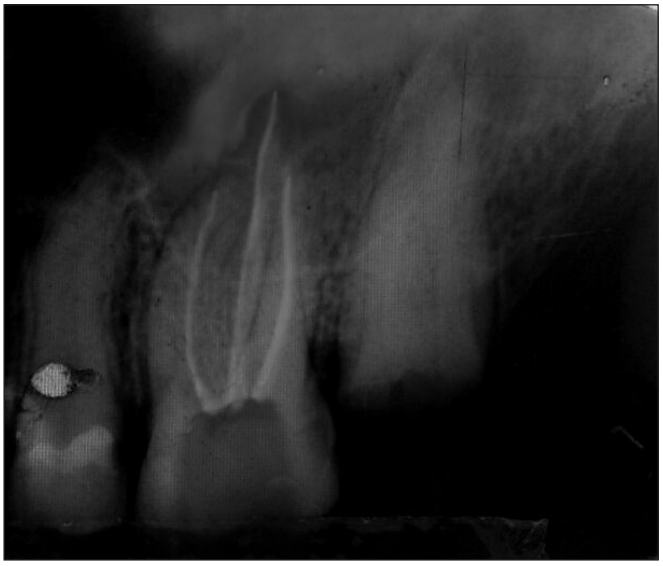

**Fig. 2.** Tooth 26 after treatment (control group).

**Fig. 3.** Tooth 46 before treatment (main group).

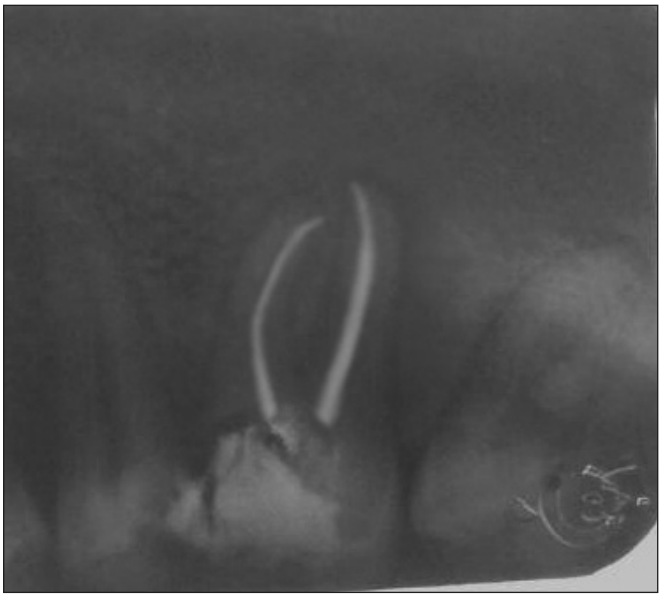

**Fig. 4.** Tooth 46 after treatment (main group).

result of treatment. The condition of pathologically altered bone tissue after treatment was evaluated according to the following parameters: size, contours, shadow intensity [3, 8]. During the observation period the patients showed positive dynamics.

After 3 months the destruction spot in periapical tissues decreased by 1/2 in 92% ± 1,2 cases in the researched group of patients.

In the control group, the inflammation spot decreased by 1/3 in 25% ± 0.7 cases (Fig. 1, 2). Border of bone tissue destruction became narrower. Pathologically modified bone tissue was replaced by a fibrous tissue, that affected in the change of intensity of the shadow. The periodontal crack decreased in the upper third of the root.

During the examination of patients in the researched and control groups the mucous membrane in the region of the projection of the top of the root did not have pathological changes, palpation was painless. Percussion of teeth was painless in patients of the researched group. In several cases a sensitive percussion of teeth was observed in patients in the control group.

After 6 months of treatment the destruction of bone tissue of patients in the main group decreased by 2/3 in 95% ± 1.3 cases (Fig. 3, 4).

In the control group positive dynamics was also noted. However, the percentage of positive results was lower. Regeneration of the periapical lesion was 73% ± 1.2 cases.

Complains in both groups of patient were absent. Objectively: mucous membrane without pathological changes, palpation was painless, painless percussion of teeth in all patients. Regional lymphatic nodes are not increased with palpation.

The obtained results allow us to recommend the usage of the complex preparation of "Cupratin" for faster and complete reduction of the periapical lesion for the treatment of chronic granulating periodontitis with destruction of bone tissue up to 0,6 cm.

## CONCLUSIONS

Thus, the research results of the treatment of chronic granulating periodontitis in patients of the researched group, where "Cupratin" was used was indicated its high clinical efficacy.

Patients treated only with "Apex-Dent" the regeneration process was significantly slower.

Consequently, usage of "Cupratin" enables to accelerate the process of regeneration in osseous tissues in the locus of periapical inflammation during the conservative treatment of chronic granulating periodontitis more effectively.

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**Authors' contributions:**
*According to the order of the Authorship.*

**ORCID numbers:**
*Liliya I. Lyashenko - 0000-0003-3411-4885*
*Vladymyr N. Petrushanko - 000-0003-4704-6877*
*Zoryana Y. Nazarenko - 0000-0002-0967-2319*
*Iryna M. Tkachenko - 0000-0001-8243-8644*

**Conflict of interest:**
*The Authors declare no conflict of interest.*

## CORRESPONDING AUTHOR
**Iryna M. Tkachenko**
Ukrainian Medical Stomatological Academy
Shevchenko 23 str., 36011 Poltava, Ukraine
e-mail: iryna tkachenkoirmix@gmail.com

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# ANAPLASMOSIS: EXPERIMENTAL IMMUNODEFICIENT STATE MODEL

**Andrey V. Bondarenko[1], Sergey I. Pokhil[2], Marianna V. Lytvynenko[3], Tatyana V. Bocharova[1], Vitaliy V. Gargin[1]**
[1]KHARKIV NATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE
[2]MECHNIKOV INSTITUTE OF MICROBIOLOGY AND IMMUNOLOGY, KHARKIV, UKRAINE
[3]ODESA NATIONAL MEDICAL UNIVERSITY, ODESA, UKRAINE

## ABSTRACT

**Introduction:** The recently described anaplasmosis infection is widespread but concerns to the insufficiently known group of diseases.

**The aim** of our research is the development of uniform biological model for reproducing of artificial immunodeficient state by experimental anaplasmosis.

**Materials and methods:** Algorithm of experimental anaplasmosis reproducing, consisted of such consecutive stages: 1) artificial forming of the immunodeficient state at nonlinear white mise (*Mus musculus* L.); 2) preparation of the tested biological material samples; 3) inoculation by prepared samples of the laboratory animals with the artificially formed immunodeficient state; 4) sampling from the dead or slaughtered (by the method of chloroformed anesthesia) experimental animals of sectional material (organs and targets tissues); 5) verification of aetiology by express detection of causative agents by the method of PCR in the selected samples of sectional material.

**Results:** Biological model of experimental anaplasmosis have been created suitable for realization of both diagnostic and epidemiological, epizootic, ecobiological and other researches of different origin biological material samples, including samples of solid and liquid consistency material. Formed model realised in premature death of experimental animals in 17.4 % cases; resulted in an onset of disease clinical signs without death during the term of supervision in 43.8 % cases; coursed in the absence of the expressed symptoms of infection in 31.3 % cases.

**Conclusions:** Developed biological model of experimental anaplasmosis consists in that as laboratory animals with the increased sensitiveness to the infection and accumulation of causative agent are used white nonlinear mice with the artificially formed immunodeficient state.

**KEY WORDS:** biological model, *Mus musculus* L., cyclophosphamide, anaplasmosis, *Anaplasma phagocytophilum*

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## INTRODUCTION

The recently described anaplasmosis infection is enough widespread in the European countries concern to the insufficiently known group of diseases. Anaplasmosis is included in the group of transmissible infectious diseases of man, cattle and mammals, and caused by bacteria of the genus *Anaplasma* [1-4]. A decision value in diagnostics of the disease is taken the methods of etiologic verification of anaplasmosis, so as clinical course is characterized only by the syndrome of general intoxication and, as a rule, not accompanied by specific clinical displays [5-7].

Laboratory models for an artificial reproducing of anaplasmosis at the experimental animals are actively developed in different countries [8, 9]. The ultimate goals of such researches are to study pathogenesis features; identification of patterns of immunological reactions and formation of specific and nonspecific immunity; determination *in vivo* conditions of etiologic diagnostics methods effectiveness (specificity, sensitiveness, producibility); efficiency of etiotropic therapy and methods of specific immunoprophylaxis; identification of natural reservoir of infection and mechanisms of pathogen transmission.

## THE AIM

A research purpose is the development of uniform biological model for reproducing of artificial immunodeficient state by experimental anaplasmosis that is characterized by simplicity of technological reconstruction, cheapness and availability for wide practical usage.

## MATERIALS AND METHODS

Algorithm of experimental anaplasmosis reproducing, consisted of such consecutive stages: 1) artificial forming of the immunodeficient state at nonlinear white mise (*Mus musculus* L.); 2) preparation of the tested biological material samples; 3) inoculation by prepared samples of the laboratory animals with the artificially formed immunodeficient state; 4) sampling from the dead or slaughtered (by the method of chloroformed anesthesia) experimental animals of sectional material (organs and targets tissues); 5) verification of aetiology by express detection of causative agents by the method of PCR in the selected samples of sectional material.

The artificial immunodeficient state for white nonlinear laboratory animals was created by a single intracutaneous injection of 250 μg/kg of cyclophosphamide in the form

of medicinal preparation "Cyclophosphanum®" (publicly traded company "Kyivmedpreparation", Kyiv, Ukraine) 3-4 hours before introduction of samples of the investigated biological material to animals. The intracutaneous method of preparation introduction (unlike intraperitoneal) provided more even entering of preparation to the system of blood circulation and hemopoietic organs, reduced speed of preparation elimination from the animal organism, that provided forming of more protracted at times (to 7-10 days) immunodeficient state, sufficient for reproduction and accumulation of *Anaplasma*. Optimal fixed by us empiric dose of preparation is 250 μg/kg. The injection of this dose provides forming of the enough expressed and stable immunodeficient state, and does not result in unforeseeable death of part (about 12 % and more) of experimental animals, that was marked at introduction of 500 μg/kg and more.

The selected samples of blood brought in sterile capacities with an anticoagulant (with absent antimicrobial activity) for prevention of blood coagulation. During realization of our researches we used vacuum systems of blood sampling Venosafe™, Terumo Europe N.V. (Belgium) and test tubes VF - 052SDK (working volume of 2 ml) with the anticoagulant K2-EDTA. The samples of blood were frozen by single-phase at the temperature of -20 °C and unfrozen at a room temperature that provided destruction of blood cells and release of pathogen microcolonies. The samples of biological material of solid consistency carefully homogenized (by trituration or grinding) and diluted with sterile distilled water in 1:9 ratio (volume/volume, respectively) with further mixing for formation of even suspension. Before homogenization, the surface of ticks was disinfected by immersion of them in 70 % ethyl spirit on 10 minutes. We homogenized all body of the tick, as causative agents could be in its different tissues and organs (salivary glands, lymph, intestine etc.). For introduction to the laboratory animals, we select the supernatant (after desilting and unassisted precipitation of fair-sized particles) of the homogenized samples suspension. All manipulations at a selection and preparation for research of biological material samples were carried out in aseptic conditions, for prevention of their additional contamination by extraneous microflora.

Samples of different biological material (in a volume 0,3 ml) were injected to nonlinear white mice with the artificially formed immunodeficient state intraperitonealy, that provided a large area for the application of causative agents with high authenticity of their contact with target-cells (macrophages, leucocytes, erythrocytes etc.). The term of observation of the infected experimental animals lasted 8-10 days as, in this period the concentration of causative agents arrives at a maximal value in tissues and organs of animals [8].

For exact verification of infectious process aetiology from the dead and slaughtered animals (by a method of chloroform hyperanesthetization), applied the most accessible and technologically cheap standard variant of PCR. Verification of ethology is based on the PCR detection of basic clinically meaningful types of *Anaplasma* (*A. phagocytophilum*) in the samples of blood (selected by puncture of heart with the observance of asepsis rules) of experimental animals infected by the investigated biological material samples. Expediency of exactly selection of blood samples is grounded by simplicity of executable for this purpose manipulations, and also complete coincidence of our PCR results (positive and negative) at parallel research of blood and other tissues and organs (spleen, bone marrow, liver, lymph nodes) samples, selected from the same experimental animals. We applied for reproducing standard PCR accessible on the territory of Ukraine, relatively cheap and already geared-up for the direct use of commercial sets of reagents "IsoGene Lab. Ltd" (Moscow, Russian federation): "Universal probepreparation reagents kit" – Diatom®DNA Prep 100 (includes reagents for a selection and cleansing of DNA from the samples of biological material with the purpose of further amplification of its certain fragment); " DNA amplification reagents kit" – Gene Pak®DNA PCR test: E2136 (includes reaction mixtures, with primer system *Eph* for amplification of specific fragment of *A. phagocytophilum* genome); "Marker of DNA molecular mass M50, M100" – GenePak™ DNA Ladder M50, M100 (includes DNA fragments mixtures of different molecular mass which differs on 50 or 100 pair of nucleotides, respectively, and used for size comparative identification of formed amplicons at the reproducing of PCR with synthesized primers); "Universal inner control UVK-90" (includes the reagents sets for monitoring of possible DNA losses during its selection from the investigated samples of biological material and for determination of possible inhibition of PCR in the process of its reproducing) [10].

The procedure was done strictly in compliance with the Helsinki Declaration, European Convention for the protection of vertebrate animals (18.03.1986), European Economic Society Council Directive on the Protection of Vertebrate Animals (24.11.1986) after approval from the Regional Ethical Review Board.

Statistical analyses were performed using the chi-square test while comparing categorical variables. For all analyses, $p<0.05$ was used to indicate statistical significance.

## RESULTS

Biological model of experimental anaplasmosis created by us is suitable for realization of both diagnostic and epidemiological, epizootic, ecobiological and other researches of different origin biological material samples, including samples of solid and liquid consistency material, with the absence and with the presence of contamination by an extraneous microflora.

Under supervision of animals during an experiment appeared their premature death and onset of clinical signs of the disease: decline of mobility and appetite, inertness at a tactile and sound irritation, hunched seat, lameness, flatulence, loss an about 30 % of body mass. We conduct determination and comparison of morbidity level (premature death and disease incidence) in three different groups of laboratory animals: group №1 are control intact animals;

group №2 are control animals with the artificially formed immunodeficient state; group №3 are experimental animals with the immunodeficient state infected by the samples of the investigated biological material. The results of these researches showed that unlike control animals from groups №1 and №2, the experimental animals of group №3 produced clinically expressed disease. Thus in future it was set at the usage of PCR method, that anaplasmosis, was the reason of premature death of experimental animals in 17,4 % cases; resulted in an onset of disease clinical signs without death during the term of supervision in 43,8 % cases; coursed in the absence of the expressed symptoms of infection in 31,3 % cases.

For confirmation of reproduction and accumulation of *Anaplasma* in experimental animals of group №3 comparative (taking into account the positive result of PCR) determination of corpuscular antigen amounts (cells and microcolonies) of *Anaplasma* spp. bacteria was conducted by the method of indirect immunofluorescence assay in the samples of the investigated biological material, which was inoculated to experimental animals, and in the samples of sectional material from the last – tissues and organs which can contain most of the causative agents cells (blood, spleen, bone marrow, liver, lymph nodes) potentially. The results of these researches showed the accumulation of bacteria in tissues and target organs of the infected animals, which exceeded the initial concentrations of these microorganisms in the corresponding samples of the investigated biological material more than in $10^2$-$10^3$ times. In addition, comparative analysis of the results of *Anaplasma* detection by PCR method in the same samples of biological material without the usage and with the usage of the pathogen reproduction and accumulation stage by growing in *in vivo* conditions (offered biological model) demonstrates the substantial ($p<0,05$) increase of causative agents detection from 6,9 % to 18,4 %.

## DISCUSSION

First of all researchers use at creation of experimental anaplasmosis biological models those types of animals, which are natural owners for causative agents: horses, cattle, sheep, white-tailed deer, dogs, pack rats and white-footed mice [8, 9]. The usage of the indicated animals in an experiment allows recreating the natural course of infectious process with large authenticity, that allow to explain peculiarities of course for different diseases in condition of immunodeficient state [11, 12]. However, it has substantial defects, related to their inaccessibility for wide application in practice. high cost of such animals, difficulties of their maintenance in laboratory conditions and technical complications of experiment realization on them, and also by limitations in possibility of standardizated laboratory model creation for all *Anaplasma* species, that associated with ability of every species of pathogen to multiply and accumulate only in the certain type of sensible animals.

Therefore, the last years noted tendency to the increase of researches, pointed at development technically of more suitable models of experimentally reproducing anaplasmosis, based on the usage of the most widespread laboratory animals, – mostly mice, considerably rare – rats, guinea-pigs, rabbits [13]. It should be noted that for ordinary white nonlinear laboratory mice experimental anaplasmosis, characterized by complete absence or extraordinarily poorly expressed symptoms of disease without substantial reproduction and accumulation of causative agents in their organism, rapid elimination of them even in the conditions of bacteraemia in experimental animals on the initial stage after their infection. The indicated circumstances induce researchers to apply the genetically cloned syngeneic lines of mice with an innate immunodeficit and that characterized by the high level of sensitiveness to the causative agents of different infectious diseases [14]. However, such linear animals are relatively expensive, scarce enough; need the special terms for their isolated maintenance and reproduction, which would prevent deaths of animals at the casual infecting. It substantially complicates the stable providing of laboratories and their practical deployment with linear immunosuppressive animals as a biological model. Therefore, potentially most perspective for wide practical application there can be a biological method, based on the usage of white nonlinear laboratory mice with the induced immunodeficient state. It is succeeded to form by the way of introduction to the experimental animal of compounds, which have a necessary spectrum of immunodepressive action. Today there is a large list of medicinal preparations, which are characterized by the polytypical mechanisms of immunosuppression without the display of antibacterial activity. It allows carrying out a reasonable choice for application of exactly those preparations that provide the adequate reproducing of the necessary immunodepressive state for experimental animals with absence of undesirable bactericidal or bacteriostatic action on *Anaplasma*.

Choice of preparation "Cyclophosphanum®" (publicly traded company "Kyivmedpreparation", Kyiv, Ukraine) for the artificial forming of the immunodeficient state for white nonlinear mice is reasonable due to the detailed study of its mechanisms of immunodepressive action [14] and by the absence of antibacterial activity, cheapness and availability.

## CONCLUSIONS

1. Developed biological model of experimental anaplasmosis consists in that as laboratory animals with the increased sensitiveness to the infection and accumulation of causative agent are used white nonlinear mice with the artificially formed immunodeficient state.
2. Biological model, based on intracutaneous introduction to the laboratory animals of immunodepressive preparation "Cyclophosphanum®" in a dose 250 μg/kg, is characterized by commonality and simplicity of reproducing, considerably cheaper than analogues and accessible for practical deployment.
3. Inoculation to white nonlinear mice with the artificially formed immunodeficient state of biological material samples, potentially infected by *Anaplasma*, allows

promoting the level of causative agents detection (with further verification by PCR method) in 2 times, that can be used for anaplasmosis diagnostics in people and animals by detection of causative agents in the samples of biological material.

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**Authors' contributions:**
*According to the order of the Authorship.*


**ORCID numbers:**
*Andrey V. Bondarenko - 0000-0002-2303-8525*
*Sergey I. Pokhil - 0000-0002-2298-9652*
*Marianna V. Lytvynenko - 0000-0001-9594-3412*
*Tatyana V. Bocharova - 0000-0002-2264-1744*
*Vitaliy V. Gargin - 0000-0001-8194-4019*


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## CORRESPONDING AUTHOR

**Vitaliy V. Gargin**
Kharkiv National Medical University
Kharkiv, Ukraine
tel: +380990498557
e-mail: vitgarg@ukr.net



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# VARICELLA-ZOSTER VIRUS CNS DISEASE CLINICAL FEATURES IN UKRAINIAN PATIENTS. PROSPECTIVE STUDY

**Pavel A. Dyachenko**
CENTER OF INFECTIOUS DISORDERS OF THE NERVOUS SYSTEM, SI "L.V. GROMASHEVSKY INSTITUTE OF EPIDEMIOLOGY AND INFECTION DISEASES OF NAMS OF UKRAINE", KYIV, UKRAINE

## ABSTRACT

**Introduction:** Herpes zoster (HZ), or shingles, is localized disease characterized by unilateral radicular pain and a vesicular rash limited to the area of skin innervated by a single dorsal root or cranial sensory ganglion. Whereas varicella, or chickenpox, results from primary exogenous varicella-zoster virus (VZV) infection, HZ is caused by reactivation of endogenous VZV that has persisted in latent form within sensory ganglia following an earlier episode of chickenpox.

**The aim:** To explore the clinical features, diagnosis, and treatment of CNS injury caused by VZV infection in a prospective single center study from January 2014 to January 2018.

**Materials and methods:** 117 adult patients, among which young women predominated with confirmed VZV infection were analyzed in the study. CSF and blood contents, antibody for herpes zoster M and G classes, and MRI scans have been studied, but the crucial diagnostic sign was the presence of specific viral DNA in the CSF or blood. The main clinical manifestations of the disease were ganglionitis and ganglioradiculoneuritis. Another brain lesion like uveitis, encephalitis and vasculitis were observed also. A clinical case of an unusual course of VZV-infection is given.

**Results and conclusions:** The most common clinical variants of HZ were ganglionitis (69.7%). Cranial localization was observed in 31% of patients, spinal one – in 38.7%, injury to the meninges was found in 16.3% of patients.

**KEY WORDS:** varicella-zoster virus, ganglionitis, ganglionneuritis, Ramsey-Hunt syndrome, vasculitis, encephalitis

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## INTRODUCTION

Herpes zoster (HZ) is an often painful disease caused by varicella-zoster virus (VZV) infection. Zoster affects approximately 1,000,000 individuals in the U.S. per year. Most patients are over age 60 [1] or immunocompromised [2]. The annual incidence of zoster is 5 to 6.5 per 1,000 patients at age 60, who visit hospitals each year, increasing to 8 to 11 per 1,000 at age 70 [2]. Unlike varicella, which occurs primarily in the spring, there is no seasonal predilection for zoster. Patients with HZ complain of painful, vesicular rashes with erythema, which usually take 3~4 weeks to heal [3].

Varicella zoster virus (VZV) is an ubiquitious, exclusively human neurotropic *alphaherpesvirus* that causes the predominantly childhood disease chicken pox (varicella) during primary infection of susceptible individuals. After resolution of primary infection by the host immune system, the virus can establish a life-long, latent infection in cranial nerve ganglia, dorsal root ganglia and autonomic ganglia along the entire neuraxis. At some stage later in life, as cell-mediated immunity to VZV declines with age or immunosuppression latent VZV eventually reactivates, presumably in a single sensory neuron, to cause herpes zoster (shingles). The reactivated virus multiplies and spreads within the ganglion, infecting many additional neurons and supporting cells—a process that causes intense inflammation and neuronal necrosis, often followed by chronic pain (postherpetic neuralgia or PHN) as well as myelopathy, encephalitis, meningitis, Ramsay-hunt syndrome with facial paralysis, retinal necrosis and cerebellitis [4-7]. VZV is able to replicate in the walls of cerebral arteries, causing vasculopathy and VZV-associated small vessel disease [8, 9]. Due to macrovascular disease, granulomatous angiitis often develops, which leads to stroke [10]. VZV-associated small vessel disease has such manifestations as migraine, convulsions, paralysis, and cognitive impairment. HZ is predominantly a marker of immunodeficiency [11]. VZV reactivation can also produce pain without rash (zoster sine herpete). In fact, all neurological complications of VZV reactivation can occur without rash. More than 90% of adults in the World have serologic evidence of prior VZV infection. Consequently, latent VZV is present in the sensory ganglia of virtually every older adult. Thus, almost every older adult in the Ukraine is at risk of developing herpes zoster. In recent years, an increase in the number of patients with herpes zoster is noted not only among the elderly, but also a shift in diseases towards the middle and younger age [8]. Because VZV becomes latent in ganglia along the entire neuraxis, zoster can develop anywhere on the body. Zoster can affect all cranial nerves [12] and

spinal nerves at all levels; zoster can also be associated with lower motor neuron type weakness in the arm or leg [13], diaphragm [14] or abdominal muscles [15].

## THE AIM

To explore the clinical features, diagnosis, and treatment of CNS injury caused by VZV infection in a prospective single center study from January 2014 to January 2018.

## MATERIALS AND METHODS

117 patients aged 18 to 74 years old, meeting the initial criteria of CNS disorders caused by VZV were enrolled in the study. VZV-etiology of the nervous system lesions was confirmed by the presence in patients of a typical exanthema, clinical neurological analysis, neuroimaging, as well as the identification of VZV infection markers (viral DNA and IgM antibodies). Among the examined patients, 62 (53.4%) were female and 55 (46.5%) males. Young people were predominant.

All experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

## RESULTS AND DISCUSSION

The main clinical manifestations of the VZV neuroinfection were ganglionitis and ganglioradiculoneuritis - in 81 (69.8%) patients. Cranial ganglioneuritis were detected in 36 (31.0%). Most commonly affects Gasser's ganglion – in 28 (24.0%) patients, less commonly - cranial nodes - 8 (6.8%). Isolated lesion of the first branch of the trigeminal nerve was observed in 21 patients, the second - in 5 one, the third - in 2 one. HZ is commonly associated with severe diffuse headache, and unilateral pain, which often precedes the rash by several days; pain usually accompanies the dermatomal rash of herpes zoster. In 9 patients with a defeat of the first branch of the trigeminal nerve the conjunctivitis on the side of the lesion developed, in 2 – keratitis, and one – uveitis. The defeat of the second and third branches of the trigeminal nerve was accompanied by the appearance of a rash on the mucous palate, inner surface of the cheeks, and lips. In 3 patients, paresis of the eye muscles was observed. Herpes zoster is virtually impossible to diagnose until the characteristic vesicular dermatomal rash appears.

In 8 patients with lesions of the cranial nerve and the tympanic strike - Ramsey-Hunt's syndrome were diagnosed. Vestibular, trigeminal, facial and sublingual nerves were also involved in the process. The rashes were localized on the skin of the auricle, external auditory canal, anterior surface of the tongue, posterior surface of the palate. Vestibular disorders, partial loss of hearing, peripheral paresis of mimic muscles accompanied with pain of neuralgic in nature, paresis of soft palate and disturbance in swallowing were observed.

Spinal ganglia were involved in 45 (38.7%) patients. Lower cervical and upper chest regions were implicated in 9 of them, chest - in 30, and lumbar sacral – in 6 patients. In the clinical picture of ganglionitis of the lower cervical and upper chest localization burning pain in the hand, sensation of swelling of the brush, muscles hand paresis dominated. Shingles pains, and paresthesia were noted in all patients with lesions of the thoracic ganglia. Weakness of the abdominal wall, decreased muscle tone, imitate neoplasia formation in the abdominal cavity of 3 patients. In 26 patients there was a defeat of several sensitive nodes. Spastic paresis, and central type function disturbance of the pelvic organs developed in 4 patients.

Ganglionitis of the lumbosacral region are characterized by the rash localized on the skin of the lumbar, buttocks, lower extremities, accompanied by significant pain syndrome, symptoms of the tension of the spinal nerve roots, weakness of the lower extremities, violation of the urination and defecation, which was considered as myeloganglionitis.

Meningoencephalitis has developed in 6 patients, in 3 - on the underlying defeat of the Gasserov's node, and 3 - in the defeat of the thoracic spin ganglia. In 2 cases, VZV-encephalitis was not accompanied by a defeat of other parts of the nervous system. Common symptoms were observed in all patients; meningeal contractures were moderate in 11 patients. Lymphocytic pleocytosis was found in the liquor. Meningitis in 13 patients accompanied with rashes in some spinal dermatomes. In one 18 years old patient with injury of the first branch of the Gasserov's node on day 7 after the onset of the disease contralateral hemiparesis developed. Ultrasound analysis of intracranial vessels, had shown a reduced blood flow in the system of the middle cerebral artery on the side of herpetic defeat, and signs of venous discirculation. The event was considered as the onset of cerebral angiitis.

The participation of VZV in lesions of the nervous system is hard to detect and prove hard to prove when there are neurological symptoms but no typical exanthema and indication on HZ in the history. 10 (8.6%) patients, have radicular pains in the chest dermatomas without anamnestic HZ. In 5 (4.3%) patients with cephalgic syndrome, cognitive impairments, multiple small subcortical foci in the hemisphere white matter VZV-vasculopathy was diagnosed, although there was no herpes history. CSF samples analysis revealed specific antibodies, and VZV DNA.

## CASE PRESENTATION

A 34-years-old mail, invalid of the III group, presented to The Center of Infectious Disorders of the Nervous System (CIDNS, Kyiv, Ukraine) in 07.09.2017 with complaints of a sharp weakness in the left limbs, left side partial loss of vision and hearing, double vision, headaches, weakness, dizziness, decreased ability to work and coordination, subfebrile. It is known from the medical history that he is ill from the middle of August 2017, when being treated in a local hospital for ketoacidosis, acute left-sided weakness and problems with vision and hearing suddenly appeared. He underwent MRI (figure 1) which showed a massive

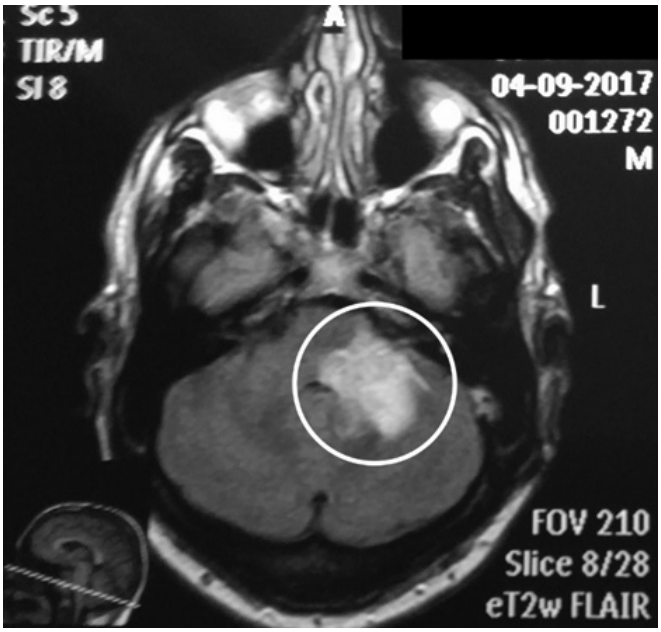


**Fig. 1.** Made on admission in a hospital, the MR image is a coronal slice of T2 FLAIR sequence showing massive area of intensive signal in the cerebellum and its legs, with a defeat of the brain stem.

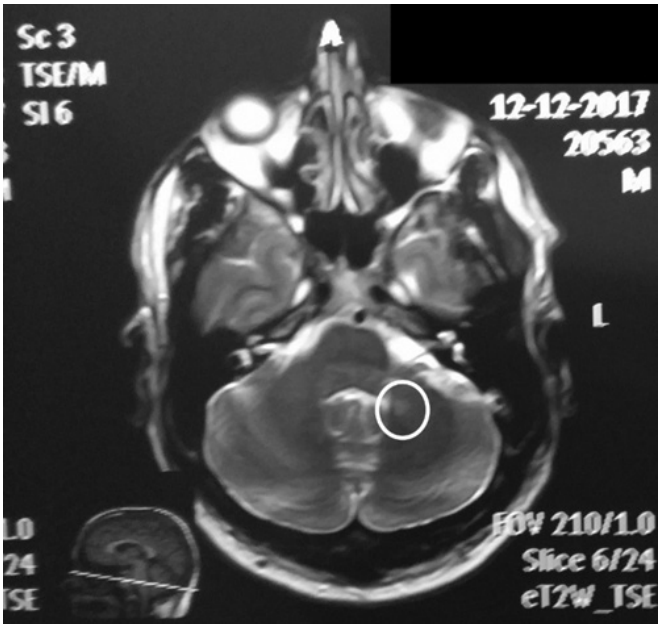


**Fig. 2.** MRI-picture of the residual effects of inflammation in the cerebellum 3 months after discharge.

formation in the cerebellum, possibly a tumor. After consulting a neurologist and a surgeon, the patient was referred to a CIDNS with suggestive diagnosis focal brain damage, probably infectious or malignant genesis. History of life: it is afflicted with chronic gastroduodenitis, spinal osteochondrosis, insulin-dependent diabetes mellitus (from 2013), stage of decompensation, ketoacidosis. In 2013, laparotomy with resection of pancreatic cysts was performed. He is alcohol abuser. He suffered chickenpox in childhood.

On admission: general condition of moderate severity. The emotionally labile, contact, answer the question adequately. Skin and mucous membranes of normal color, mucous pharynx is hyperemic. Injection of vessels of sclera. Pupils are the same, photoreaction is not reduced. Eyelid tremor with ptosis of the left eyelid, and not completed convergence, more right, are observed. There are left, horizontal nystagmus, smoothness of the left nasolabial fold, deviation of the tongue and uvula to the left. Muscular strength is reduced on the left limbs (hand to 3 points, foot up to 2 points). Abdominal reflexes are absent. Tendon reflexes on the upper limbs saved, S> D, on the lower extremities S> D. Barre-probe as well as Gordon, Stryumpel Sharapov, Babynsky symptoms were positive on the left side. Meningeal symptoms were not detected. He performed the coordinate tests with light intent. In the Romberg pose he fell to the left and back. The function of pelvic organs was not disturbed.

On admission, the blood analysis had shown normocytosis (5 x $10^9$ / l) with relative lymphocytosis (50%), increase gamaglutamyltransferase (59.8U/l), and hyperglycemia (15.9 mmol / l). IgM antibodies to VZV and elevated levels of autoantibodies to neuroantigens were also detected (BMP of 42.8 U / ml, S-100 of 13.9 U / ml, NSE of 32.8 Un / ml, GHMA of 37 Un / ml). All CSF indicators were within normal range. Microflora, herpesvirus DNA, toxoplasma and mycobacterium tuberculosis have not been detected.

The presumptive diagnosis was: encephalitis with lesion of cerebellar and brain structures, pronounced vestibular atactic, cerebrospinal symptoms, left-side hemiparesis, polyneuropathy, underlying with VZV infection in the phase of reactivation. Diabetes mellitus type 1, severe course, stage of decompensation. Chronic gastroduodenitis. Osteochondrosis of the lumbar spine.

He was treated with iv acyclovir, 1500 mg / per day; human immunoglobulin for iv administration, neuroprotective, hepatoprotective, and anti-inflammatory therapy. As a result of treatment, stay of the patient improved: increased muscle strength, vision and hearing normalized, polyneuropathy, and ataxia almost disappeared, glucose blood level normalized. IgM VZV antibodies in the blood test of September 20, 2017, were not detected. The patient was discharged for further outpatient treatment. Three months after discharge, the control test of CSF sample revealed not VZV DNA nor antibodies against virus. The level of autoantibodies to neuroantigens became almost normal.

## CONCLUSIONS

The most common clinical neurological variations of HZ were ganglionitis (69.7%) had cranial localization in 31% of patients with spinal - 38.7%, the defeat of the meninges - the 16.3% lumbar puncture should be conducted in patients with herpes zoster, especially with lesion of cranial ganglia. Lack typical exanthema not preclude nervous system VZV and should use targeted methods etiology decoding process, cerebrospinal fluid testing for DNA specific antibodies.

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**ORCID numbers:**
*Pavel A. Dyachenko - 0000-0002-0459-9861*


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## CORRESPONDING AUTHOR

**Pavel A. Dyachenko**
Center of infectious disorders of the nervous system,
SI "L.V. Gromashevsky institute of epidemiology
and infection diseases of NAMS of Ukraine"
4 Galytska St., 04123, Kyiv, Ukraine
tel: +380444343288
e-mail: duieih@amnu.gov.ua



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ORIGINAL ARTICLE
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# QUALIMETRIC ANALYSIS OF PROTON PUMP INHIBITORS IN UKRAINE

**Olha V. Makarenko, Malika M. Karimova, Alona M. Masheiko, Nataliia M. Onul**
STATE INSTITUTION "DNIPROPETROVSK MEDICAL ACADEMY OF HEALTH MINISTRY OF UKRAINE", DNIPROPETROVSK, UKRAINE

## ABSTRACT

**Introduction:** On the pharmaceutical market of Ukraine, there are six international non-proprietary names of proton pump inhibitors (PPIs) – Omeprazole, Pantoprazole, Lansoprazole, Rabeprazole, Esomeprazole, Dexlansoprazole, which differ in a number of pharmacokinetic and pharmacodynamic parameters, safety profile, range of dosage forms and their cost.

**The aim:** To investigate the competitiveness of proton pump inhibitors registered in Ukraine by comparing the parameters of their quality properties using the method of qualimetric analysis.

**Materials and methods:** Qualimetric analysis is based on the deductive-axiomatic approach, which allows quantifying the qualitative properties of drugs and determining the degree of competitiveness of each of them in the pharmaceutical market of Ukraine. The qualitative properties of PPIs in terms of consumer are efficacy, safety, convenience of use and cost. The subject of the study was 133 trademarks of PPIs registered in Ukraine.

**Results:** The highest qualimetric values were obtained by omeprazole ($K^k = 0.73$) and its S-isomer esomeprazole ($K^k = 0.66$). Pantoprazole was inferior to them to a certain extent ($K^k = 0.64$). Lansoprazole ($K^k = 0.53$), rabeprazole ($K^k = 0.50$) and dexlansoprazole ($K^k = 0.44$) had the lowest values of the quality indices.

**Conclusions:** According to the results of the study of the PPIs' competitiveness for parameters characterizing efficacy, safety, convenience of use and cost, assessed by qualimetric analysis, it has been established that the most completely and qualitatively satisfying consumer's needs are omeprazole and its S-isomer, esomeprazole.

**KEY WORDS:** Competitiveness, Proton pump inhibitors, Pharmaceutical market, Qualimetric analysis, Ukraine

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## INTRODUCTION

Proton pump inhibitors (PPIs) are "drugs of choice" for the treatment of acid-related gastrointestinal diseases such as benign peptic ulcer and duodenal ulcer, gastroesophageal reflux disease (GERD), Zollinger-Elison syndrome [1].

The pharmaceutical market of Ukraine currently offers six international nonproprietary PPIs: Omeprazole (A02BC01), Pantoprazole (A02BC02), Lansoprazole (A02BC03), Rabeprazole (A02BC04), Esomeprazole (A02BC05), Dexlansoprazole (A02BC06) [1].

The basis of the molecular structure of all PPIs is the heterocyclic core of benzimidazole, which causes a single mechanism of action and the same efficacy of PPIs in the treatment of the acid-related diseases of the gastrointestinal tract [2].

PPIs differ in the structure of radicals on pyridine and benzimidazole cycles, which causes some difference in the pharmacokinetic and pharmacodynamic properties of these drugs [3, 4]. The peculiarities of the pharmacokinetic and pharmacodynamic profiles of certain PPIs may affect the patient's compliance and, consequently, the effectiveness of PPIs.

Qualimetric analysis allows comparing the proton pump inhibitors for the pharmacokinetic and pharmacodynamic parameters, the safety profile, the range of available dosage forms and their cost [5, 6, 7, 8].

The basis of the qualimetric analysis is deductive-axiomatic approach, which allows quantifying the qualitative properties of drugs and determining the level of competitiveness of each of them in the pharmaceutical market [5, 6, 7, 8].

## THE AIM

The objective of the paper is to investigate the competitiveness of proton pump inhibitors registered in Ukraine by comparing the parameters of their quality properties using the method of qualimetric analysis.

## MATERIALS AND METHODS

The subject of the study is the 133 trade names of proton pump inhibitors registered in Ukraine – Omeprazole (28 TN), Pantoprazole (54 TN), Lansoprazole (5 TN), Rabeprazole (15 TN), Esomeprazole (29 TN) and Dexlansoprazole (2 TN) [1].

Since qualitative properties of drugs are constant objective parameters, the qualimetric analysis was carried out by the non-expert (also known as analytical) method. The qualimetric analysis included the following steps: 1) determining the property indicators characterizing the PPIs and creating a so-called «property tree» in the table

form; 2) calculating the values of the weight factors of the individual properties; 3) defining the values of absolute property indices including reference and acceptable values for property indices; 5) bringing the values of absolute property indices to one unit of measure (relative property indices); 6) defining the values of objects quality indices; 7) the ranking of PPIs [6, 8].

## RESULTS

The qualitative properties of PPIs in terms of consumer are efficacy, safety, convenience of use and cost.

Indicators that characterize the *efficacy* of PPIs were the following pharmacokinetic and pharmacodynamic parameters, such as the absolute bioavailability, the median time to reach to $C_{max}$ ($t_{max}$), 24-hour median intragastric *pH,* the mean percent duration of time with intragastric $pH > 4$ and the number of clinical indications approved in the instructions for the medical use of PPIs.

Indicators that characterize PPIs' *safety* were PPIs acid trapping, the number of adverse reactions that may occur at a frequency of ≥ 1%, the possibility of appointment in hepatic and renal insufficiency without dose adjustments, the possibility of use for children and elderly, the possibility of use for pregnant women and women during breastfeeding.

Indicators characterizing PPIs' *convenience of use* were the market availability of brand-name drugs, generics, OTC-drugs, registration of parenteral dosage forms and children's medical forms, the number of registered doses in Ukraine.

The average cost of the oral dose was chosen as an indicator that characterize PPIs' cost.

The property weight factors were determined by the Delphi method with the participation of five experts and calculated according to the formula [8]:

$$G_i' = \frac{G_i''}{\sum_{i=1}^{n} G_i''}$$

Where $G_i'$ – the property weight factor;

$G_i''$ – the weight of the individual properties for 5-point scale;

$\Sigma G_i''$ – the total value of the weight of the individual properties.

It was established, that the most significant property weight factors of PPIs were 24-hour intragastric *pH*, the mean percent duration of time with intragastric $pH > 4$, the number of clinical indications and the possibility of use for children ($G_i' = 0.06$).

"Tree of properties" and the property weight factors of PPIs are provided in Table I.

The value of absolute property indices – efficacy, safety and convenience of use were determined by the documentary method with instructions for the drug's use. The value of the cost absolute property was determined by the calculation method. Quantitative assessment of the absolute property indices were carried out on a scale of absolute values [8].

To bring the values of absolute property indices to one unit of measurement and provide their comparability among themselves, the conversion of absolute indices into relative ones was carried out using the rationing operation [8]:

$$K_{ij} = \frac{Q_{ij} - q_i^{rej}}{q_i^{ref} - q_i^{rej}}$$

Where $K_{ij}$ – the relative index value;

$Q_{ij}$ – the absolute property index value;

$q_i^{ref}$ – reference value of the absolute property index;

$q_i^{rej}$ – acceptable value of the absolute property index.

The quality index ($K^k$) of PPIs was calculated as arithmetic average by the formula [6, 8]:

$$K^k = \sum_{i=1}^{n} K_{ij} G_i'$$

Where $K^k$ – the quality index;

$G_i'$ – the property weight factor;

$K_{ij}$ – the relative index value;

$n$ – the number of indicators of the object properties taken into account.

Table II presents the results of a qualitative analysis of PPIs.

Thus, it was found that omeprazole ($K^k = 0.73$) and esomeprazole ($K^k = 0.66$) had the highest qualimetric rating. Pantoprazole was inferior to them to a certain extent ($K^k = 0.64$).

Lansoprazole ($K^k = 0.53$), rabeprazole ($K^k = 0.50$) and dexlansoprazole ($K^k = 0.44$) had the lowest values of the quality indices.

## DISCUSSION

This study was conducted to quantify the competitive advantages of IPPs.

The quality index is a complex parameter that represents the sum of intermediate indicators – the quality indices of efficacy, safety, convenience of use and cost.

Thus, it was found that the highest *quality index of efficacy*, had esomeprazole ($K^k_{efficacy} = 0.22$). This is due to the high bioavailability (89 %) of esomeprazole, the fast achievement of the peak concentration of the drug in the blood (1-2 hours), the high antisecretory effect (24-hour median intragastric *pH* is 4.8±0.7) and the duration of $pH > 4$ in the stomach during 15,5 hours (64.6%±15.2).

Lansoprazole ($K^k_{efficacy} = 0.20$) is slightly inferior to esomeprazole in terms of the quality index of efficacy. The only competitive advantage of lansoprazole compared to esomeprazole is large quantity of the clinical indications for use (10 vs. 7). Unlike esomeprazole, lansoprazole is recommended for healing of active benign gastric ulcer and active duodenal ulcer, maintenance of healed duodenal ulcers in adults [13, 16].

Dexlansoprazole, the proton pump inhibitor of the last generation, ranks third in terms of the quality index of efficacy ($K^k_{efficacy} = 0.17$). Despite the competitive values of pharmacokinetic and pharmacodynamic parameters, dexlansoprazole has only three indications – healing of erosive esophagitis, maintenance of healed erosive esophagitis and treatment of symptomatic non-erosive gastroesophageal reflux disease [13, 20].

**Table I.** The property weight factors of PPIs

| Property indicators | The weight of the criterion for 5-point scale (average value), $G''_i$ | The property weight factor, $G'_i$ |
|---|---|---|
| **Efficacy** | | |
| The absolute bioavailability, % | 3,80 | 0,05 |
| The median time ($T_{max}$) to peak plasma concentrations ($C_{max}$), h | 3,40 | 0,05 |
| 24-hour median intragastric *pH* | 4,40 | 0,06 |
| Mean percent duration of time with intragastric *pH* > 4, % | 4,80 | 0,06 |
| Clinical indications, units. | 4,80 | 0,06 |
| **Safety** | | |
| Acid trapping *(pKa)* | 3,00 | 0,04 |
| Number of most common adverse reactions in adults (incidence ≥ 1 %) | 3,80 | 0,05 |
| The possibility of use in liver failure | 3,40 | 0,05 |
| The possibility of use in renal failure | 3,40 | 0,05 |
| The possibility of use for children under 12 years | 4,40 | 0,06 |
| Possibility of use for elderly people without dose adjustment | 2,60 | 0,03 |
| Possibility of use for pregnant women | 4,00 | 0,05 |
| Possibility of use for women during breastfeeding | 3,80 | 0,05 |
| **Convenience of use** | | |
| Registration of brand-name drugs in Ukraine | 4,00 | 0,05 |
| Registration of generics in Ukraine | 3,60 | 0,05 |
| Registration of OTC-drugs in Ukraine | 4,00 | 0,05 |
| Registration of parenteral dosage forms | 3,60 | 0,05 |
| Registration of children's medical forms | 3,60 | 0,05 |
| Number of registered doses, units. | 3,00 | 0,04 |
| **Cost** | | |
| The average cost of the oral dose, UAH. | 3,60 | 0,05 |
| TOTAL | $\sum G''_i = 75{,}00$ | 1,00 |

The lowest value of the quality index of efficacy was established for rabeprazole ($K^k_{efficacy} = 0.13$), which is due to the lack of competitive advantages of its pharmacodynamic and pharmacokinetic parameters compared to other IPPs.

Calculation results of *the quality index of safety* showed that omeprazole ($K^k_{safety} = 0.28$) and its S-isomer esomeprazole ($K^k_{safety} = 0.25$) were identified as the safest. These drugs, unlike other PPIs, are allowed during pregnancy [15–20].

The lowest value of the quality index of safety was found in rabeprazole ($K^k_{safety} = 0.16$). Due to low acid trapping (*pKa* = 4.9), rabeprazole has limited use in pediatric practice [12, 18]. The ability of rabeprazole to work in a wide range of *pH* enables it to inhibit proton pump of the immune system cells [3, 14], which causes a number of specific adverse reactions, in particular, Flu-like symptoms, infections and inflammation of the throat and lining of the nose [18].

It is necessary to mention that all PPIs may be prescribed for hepatic and renal insufficiency without dose adjustment [15-20].

According to *the quality index of convenience of use*, it has been found that the most fully satisfying the needs of consumers are drugs of omeprazole ($K^k_{convenience} = 0.24$) and pantoprazole ($K^k_{convenience} = 0.22$) registered in Ukraine. In particular, OTC-forms of these drugs are available for consumers.

It should be noted that in Ukraine there are very limited presented children's dosage forms of IPPs. Among the IPPs registered in Ukraine in the form of powder or granules for preparing oral suspensions, only omeprazole is available in one trade name of Indian production. In addition, a distinctive feature of the pharmaceutical market in Ukraine is non-availability of the brand-name drugs of omeprazole and lansoprazole.

Drugs of omeprazole ($K^k_{cost} = 0.05$) have a competitive advantage in terms of *the quality index of cost*, which is due to the low average cost of the oral dose. The drugs of lansoprazole, rabeprazole and pantoprazole follow ome-

**Table II.** Results of qualimetric analysis of proton pump inhibitors in Ukraine

| Indicators of qualitative properties | | Reference value, $q_i^{ref}$ | Acceptable value, $q_i^{rej}$ | INN | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Omeprazole | Lansoprazole | Pantoprazole | Rabeprazole | Esomeprazole | Dexlansoprazole |
| **Efficacy** | | | | | | | | | |
| The absolute bioavailability, % | absolute | 90 | 50 | 60* [9, 15] | 80-90 [9, 16] | 77 [9, 17] | 52 [9, 18] | 89* [19] | Not found [11, 20] |
| | relative | | | 0,25 | 0,75 | 0,68 | 0,05 | 0,98 | 0,75 |
| The median time ($T_{max}$) to peak plasma concentrations ($C_{max}$), h | absolute | 1 | 5 | 1.5 (1-2) [15] | 1.75 (1.5-2) [16] | 2.5 [9, 17] | 3.5 (2-5) [9, 18] | 1.5 (1-2) [19] | 1.5 (1-2; 4-5) [11, 20] |
| | relative | | | 0,88 | 0,81 | 0,63 | 0,38 | 0,88 | 0,88 |
| Mean intragastric *pH*±standard deviation over 24 h after multiple doses of PPIs for healthy volunteers | absolute | 5.5 | 2.1 | 3.5±1.0 [10] | 4.1±0.7 [10] | 3.5±1.4 [10] | 4.5±0.5 [10] | 4.8±0.7 [10] | 4.55 [20] |
| | relative | | | 0,41 | 0,59 | 0,40 | 0,71 | 0,79 | 0,72 |
| Mean percent duration of time with intragastric *pH* > 4 after multiple doses of PPIs % | absolute | 79,8 | 28,2 | 48.7±20.5 [10] | 55.1±14.4 [10] | 53.6±19.8 [10] | 57.7±14.2 [10] | 64.6±15.2 [10] | 71 [20] |
| | relative | | | 0,40 | 0,52 | 0,49 | 0,57 | 0,71 | 0,83 |
| Indications, units | absolute | 10 | 3 | 10 [4, 15] | 10 [4, 16] | 7 [4, 17] | 7 [4, 18] | 7 [4, 19] | 3 [4, 20] |
| | relative | | | 1,00 | 1,00 | 0,57 | 0,57 | 0,57 | 0,00 |
| The quality index of efficacy, $K^k_{efficacy}$ | | | | 0,17 | 0,20 | 0,15 | 0,13 | 0,22 | 0,17 |
| **Safety** | | | | | | | | | |
| Acid trapping *(pKa)* | absolute | 3,0 | 5,0 | 4,13 [12] | 4,01 [12] | 3,96 [12] | 4,9 [12] | 4,13 [12, 21] | 4,01 [12] |
| | relative | | | 0,44 | 0,50 | 0,52 | 0,05 | 0,44 | 0,5 |
| Number of most common adverse reactions in adults (incidence ≥ 1 %) | absolute | 1 | 10 | 6 [15] | 4 [16] | 7 [17] | 5 [18] | 6 [19] | 5 [20] |
| | relative | | | 0,44 | 0,67 | 0,33 | 0,56 | 0,44 | 0,56 |
| The possibility of use in liver failure without dose adjustment | absolute | Yes | No | Yes [15] | Yes [16] | Yes [17] | Yes [18] | Yes [19] | Yes [20] |
| | relative | | | 1,00 | 1,00 | 1,00 | 1,00 | 1,00 | 1,00 |
| The possibility of use in renal failure without dose adjustment | absolute | Yes | No | Yes [15] | Yes [16] | Yes [17] | Yes [18] | Yes [19] | Yes [20] |
| | relative | | | 1,00 | 1,00 | 1,00 | 1,00 | 1,00 | 1,00 |
| The possibility of use for children under 12 years | absolute | Yes | No | Yes [4, 15] | Yes [4, 16] | Yes [4, 17] | No [4, 18] | Yes [4, 19] | No [4, 20] |
| | relative | | | 1,00 | 1,00 | 1,00 | 0,00 | 1,00 | 0,00 |
| Possibility of use for elderly people without dose adjustment | absolute | Yes | No | Yes [15] | No [16] | Yes [17] | Yes [18] | Yes [19] | Yes [20] |
| | relative | | | 1,00 | 0,00 | 1,00 | 1,00 | 1,00 | 0,00 |
| Possibility of use for pregnant women | absolute | Yes | No | Yes [15] | No [16] | No [17] | No [18] | Risk/benefit [19] | No [20] |
| | relative | | | 1,0 | 0,00 | 0,00 | 0,00 | 0,5 | 0,00 |
| Possibility of use for women during breastfeeding | absolute | Yes | No | No [15] | No [16] | No [17] | No [18] | No [19] | No [20] |
| | relative | | | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 |
| The quality index of safety, $K^k_{safety}$ | | | | 0,28 | 0,21 | 0,23 | 0,16 | 0,25 | 0,18 |
| **Convenience of use** | | | | | | | | | |
| Registration of brand-name drugs in Ukraine | absolute | Yes | No | No [1] | No [1] | Yes [1] | Yes [1] | Yes [1] | Yes [1] |
| | relative | | | 0,0 | 0,0 | 1,0 | 1,0 | 1,0 | 1,0 |
| Registration of generics in Ukraine | absolute | Yes | No | Yes [1] | Yes [1] | Yes [1] | Yes [1] | Yes [1] | No [1] |
| | relative | | | 1,0 | 1,0 | 1,0 | 1,0 | 1,0 | 0,0 |
| Registration of OTC-drugs in Ukraine | absolute | Yes | No | Yes [1] | No [1] | Yes [1] | No [1] | No [1] | No [1] |
| | relative | | | 1,0 | 0,0 | 1,0 | 0,0 | 0,0 | 0,0 |
| Registration of parenteral dosage forms in Ukraine | absolute | Yes | No | Yes [1] | No [1] | Yes [1] | Yes [1] | Yes [1] | No [1] |
| | relative | | | 1,0 | 0,0 | 1,0 | 1,0 | 1,0 | 0,0 |
| Registration of children's medical forms (suspension for oral use) | absolute | Yes | No | Yes [1] | No [1] | No [1] | No [1] | No [1] | No [1] |
| | relative | | | 1,0 | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 |
| Number of registered doses, units. | absolute | 3 | 1 | 3 [1] | 2 [1] | 2 [1] | 2 [1] | 2 [1] | 2 [1] |
| | relative | | | 1,0 | 0,5 | 0,5 | 0,5 | 0,5 | 0,5 |
| The quality index of convenience of use, $K^k_{convenience}$ | | | | 0,24 | 0,07 | 0,22 | 0,17 | 0,17 | 0,07 |
| **Cost** | | | | | | | | | |
| The average cost of the oral dose, UAH. | absolute | 2,00 | 20,00 | 20 mg- 2,15 [22] | 30 mg - 4,07 [22] | 20 mg - 6,16 [22] | 20 mg - 5,44 [22] | 20 mg - 13,09 [22] | 30 mg - 13,99 [22] |
| | relative | | | 0,99 | 0,89 | 0,77 | 0,81 | 0,25 | 0,33 |
| The quality index of cost, $K^k_{cost}$ | | | | 0,05 | 0,04 | 0,04 | 0,04 | 0,01 | 0,02 |
| The quality index, $K^k$ | | | | 0,73 | 0,53 | 0,64 | 0,50 | 0,66 | 0,44 |
| Rank | | | | 1 | 4 | 3 | 5 | 2 | 6 |

Note: * – the absolute bioavailability of repeated doses.

prazole. Drugs of esomeprazole and dexalanesoprazole have the highest average cost of the oral dose.

## CONCLUSIONS

According to the results of the study of the PPIs' competitiveness for parameters characterizing efficacy, safety, convenience of use and cost, assessed by qualimetric analysis, it has been established that the most completely and qualitatively satisfying consumer's needs are omeprazole and its S-isomer, esomeprazole.

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**Authors' contributions:**
*According to the order of the Authorship.*



**ORCID numbers:**
*Olha V. Makarenko - 0000-0001-8730-1081*
*Malika M. Karimova - 0000-0001-5961-403X*
*Alona M. Masheiko - 0000-0001-7960-6061*
*Nataliia M. Onul - 0000-0002-4968-3469*



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## CORRESPONDING AUTHOR

**Olha Makarenko**
Department of Social Medicine and Health Management,
SI "Dnipropetrovsk Medical Academy"
Vernadsky str., 9, 49044. Dnipro, Ukraine
tel: +380567135184
e-mail: olgamakarenko977@gmail.com



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# PHENOMENON OF SELF-DESTRUCTIVE BEHAVIOR IN FEMALE SEX WORKERS: DISCRIPTORS, PREDICTORS, TYPOLOGY, PSYCHOLOGICAL CORRECTION

**Marianna V. Markova[1], Tsira B. Abdriakhimova[2], Olga V. Grishina[1], Maya V. Savina[3], Cornelia A. Kosenko[4], Helen E. Falyova[1], Artur R. Markov[1]**

[1]KHARKIV MEDICAL ACADEMY OF POSTGRADUATE EDUCATION, KHARKIV, UKRAINE
[2]BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE
[3]V. N. KARAZIN KHARKIV NATIONAL UNIVERSITY, KHARKIV, UKRAINE
[4]ODESA NATIONAL MEDICAL UNIVERSITY, ODESA, UKRAINE

## ABSTRACT

**Introduction:** Engaging in sex, which is obligatory associated with the extraordinary risks of harm to their own safety and physical health, can be considered as one of the variants of self-destruction.

**The aim** is to analyze the leading descriptors and predictors of self-destructive behavior among female sex workers, on the basis of which to propose measures for their psycho-correction.

**Materials and methods:** The main group of the study was 135 women - female sex workers, a comparative group of 50 women who had no relation to such activities. The research methods were clinical-psychological, socio-demographic, psycho diagnostic, mathematical-statistical.

**Results:** Suicidal mood was investigated as a descriptor of self-destructive behavior in female sex workers. Features of suicidal ideas and the basis of committing suicide are revealed. The motivating emotions of a suicidal act are shame, anger and resentment. Psychological protection as a mechanism for maintaining risky sexual behavior has been studied. Identified destructive forms of primitive level mechanisms of psychological defense. It was revealed that in women engaged in prostitution the overall viability is not sufficiently formed, mainly due to the low level of inclusion. The presence of sacrifice in the form of increased propensity to active victim behavior has been established. An increased tendency toward an active type of victim behavior has been established. Leading individual psychological and behavioral patterns in the genesis of self-destructive behavior in female sex workers have been identified and its clinical and psychological options have been singled out. Based on the data obtained, a program of measures for differentiated psycho-correction of self-destructive behavior among female sex workers was developed.

**Conclusions:** As a result of work, the conceptualization of occupation of prostitution as a self-destructive behavior is grounded. The isolation of its specific pathognomonic psycho-emotional, individual psychological and behavioral features, made it possible to propose effective measures of its psycho-correction and of psycho-processing.

**KEY WORDS:** prostitution, self-destructive behavior, psychological correction

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## INTRODUCTION

The study of the phenomenon of commercial sex is carried out from the moment of its occurrence, that is, throughout the history of mankind. As a phenomenon of commercial sex, and the features of people engaged in sex business have always attracted the attention of researchers. Attempts to understand the origins and risks of this activity were made by scientists from various fields and spheres of scientific knowledge - sociology, cultural studies, anthropology, jurisprudence, medicine and psychology [1 - 9]. However, until now, there is no consensus among scientists of the medical and psychological direction regarding its conceptualization and origin. It is considered within the framework of deviant, and auto-aggressive, and self-destructive behaviors, such as the propensity to dependence illnesses [10 - 16]. In our opinion, engaging in commercial sex, which is obligatory associated with unimportant risks of harm to one's own safety and physical health, can be interpreted as one of the variants of self-destruction, as well as the tendency to addictive behavior in any form of implementation [17-19].

## THE AIM

The purpose of the publication - based on the hypothesis of conceptualizing of engaging in commercial sex as self-destructive behavior, to define its leading descriptors and predictors, on the basis of which to propose measures of their psycho-correction.

## MATERIALS AND METHODS

By providing informed consent, 185 women -residents of the big city of Ukraine participated in the research. The

research was conducted in the «Communicator Center for Workers of Commercial Sex» on the basis of the All-Ukrainian Charitable Foundation «Drop In Center». The main group (MG) of the research was 135 women -female sex workers (FSW), comparative (GC) 50 women who had no relation to this activity.

The age of women MG was between 18 and 41 years (mean age 26.0 ± 6.2 y.). 43.7% of them had higher education, others - secondary / secondary special education. 14.1% were in active marriage, 23.7% - lived in a civil marriage, others were unmarried. Almost half of the women (49.6%) had children (31.9% - brought up a child, 17.8% - two children). The overwhelming majority - 94.1% of women came from other cities (41.5%) or settlements (52.6%) of Ukraine. The average length of commercial sex on the sample was 4.8 ± 5.8 years, of which 60.0% worked in the sex business less than 3 years. 69.6% provided sex services in a specialized premise, and the rest 30.4% - in their apartment. In addition, 83.0% also worked on the call, leaving for clients. The experience of using narcotic substances was 45.9%, while other 54.1% did not use drugs. 77.0% used alcohol (at the level of harmful or dangerous use). The average age of the beginning of sexual life in the surveyed MG is 16.02 ± 2.8 years, which is not identical to the age of the first sexual experience, since most women (83.7%) talked about the presence of sexual abuse in childhood and subjectively did not perceive this event as the beginning of sexual life. The GC includes 50 women who never offered sexual services for rewards, aged of 18 to 40, 64.0% of which had higher education, 36.0% had secondary education, the average age of their sexual life was 17.1 ± 1.9 years.

The research methods were socio-demographic, clinical-psychological, psycho- diagnostic, systemic-structural analysis of sexual health and mathematical and statistical. Psycho-diagnostic study tools consisted of: Colombian scale for assessing the severity of suicide (C-SSRS) [20]; the questionnaire "The Index of Life Style" by R.Plutchek, G.Kellerman, H.R.Conte [21], the method of characterizing the accentuations of the character of K. Leonhard - G. Shmyshek [22], "The method of research of predisposition to victim behavior" O.O. Andronikovka, modified for interrogated adults [23], durativity test of S.R. Maddi in the adaptation of D. A. Leontiev, O. I. Rasskazova [24]. The statistical processing of the obtained results and indicators was carried out by means of the method of determining the significance of the differences in the samples (in accordance with the t-criterion of the Student, the Fisher-φ-criterion, and the Mann-Whitney criterion for non-parametric samples). Mathematical processing was carried out with using of the package of computer programs Excel and SPSS 16.0 for Windows.

## RESULTS

An analysis of the presence and structure of suicidal ideas revealed shocking results: 129 women (95.6%) had a history or present desire to die in the form of "I want to be dead or go to bed and not pretend to be"; 124 women (91.9%) thought about committing suicide; 46 women were contemplating a suicide without a specific plan (34.1%); 29 women (21.5%) had intentions to act; 54 persons intended to carry out a detailed planned suicide (40.0% of the surveyed). 56 women (41.5%) tried to commit suicide by making a real attempt, carried out preparatory actions - 55 (40.7%) of the surveyed, but 38 people (28.1% of the total number of surveyed and 67.9% of the number of women who tried to commit suicide) stopped themselves. religious beliefs helped them (belief that this is a great sin), thoughts about parents or children, fear, emotional sedation during preparatory actions; among 18 women (13.3% of the total number of surveyed and 32.1% of the number of women attempting to commit suicide) attempted suicide was interrupted by external circumstances, first of all such as telephone, intercourse of friends or relatives (convinced not to do). Consequently, the results of the study showed the presence of almost all of the sample of investigated FSW with a marked suicidal tendency, with nonspecific or specific thoughts about committing suicide, and, slightly less than half of them (40.7%) had in their own experience of stopped attempts to commit suicide. However, the grounds for suicidal attitude were unevenly distributed in the sample: 22 women (16.3%) were guided by the desire to attract attention, revenge or gain retaliation from other people; others, in one degree or another, wanted to stop psychological pain from which they suffered (113 people, 83.7%). Among the women of GC suicidal ideas, and, moreover, suicidal attempts in history were not observed.

Signs of the transformation of sexual activity were found in 36 women (26.7%) and in 87 cases (64.4%) were manifestations of hypertrophic behavior. The psychosocial orientation in the vast majority of respondents was normative, but in 34 women (25.2%) there were bisexual tendencies. Education in matters of sexual behavior and the interpretation of sexual manifestations were inadequate in more than half of the surveyed (79 people, 58.5%). Of the types of sexual culture, FSW prevalent: neurotic (65 people, 48.1%), primitive (33 people, 24.4%), liberal (26 people, 19.3%) and hypertrophic (11 people, 8.1%). Among the types of sexual motivation for FSW were characteristic: passive-conquering (75 people, 55.6%), frivolously irresponsible type (26 people, 19.3%), genital type (25 people, 18.5%) and aggressive selfish type (12 people, 8.9%). The main motive for sexual activity was a material benefit, although 19 women (14.1%) noticed self-affirmation as the main motive for their own sexual behavior. The vast majority of respondents did not feel psychosexual pleasure (109 women, 80.7%). Thus, in FSW, the social, psychological and socio-psychological components of sexual realization were violated, and the presence of almost all suicidal attitudes testified to the defeat of the psychological component of the biological component of sexuality in the surveyed.

Among women of GC predominated the normative sex-role behavior, the apolon type of sexual culture, the mutually altruistic communicative-hedonic type of sexual motivation.

All surveyed MG had a lack of general education, which led to the formation of an unharmonious personality and the lack of adaptability. Thus, 69 people have education by the type of emotional rejection (51.1%); 22 persons- by the type of dominant hyperprotection (16,3%); by the type of hepatoprotection - 20 people (14.8%); 18 people were raised in the conditions of strict relations (13.3%); 6 people were raised in the conditions of increased moral responsibility (4.4%). A significant number of the surveyed did not receive any sexual education at all in the family (87 people, 64.4%). Among others, there were immoral (26 people, 19.3%) or puritanical and repressive (22 persons, 16.3%) types of sexual education. The deformation of general and sexual education, undoubtedly, left a negative imprint on both the process of personality formation and the sexual realization of FSW.

All women in MG have over norm tensions in all mechanisms of psychological protection (MPP), in contrast to the results obtained in women with GC, in which the tensile strengths of all MPP were within normative values (statistical-mathematical analysis using nonparametric Mann-Whitney test proved statistic the significance of the discrepancies detected between MG and GC for all indicators of MPP is $p < 0.05$ or less). In all FSW, within the limits of the above normative, were the indicators of tension by the projection and intellectualization mechanisms (100%, respectively), 124 persons (91.9%) - by the mechanisms of regression and reactive formation (respectively), 113 persons (83.7 %) – by compensations, 103 people (76.3%) - by negation and substitution (respectively), 81 women (60.0%) – by displacement, which allowed them to consider their own inadmissible or unacceptable feelings as strange and not feel responsible for these.

In practically all women of MG there was a combination of certain accentuations (varying degrees of manifestation, however, greater than the normative value). In the general sample, almost all of types were found: emotional (87 persons, 64.4%), dysthymic (82 persons, 62.2%), anxiety (53 persons, 39.3%), affective exaltation (26 people, 19, hypertensive (24 persons, 17.8%), demonstrative (22 persons, 16.3%), excitatory (22 persons, 16.3%), stuck (19 people, 14.1%) and cyclothymic (17 people, 12.6%). Among the women of the GC, the combined/isolated increase to the average emotional (37, 74.0%) and hypertensive (29 persons, 58.0%) accentuation was revealed (differences between the MG and the GC by severity and prevalence of accentuations according to nonparametric statistical analysis (Mann-Whitney and Fischer's exact criteria) are statistically significant, $p < 0.05$ or less). The analysis of the distribution and severity of accentuated character traits among FSW with the conduct of cluster analysis allowed to distinguish three variants of the combination of types of accentuation ($p < 0.01$) that determined the specifics of the intrapsychic response of the surveyed, and became the basis for the implementation of self-destructive behavior in the form of occupation by prostitution.

Option № 1 - emotional-anxiety-dysthymic - was installed in 87 people (64,4%). The average indicators of the severity of these types of accentuation in this group were 18.4 ± 0.8 points for emotional, 18.1 ± 1.0 for anxiety and 16.8 ± 0.9 for dysthymic accentuation. They were characterized by increased emotional lability, a tendency to the pessimistic perception of reality, reduced mood, self-doubt, lack of skills of adequate social adjustment, weakness and helplessness, underestimation of their own abilities, constant anticipation of troubles and alarming expectations.

Option № 2 - affective exalted hypertinic-cyclotomic - was allocated among 26 people (19.3%). In this group, women had a combination of affective exaltation (mean severity of 17.8 ± 0.7 points), cyclothymic (mean severity of 17.1 ± 1.1 points) and hypertension (mean severity of 16.6 ± 1.1 points) accented types. These women were characterized by turbulence with an unstable emotional response with a wide range of emotional manifestations, a desire for entertainment and life pleasures, reduced sense of duty, frivolity, increased risk aversion, superficiality, inability to distinguish between "good" from "bad", abusive and inconsistent.

Option № 3 - demonstratively exciting and stucked - was allocated among 22 people (16.3%). These women were characterized by high indicative (average severity of 17.9 ± 1.1 points), excitatory (mean severity 16.2 ± 0.9 points) and stucking (average 15.3 ± 1.2 points) accentuation. This group of women differed in egocentrism and selfishness, in pathological stability of affect, first of all, negative experiences, irritability, conflict as a result of rejection of another point of view, especially in accordance to one's own personality, authoritarianism against the backdrop of weakness of the volitional sphere and uncontrollable outbursts of anger, indifference to the future with the desire for entertainment and pleasures.

In the study of viability, it was found that 97 women (71.9%) had low levels of MG (less than 62 points), that is, their behavioral repertoire lacked effective coping strategies for stress management, and the ability to assess their own capabilities and resources of surroundings was dubious. Other 38 (28.1%) of MG examined had an average level of viability (in the amplitude of values 62 - 81 points): they showed the ability to function only in conditions of everyday stress factors. Among the women of GC, 38 people (78.0%) had average viability indexes (62-81 points in the amplitude), the remaining 12 people (24.0%) had higher mean values (in the range of 82-100 points).

Practically all the possible types of victim behavior in FSW were registered with abnormal indicators. The analysis of the results pointed to the existence of a self-destructive self-destruction predictor in FSW as victimism, which is associated with active and even provocative behavior and characteristics such as an irrational and unreasonable predisposition to risk. They had a tendency toward antisocial behavior, violations of social norms, rules and ethical values.

On the basis of clusterization of the received results, three clinical and psychological variants of self-destructive behavior, characteristic for FSW are distinguished: passively helpless (87 persons, 64,4%); frivolously irresponsible (26 people, 19.3%); demonstratively aggressive (22 people, 16.3%) (Table I).

**Table I.** Representation and content of clinical and psychological variants of self-destructive behavior in FSW

| Predictor / Descriptor | Demonstration-aggressive, n=22 | Passive-helpless, n=87 | Frivolous-irresponsible, n=26 |
|---|---|---|---|
| | | ***Suicidal mood*** | |
| General features | expressed suicidal attitude with nonspecific or specific thoughts about committing a suicide | | |
| Specific features | 100% felt the desire to die throughout life | 100% felt the desire to die throughout life | 76,9% felt the desire to die throughout life |
| | motive: desire to attract attention, revenge or get feedback from other people (100%) | motive: to stop psychological pain from which they suffered (100%) | motive: to stop psychological pain from which they suffered (100%) |
| | real suicide attempt – 9,1% | real suicide attempt – 44,8% | real suicide attempt – 57,7% |
| | | ***Sexual realization*** | |
| General features | violation of social, psychological, socio-psychological and biological components of sexual realization | | |
| Specific features | transformation of sexual behavior (100%) | hyper role-playing behaviuor (100%) | transformation of sexual behavior (53,8%) |
| | 68,2% – bisexual orientation | 90,8% – lack of education in sex | 73,1% – bisexual orientation |
| | primitive type of sexual culture (100%) | neurotic (74.7%), primitive (12.6%), hypertrolytic (12.6%) types of sexual culture | liberal type of sexual culture (100%) |
| | aggressive selfish (54.5%), genital (45.5%) types of sexual motivation | passive-conquering (86.2%), genital (13.8%) types of sexual motivation | frivolously irresponsible (100%) type of sexual motivation |
| | | ***General and sexual education*** | |
| General features | deformation of general and sexual education | | |
| Specific features | exposure / dominant hyperprotection (100%) | emotional rejection (79.3%), hard-line relationship (20.7%) | hypoprotection (76.9%), increased moral responsibility (23.1%) |
| Specific features | puritanical and repressive types of sexual education (100%) | no sexual education (100%) | immoral type of sexual education (100%) |
| | | ***Individual-psychological patterns*** | |
| | | *Mechanisms of psychological protection* | |
| General features | fears of self-acceptance and rejection, devaluation with feelings of confusion, panic and feelings of guilt; fear of independence and initiative and shame and punishment; amounts, fears and feelings of inferiority; vulnerability to the indifference of others and a sense of inferiority, as well as anger with shame and the desire for revenge and punishment; existence in fear of being depreciated and shameful | | |
| Specific features | projection, regression, reactive formation, substitution, intellectualization | projection, regression, compensation, reactive formation, substitution, negation, intellectualization, displacement | projection, regression, reactive formation, compensation, negation, intellectualization |
| | | *Accentuations* | |
| General features | the presence of a combination of those or other accented rice | | |
| Specific features | demonstration-excitatory-jamming variant | emotion-anxiety-dysthymic option | affective exalted hyperthyroid cyclotamine variant |
| | | ***Behavioral patterns*** | |
| | | *Vitality* | |
| General features | lack of viability and effective coping strategies for stress management, questionable ability to assess own capabilities and resources of the environment; the difficulty of adapting to the inability to reconcile with the existing traumatic situation in the sex business; a sense of uncertainty in the future; perception of the surrounding reality as an incomprehensible, dangerous, cruel, uninteresting and devoid of meaning of being; feeling of helplessness and finding «out of life» | | |
| Specific features | lack of control (100%), risk capability (90.9%) | low inclusiveness (100%), lack of control (100%), risk capability (100%) | low inclusiveness (73.1%) lack of control (100%) |
| | | *Victimic behavior* | |
| General features | pathological victim behavior, a tendency to increased victimhood | | |
| Specific features | aggressive victim (100%), active victim (9.1%) | active victim (100%), initiative victim (40.2%), uncritical victim (39.1%) | active victim (100%), Initiative Victim (100%), aggressive victim (19.2%) |

Guided by the established clinical and psychological typology of self-destructive behavior of FSW, we have developed a program of measures of differentiated psycho-correction, aimed at reducing the risk of self-destruction in this contingent. The following general tasks were determined: 1) increasing the stability and resistance to psycho-traumatic conflict situations; 2) the development of the ability to control their own behavior and their own reactions to provocative factors; 3) raising awareness of causal relationships between personality-characterological and sexual-behavioral components in the structure of personality; 4) the formation of skills for independent decision making and conflict resolution in the field of gender interaction; 5) identification of priority directions in the development of relations and the formation of a responsible attitude to their behavior.

An important factor that determined the format of psycho-corrective work was the impossibility of long-term interventions, which was related to the conditions of FSW life, namely, the lack of independence in the actions as a result of dependence on the pimp, migration to other cities on the order of the client, etc.

The implementation of the program included the implementation of a series of consecutive steps, some of which were non-specific, and others - having a specific focus, depending on the version of the self-destructive behavior of FSW.

According to the general structure, the program contained classical blocks that determined its informative and methodological content: psycho-education, psycho-correction, psycho-progression.

The program consisted of 20 thematic meetings lasting up to 90 minutes (total duration - no more than 4 days). According to the form the work was built in the form of group meetings and psychological training (using the psycho-corrective benefits of group work) on the basis of cognitive-behavioral therapy.

Psycho-education was implemented within the framework of discussion on thematic lessons on topics such as: a) general concepts: "health", "reproductive health", "sexual health", "sex", "gender", "sexuality", "self-destructive behavior", "suicidal behavior", "basic psychological needs of the person"; b) violence and its types, violence in the context of sex work, violence and risky behavior, risky sexual behavior, victimization and victimblade, safe responsible sexual behavior, stigmatization and self-incrimination in sex business; c) factors influencing sexual and reproductive health and safe sexual behavior (psychological, physical, social); d) the rights of men and women to sexual and reproductive health; e) laws, regulations, regulatory protocols regulating the rights to sexual and reproductive health; f) sex work as a type of work; g) the specifics of the risks of transmission of HIV infection, STDs among people involved in commercial sex; h) risks of drug use by people involved in commercial sex; i) the risks of suicidal attitude and self-directed behavior among FSW .

The psycho-correction block of the program was created based on the fact that FSW -are women in the conditions of the long-term stressful impact of a complex crisis life situation, as a result of which they need special measures of psychological support and self-help skills. Psycho-correctional influences were directed at the targets determined during the work, first of all, suicidal mood, the tension of psychological protective mechanisms, victim behavior.

In the framework of group discussion on the method of group discussion with elements of reproduction of life situations, measures were taken to master the skills of stabilization of the emotional-volitional and behavioral sphere, such as: a) help and self-help in removing of psycho-emotional stress and normalizing the psycho-emotional state; b) identification of manifestations of suicidal attitude and their leveling; c) identification of the pathological consequences of experienced violence and their capture; d) identification and overcoming the propensity to victimization and victim-blaming; e) recognition of own motives of predisposition to self-destructive risk behavior and their elimination; f) overcoming self-stigmatization, etc.

To resolve issues related to the ability to identify and constructively analyze of the character traits which produce and provocative the self-destructive behavior, and the ability to cope with them, carried out a meaningful differentiation of psycho-correction effects, taking into account the option of self-destructive behavior, inherent in the surveyed.

Psycho-preventive measures consisted from discussing and developing a strategy for minimizing risks and reducing harm in sex work, preventing victim-blaming and stigmatization, overcoming the barriers associated with seeking treatment (legal, psychological, medical), strengthening self-help and self-help skills, and psychological support.

At the end of the program, upon request, women received psychological assistance in telephone or Skype counseling.

In total, 54 FSW were involved in psycho-correction: 36 persons (41.4%) with a passively-helpless version of self-destructive behavior, 10 people (38.5%) with frivolously irresponsible and 8 women (36.4%) with demonstratively aggressive options. Six months after the implementation of the psycho-correction program, for feedback on its effectiveness, groups were organized that covered 45 FSW, of those who participated in the developed events. It was noted that, according to the respondents' self-assessment, the severity of suicidal attitude was reduced due to the acquired skills to avoid risky situations associated with increased victimization and tendency to self-destruct general mood were increased, the number of conflicts with others and relatives was decreased. Also, as positive, changes were noted for activating and integrating FSW community members for mutual assistance and disseminating knowledge about preventing self-destructive behavior among this contingent.

## DISCUSSION

Taking into account that during our work we have substantiated the previous hypothesis about the conceptualization of the occupation of prostitution as a form of

self-destructive behavior, we believe that the aim of the work was achieved.

The obtained results allow to state that the leading descriptors of self-destructive behavior in FSW are: 1) expressed suicidal tendency with non-specific or specific thoughts about committing a suicide (and in 41.5% of cases with a suicidal attempt in the history); 2) distortion of the realization of sexuality; 3) excessive tension of the mechanisms of psychological protection.

Predictors involved in the mechanisms of the formation of this phenomenon can be divided into: -family - non-harmonic general education and, for the most part, the absence of sexual, and 2) individual psychological, which include: a) non-harmonic characterological features, b) lack of viability, c) distortion of the mechanisms of psychological protection, and d) predisposition to victim behavior.

In our opinion, depending on the ratio and content of identified predictors, one of the three variants of self-destructive behavior is formed in FSW - demonstratively aggressive, passively helpless, and frivolously irresponsible. However, despite the presence of three clinical and psychological variants of self-destructive behavior in FSW, psycho-corrective measures should include both general, common for all FSW, and personalized, differentiated depending on its variant, influences.

In our opinion, depending on the ratio and content of identified predictors, one of the three variants of self-destructive behavior is formed in FSW - demonstratively aggressive, passively helpless, and frivolously irresponsible. However, despite the presence of three clinical and psychological variants of self-destructive behavior in FSW, psycho-corrective measures should include both general, common for all FSW, and personalized, differentiated depending on its variant, influences.

The results obtained are original and reflect the results of the work of the author's team during 2015-2018.

## CONCLUSIONS

Consequently, as a result of the work among PSC a number of specific pathognomonic psycho-emotional, individual-psychological and behavioral features were distinguished, that made it possible to conceptualize occupations of prostitution as form of self-destructive behavior, and to propose effective measures of its psycho-correction and psycho-processing. Knowledge of genuine, though hidden, incentives for the engaging in commercial sex, the definition, and understanding of descriptors and predictors of self-destructive behavior among FSW has made it possible to improve the effectiveness of preventive and corrective work that has become a step towards overcoming the epidemic of HIV and sexually transmitted diseases.

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**Authors' contributions:**
*According to the order of the Authorship.*

**ORCID numbers:**
*Marianna V. Markova - 0000-0003-0726-4925*
*Tsira B. Abdriakhimova - 0000-0002-9723-3067*
*Olga V. Grishina - 0000-0002-2809-6994*
*Maya V. Savina - 0000-0002-1292-7482*
*Cornelia A. Kosenko - 0000-0001-6656-1802*
*Helen E. Falyova - 0000-0001-5983-0090*
*Artur R. Markov - 0000-0002-2164-7159*

**Conflict of interest:**
*The Authors declare no conflict of interest.*

**CORRESPONDING AUTHOR**
**Marianna V. Markova**
Kharkiv Medical Academy of Postgraduate Education
Street Amosova 58, 61176 Kharkiv, Ukraine
tel: +380506068145
e-mail: mariannochka1807@gmail.com

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# THE CHANGES IN DYNAMICS OF ORNITHINE CYCLE COMPONENTS LEVELS DURING THE ACUTE PERIOD OF POLYTRAUMA

**Nataliya Matolinets**
DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

## ABSTRACT

**Introduction:** Polytrauma or multiple organ damage is associated with shock and lead to systemic inflammation, oxidative stress and endothelial dysfunction. A severe mechanical injury causes an increased proinflammatory mediators and cytokines levels. Among them, the overproduction of nitric oxide and its oxidation products play a key role in tissue damage.

**The aim:** To evaluate the changes in dynamics of some ornithine cycle components levels during acute period of polytrauma.

**Materials and methods:** We measured standard biomechanical parameters and serum levels of NO, sum of nitrite and nitrate (NOx), L-arginine, arginase, and peroxynitrite. According to the ISS, the study included patients with moderate (n=15) to severe (n=15) polytrauma.

**Results:** In 24 hours after polytrauma on the background of intensive care, it was observed significant increasing of NO, NOx, and arginase levels (severe cases) with decreasing of L-arginine and peroxynitrite levels.

**Conclusions:** Elevated NO and NOx serum levels in patients with polytrauma is associated with increasing of arginase activity with decreasing of L-arginine and peroxynitrite levels on the background of intensive care.

**KEY WORDS:** polytrauma, nitric oxide, arginine, arginase, peroxynitrite

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## INTRODUCTION

Polytrauma or multiple organ damage is associated with shock and organ failure, which is injuring patients severely and can lead quickly to death if untreated [1,2]. It is well known that every tissue damage is related to systemic inflammation, oxidative stress, and endothelial dysfunction. A severe mechanical injury causes an increased production of proinflammatory mediators and cytokines [3,4,5]. Among them in case of tissue damage, nitric oxide plays a great role and is produced in high concentrations due to increased expression of inducible isoform of NO-synthase enzyme [6,7]. As it is known, the source of nitric oxide is L-arginine that is metabolized by arginase to urea and L-ornithine [8]. Arginase is a critical regulator of nitric oxide synthesis [9]. Depending on circumstances, arginase can inhibit the NO production via competition with NO synthase for the substrate L-arginine or uncoupling of NO-synthase resulting in the generation of the NO scavenger, superoxide and peroxynitrite [10,11,12]. Majority of NO cytotoxic effects belong to peroxynitrite which interacts with $O_2$. Peroxynitrite can damage vascular endothelium, increases platelets aggregation, participates in endotoxemia processes in cases of polytrauma [13]. Peroxynitrite toxicity depends on its concentrations. At low levels, peroxynitrite has regulatory and protective properties, while at high levels in ischemic tissues its toxic effects are demonstrated. Peroxynitrite increases arginase activity and decreases endothelial nitric oxide synthase level [14].

However, changes in dynamics of ornithine cycle components levels during the acute period of polytrauma are not well established.

## THE AIM

The aim of the investigation was to determine changes in dynamics of ornithine cycle components levels during the acute period of polytrauma.

## MATERIALS AND METHODS

The study included collected data of 30 patients with polytrauma who were treated in the intensive care unit (ICU) of the Lviv Emergency Hospital. The mean age of all patients was 48.4 ± 5.2 years. On average, it took 0.5 hours from the time of trauma till the admission into our ICU. In the pre-hospital period, the patients received adequate analgo-sedation, were immobilized and received infusion therapy during transportation.

The gravity of traumatic damage was determined using the Injury Severity Score (ISS), while the APACHE II score was used to predict ICU mortality. According to the ISS, the study included patients with moderate (n=15) to severe (n=15) polytrauma. Patients with decompensated chronic comorbidities were excluded from the study.

All patients with polytrauma were hospitalized to the shock-ward of our ICU, where a complex of clinical, labo-

**Table I.** Comparable levels of biochemical parameters in patients with moderate polytrauma in different trauma periods

| Blood parameters | Acute period | After 24-hours | P-value |
|---|---|---|---|
| Hemoglobin, g/L | 100,5±2,4, p1<0,05 | 112,4±1,9,p1<0,001 | p<0,001 |
| Hematocrite, % | 28,8±1,3 | 30,2±0,9 | p>0,5 |
| White blood cells, x10$^9$/L | 8,8±0,4 | 11,0±0,4 | p<0,01 |
| Urea, mmol/L | 8,4±1,1 | 8,8±0,6, p1<0,05 | p>0,5 |
| Protein, g/L | 58,5±1.2 | 56,3±1,3, p1<0,05 | p>0,5 |
| Glucose, mmol/L | 5,5±0,1 | 7,2±0,4 | p<0,01 |
| Total Bilirubin, mmol/L | 12,2±0,9 | 12.5±0,8 | p>0,5 |

**Table II.** Comparable levels of biochemical parameters in patients with severe polytrauma in different trauma periods

| Blood parameters | Acute period | After 24-hours | P-value |
|---|---|---|---|
| Hemoglobin, g/L | 91,2±2,8 | 84,9±2,9 | p>0,05 |
| Hematocrite, % | 31,8±1,4 | 28,7±0,8 | p>0,05 |
| White blood cells, x10$^9$/L | 9,9±0,6 | 12,6±0,6 | p<0,05 |
| Urea, mmol/L | 8,4±0,7 | 12,2±0,8 | p<0,05 |
| Protein, g/L | 56,9±1,3 | 50,5±1,7 | p<0,05 |
| Glucose, mmol/L | 6,2±0,3 | 7,7±0,3 | p<0,01 |
| Total Bilirubin, mmol/L | 14,4±1,2 | 15,8±1.0 | p>0,5 |

ratory and instrumental studies were conducted to assess the clinical signs and severity of traumatic shock at the time of ICU admission.

Diagnostic studies and consecutive therapy were carried out in accordance with the International Trauma Life Support guidelines (ATLS®).

The provided anti-shock therapy included hemostatic measures, adequate anesthesia and securing of an adequate gas exchange. The central venous access was provided by means of catheterization of the subclavian vein. Furthermore, a nasogastric tube and a urinary catheter were placed. The volume and rate of infusion therapy was determined by the deficit of circulating blood volume. Post-traumatic hemorrhagic anemia was restored with by means of blood transfusion. Emergency surgical interventions were carried out in acute life-threatening conditions. All patients routinely received a correction of water-electrolyte balance and metabolic disorders, respiratory therapy as indicated, antibacterial therapy, analgesia, correction of hemostatic disorders and symptomatic therapy as required.

The biochemical analysis of blood was carried out by the laboratory of the Department of Biochemistry of the Lviv National Medical University (LNMU). The analysis of NO, NOx, L-arginine, arginase, and peroxynitrite in serum was carried out on admission and after 24 hours of intensive care.

The blood serum was analyzed for the concentration of nitrite anions (NO2-) (μmol/l), the final stable product of the NO-metabolism and the sum of nitrite $NO_2$ + $NO_3$ (NOx) (μmol/l), using cooled centrifuged blood and Griess reagent [15].

The investigation of arginase activity (μmol/min×ml) was performed according to the method of Geyer J.W., 1971 [16]. Enzyme activity was determined by the amount of urea formed in the reaction. Investigation of the content of L-arginine (μg/ml) in blood plasma was carried out by the method of Aleinikova TL, Rubtsova GV 1988 [17].

Determination of serum peroxynitrite (ONOO) ONOO-mediated nitration of phenol was measured as described by van Uffelen et al. [18].

The levels of urea (mmol/l) and total protein (g/l) in the blood plasma were determined by a BioChem FC-360 auto-biochemical analyzer using a completely enzymatic method of kinetic determination of urea (GLDH Method) and a photocolorimetric determination of the total protein (Biuret Method).

Continuous characteristics were represented using means and standard deviations. Independent Student t-test was used to compare discrepancies between the different groups. Analysis of data was performed and expressed as mean ± SD.

## RESULTS AND DISCUSSION

During analyses of damage severity it was revealed that among investigated group of patients major were modest damage (ISS and APACHE II). Intensive care therapy and surgical treatment in patients during first 24 hours leads to improvement of hemodynamic parameters. On the second day was noticed increase of systolic blood pressure and decrease of heartburn. During first 24 hours, diuresis increased from 800 to 1300 ml. Standartization of hemodynamic parameters and 24-hours diuresis evidenced about patients improvement from traumatic shock.

Systemic inflammation developed after traumatic shock and manifested by increase of systemic inflammation indicators

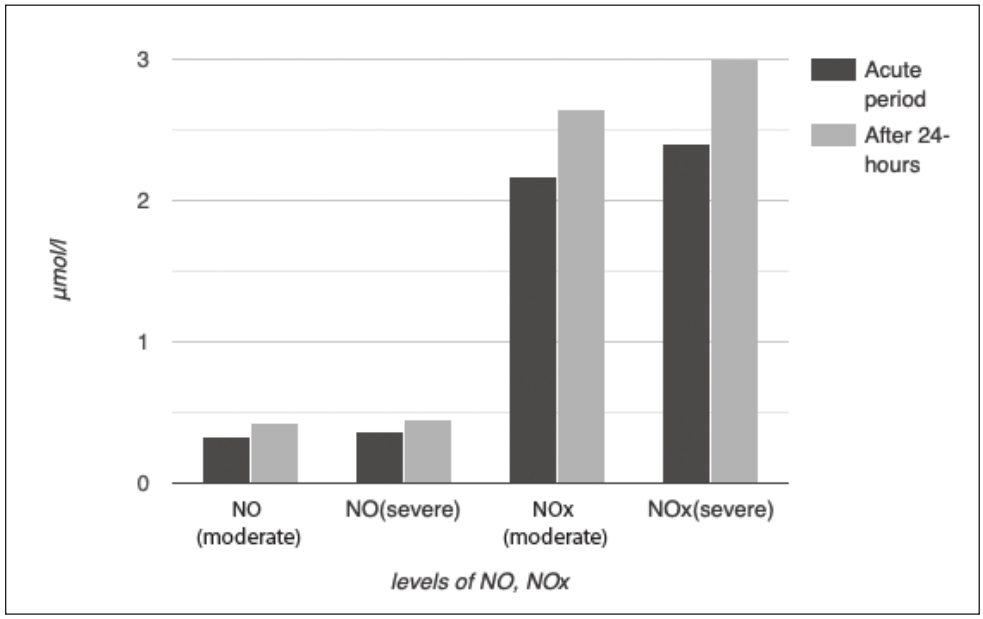


**Fig. 1.** Comparable levels of NO, NOx in patients with moderate and severe polytrauma in acute periods.

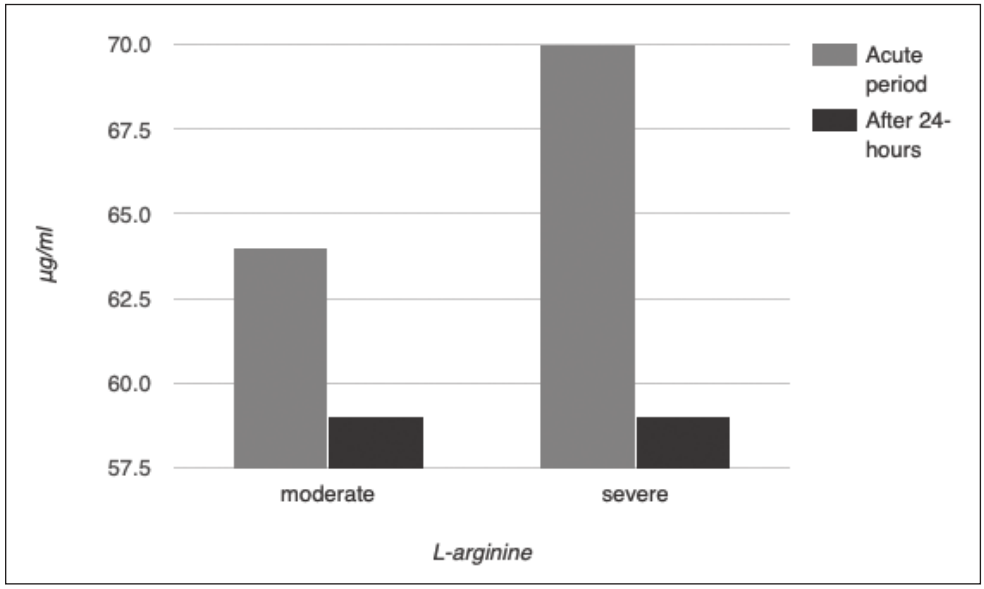


**Fig. 2.** Comparable levels of L-arginine in patients with moderate and severe polytrauma in acute periods.

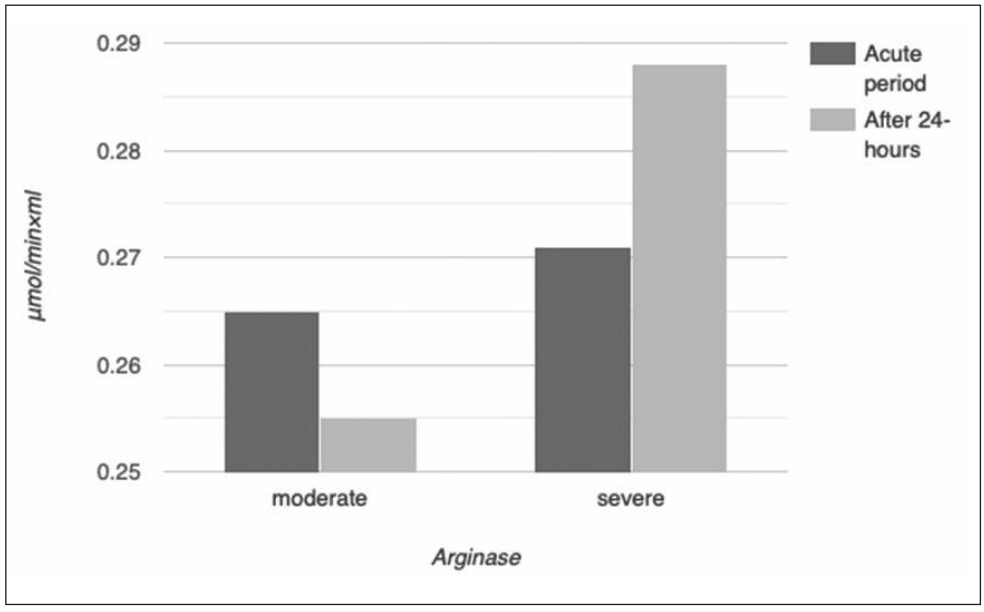


**Fig. 3.** Comparable levels of arginase in patients with moderate and severe polytrauma in acute periods.

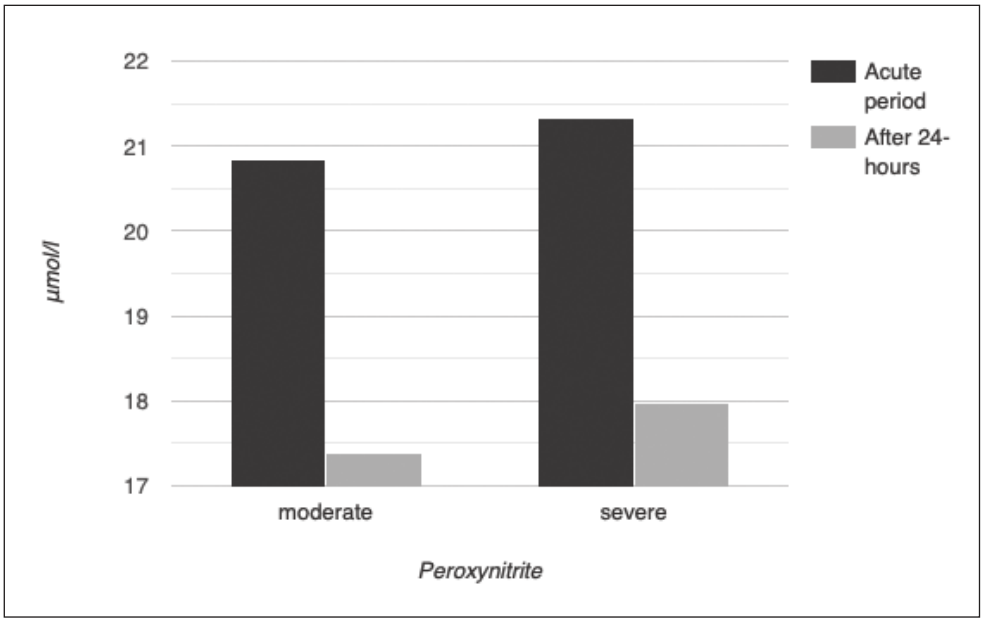


**Fig. 4.** Comparable levels of Peroxynitrite in patients with moderate and severe polytrauma in acute periods.

(leucocitosis, neutrofilosis), hyperglycemia, hyperfibrinemia, and subfebrile body temperature. Blood biochemical parameters during hospitalization were in the range of normal levels. But albumin and prothrombin index (PTI) decrease on the second day while fibrinogen and glucosae increase (Table I).

In both groups of patients with moderate and severe polytrauma, there was observed increasing of NO and NOx levels after 24 h of intensive care. In patients with moderate polytrauma, level of NO increased from 0,328±0,023 µmol/L to 0,425±0,033 µmol/L ($p < 0,01$) and level of NOx increased from 2,173±0,168 µmol/L to 2,652±0,181 µmol/L ($p < 0,01$). In patients with severe polytrauma, level of NO increased from 0,365±0,021 µmol/L to 0,455±0,025 µmol/L ($p < 0,01$) and level of NOx increased from 2,40±0,15 µmol/L to 3,00±0,14 µmol/L ($p < 0,01$) (Figure 1).

In both groups of patients with moderate and severe polytrauma, there was observed decreasing of L-arginine levels after 24 h of intensive care. In patients with moderate polytrauma, level of L-arginine decreased from 64.14±1.44 µg/mL to 59.05±1.08 µg/mL ($p < 0.01$). In patients with severe polytrauma, level of L-arginine decreased from 70.23±1.42 µg/mL to 59.28±1.24 µg/mL ($p < 0.01$) (Figure 2).

In group of patients with moderate polytrauma, there was not observed statistically significant difference in arginase levels after 24 h of intensive care. However, arginase levels significantly increased from 0.271±0.08 µmol/min×mL to 0.288±0.007 µmol/min×mL in patients with severe polytrauma ($p < 0.01$) (Figure 3).

In both groups of patients with moderate and severe polytrauma, there was observed decreasing of peroxynitrite levels after 24 h of intensive care. In patients with moderate polytrauma, level of peroxynitrite decreased from 20.42±0.34 µmol/L to 16.96±0.36 µmol/L ($p < 0.01$). In patients with severe polytrauma, level of peroxynitrite decreased from 22.88±0.64 µmol/L to 17.97±0.40 µmol/L ($p < 0.01$) (Figure 4).

When comparing some indicators of the ornithine cycle at moderate and severe polytrauma, there was observed a general tendency of changes in these indicators, as well as features of changes in the course of severe polytrauma were shown.

For acute period of polytrauma, there is observed significant increasing of NO and its oxidation products levels after 24 hours that can be associated with increased expression of inducible isoforms of NO-synthase (Beitl et al., 2016).

However, there was observed a significant decreasing of L-arginine and peroxynitrite levels with a substantial increasing of arginase in patients with severe polytrauma.

It should be noted that these metabolic processes are more pronounced in severe polytrauma that is demonstrated by significant changes in L-arginine, arginase, and peroxinitrite levels compared to these parameters at moderate polytrauma. These results are confirmed by negative correlation between arginase and NOx ($r = -0.52$) (Caldwell 2018).

Therefore, the presented data demonstrate that in acute period of polytrauma with systemic inflammation processes there is simultaneously occurring functions recovery via arginase regulatory activity regarding L-arginine level with further decreased NO synthesis.

## CONCLUSION

Elevated NO and NOx serum levels in patients with polytrauma is associated with increasing of arginase activity with decreasing of L-arginine and peroxynitrite levels on the background of intensive care.

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**ORCID numbers:**
*Nataliya Matolinets - 0000-0001-6656-3621*

**Conflict of interest:**
*The Author declare no conflict of interest.*

## CORRESPONDING AUTHOR
**Nataliya Matolinets**
Department of Anesthesiology and Intensive Care,
Lviv National Medical University named after Danylo Halitsky,
69a, Pekarskaya str., Lviv, 79010, Ukraine
tel: +380677741348
e-mail: nmatolinets@gmail.com

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# SOME TRENDS OF CLINICAL AND SYMPTOMATIC PATHOMORPHOSIS OF DEPRESSIVE DISORDERS TAKING INTO ACCOUNT THE AGE FACTOR

**Oleksandr O. Belov, Nataliya G. Pshuk**
NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE

## ABSTRACT

**Introduction:** Depressive disorders are one of the most complex and pressing problems of modern psychiatry; important scientific and practical importance is the study of the pathomorphosis of depression.

**The aim** of the study is to study the features of clinical pathomorphosis of depressive disorders, taking into account the age factor.

**Materials and methods:** Medical documentation of 115 men and 121 women with depressive disorders who applied for psychiatric care in 1971–1995 were studied, and 81 men and 108 women with similar depressive disorders who applied for medical care in 2015–2018 were examined clinically.

**Results and conclusions:** In modern patients, pathomorphosis is most pronounced in young patients (under 30 years of age): asthenia and pessimism were more common in them (65.9% versus 81.9%, $p<0.05$), suicidal thoughts (52.7% versus 68,7%, $p<0.05$), dyssomnias. In this age group, there was a decrease in anesthetic symptoms (34.8% versus 12.2%, $p<0.01$) with an increase in depressions with psychopathological symptoms, mainly in the form of obsessions (42.9% versus 59.0%, $p<0,05$), depressions with disturbances of biological rhythms, mainly in the form of postsomnic disorders (73.6% versus 96.4%, $p<0.05$), with vegetative-somatic disorders (63.7% versus 79.5%, $p<0.05$), asthenic (67.0% versus 81.9%, $p<0.05$) and agitated symptoms (26.4% versus 39.8%, $p<0.05$). In the middle age group (30-44 years), the share of vital forms of depression in the structure of depressive symptoms decreased (65.8% versus 44.6%, $p<0.01$) and depressions with senesto-algic symptomatology (6.6% against 9.6%, $p<0.05$). In patients of the older age group (45 years and more), the main trends in clinical pathomorphosis were a decrease in anhedonia (90.9% versus 70.7%, $p<0.01$) and low self-esteem (89.4% versus 65.9%, $p<0.01$), as well as an increase in apathetic depressions (13.6% versus 29.3%, $p<0.05$). The general tendency of modern pathomorphosis of depressive disorders is the reduction of vital forms of depression with an increase in depressions with asthenic, anxious and somatic symptomatology.

**KEY WORDS:** depressive disorders, clinical pathomorphosis

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## INTRODUCTION

Depressive disorders are one of the most complex and topical problems of modern psychiatry [1-3]. The presence of depressive disorders is an important risk factor for suicidal behavior, as well as a factor showing disorders of social adaptation both in patients with depressions and in their microsocial environment [4, 5]. One of the most important trends in the study of depression is the study of their pathomorphosis; several studies have convincingly demonstrated the presence of gender and age-related pathomorphosis of depressive disorders [6–8]. We have described some trends in the current socio-demographic and clinical pathomorphosis of endogenous depressions [9, 10]. At the same time, a number of important issues of clinical pathomorphosis of depressive disorders remain insufficiently studied, and the data of existing studies are incomplete and contradictory; special attention should be paid to the problem of a comprehensive assessment of modern pathomorphosis of depressive disorders.

## THE AIM

The aim of the study is to study the features of clinical pathomorphosis of depressive disorders, taking into account the age factor.

## MATERIALS AND METHODS

We have analyzed the clinical features of depressive disorders in 236 patients who applied for medical care at Vinnitsa Regional Psycho-Neurological Hospital from 1971 to 1995, based on an analysis of medical records (case histories, outpatient records, epicrises, extracts). Gender and nosological structure of the studied contingent is given in table. 1. These patients constituted group A. The average age of the patients in this group was 37.5 ± 12.2 years (men 38.3 ± 13.1 years, women 36.8 ± 11.2 years), the average duration of depression was 7 5 ± 4.6 years (men 7.7 ± 5.0 years, women 7.3 ± 4.2 years).

Besides, with the observance of the principles of biomedical ethics, we have clinically examined 189 patients with depressive disorders who applied for medical assistance at Vinnitsa Regional Psycho-Neurological Hospital from 2015 to 2018. Gender and nosological structure of the studied contingent is given in table I. These patients constituted group B. The average age of patients in this group was 32.6 ± 10.1 years (men 31.8 ± 9.5 years, women 33.3 ± 10.5 years), the average duration of depression was 7 , 8 ± 5.6 years (men 7.6 ± 5.8 years, women 7.9 ± 5.5 years).

**Table I.** Gender and nosological structure of the studied patients

| ICD-9, ICD-10 code | Nosology | Number of patients | | | | | |
|---|---|---|---|---|---|---|---|
| | | men | | women | | total | |
| | | abs. | % | abs. | % | abs. | % |
| **Patients who applied for psychiatric care in 1971–1995 (Group A)** | | | | | | | |
| 296.3 | Manic-depressive psychosis, circular type but currently depressed | 51 | 44,3 | 38 | 31,4 | 89 | 37,7 |
| 296.1 | Manic-depressive psychosis, depressive type | 64 | 55,7 | 83 | 68,6 | 147 | 62,3 |
| | Total | 115 | 100 | 121 | 100 | 236 | 100 |
| **Patients who applied for psychiatric care in 2015–2018 (Group B)** | | | | | | | |
| F. 31.3, F. 31.4 | Bipolar affective disorder, current episode mild or moderate depression | 32 | 39,5 | 31 | 28,6 | 63 | 33,4 |
| F. 32.0, F. 32.1, F. 32.2 | Depressive episode | 28 | 34,6 | 39 | 36,1 | 67 | 35,4 |
| F. 33.0, F. 33.1, F. 33.2 | Recurrent depressive disorder | 21 | 25,9 | 38 | 35,3 | 59 | 31,2 |
| | Total | 81 | 100 | 108 | 100 | 189 | 100 |

Groups A and B were comparable by gender and age characteristics and according to the severity of depressive disorders.

3 subgroups were allocated in each group depending on the age of patients at the time of the study: up to 30 years (A1 and B1, respectively), from 33 to 44 years (A2 and B2 groups, respectively), 45 years and older (A3 and B3 groups, respectively).

Symptoms of depressive disorders were analyzed in relation to the criteria for depression ICD-10 (1996-2017) and the classification of depressions, as well as in the context of individual syndromes.

Statistical analysis of differences between groups was carried out using Fisher's exact test.

## RESULTS AND DISCUSSION

The results of the analysis of clinical symptoms are given in table II.

When analyzing the specific features of clinical pathomorphosis of depressive disorders, it was found that under modern conditions asthenia in the form of increased fatigue and decreased performance was found to be significantly more frequent in young patients under the age of 30 years (65.9% in group A1 versus 81.9% in group B1, $p<0.05$). The same ratio (65.9% versus 81.9%, $p<0.05$) was found for pessimism; suicidal thoughts were also significantly more frequently found in modern young patients (52.7% versus 68.7%, $p<0.05$), as well as various dissomnias (86.8% versus 96.4%, $p<0.05$). Less significant differences ($p<0.1$) were found for gastrointestinal symptoms (impaired appetite, change in body weight): 53.2% versus 64.6%.

In patients aged 30-45, the differences are less evident: the most apparent was an increase in the specific gravity of patients with manifestations of pessimism (72.2% in group A2 versus 84.6% in group B2, $p<0.1$), and a decrease in the specific gravity of patients with low self-esteem (83.5% versus 72.3%, $p<0.1$).

In the older age group (45 years and more), the main trends in clinical pathomorphosis were a statistically significant decrease in the specific gravity of patients with symptoms of anhedonia (90.9% in group A3 versus 70.7% in group B3, $p<0.01$) and with underestimated self-esteem (89.4% versus 65.9%, $p<0.01$). Less apparent ($p<0.1$) were a decrease in the specific gravity of patients with manifestations of pessimism (83.3% versus 70.7%), and an increase in the specific gravity of patients with manifestations of guilt, feelings of worthlessness, anxiety or fear (77.3% versus 90.2%), as well as complaints of the reduced ability to concentrate and make decisions (from 63.6% to 78.0%).

As it can be seen from table III, in the structure of depressive symptoms, the specific gravity of vital forms of depression in the age group 30-44 years decreased (from 65.8% to 44.6%, $p<0.01$) and anesthetic depression in age groups up to 30 years (from 34.8% to 12.2%, $p<0.01$). The specific gravity of apathetic depressions in the older age group increased (from 13.6% to 29.3%, $p<0.05$); depression with vegetative-somatic (from 63.7% to 79.5%, $p<0.05$), asthenic (from 67.0% to 81.9%, $p<0.05$) and agitated symptoms (from 26, 4% to 39.8%, $p<0.05$) in the group of young patients (up to 30 years); as well as with senesto-algic symptoms in the middle (30-44 years) age group (from 6.6% to 9.6%, $p<0.05$).

The study revealed some trends in modern clinical pathomorphosis of depressive disorders in different age groups.

It has been established that, in general, modern pathomorphosis of depressive disorders is characterized

**Table II.** Features of clinical symptoms in patients of different age groups who applied for psychiatric care in 1971–1995 and 2015-2018

| Symptoms | Age groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | abs. | % | abs. | % | abs. | % | abs. | % |
| | A1 | | A2 | | A3 | | Total | |
| Low mood | 90 | 98,9 | 79 | 100 | 65 | 98,5 | 234 | 99,2 |
| Anhedonia | 72 | 79,1 | 67 | 84,8 | 60 | 90,9 | 199 | 84,3 |
| Severe fatigue | 60 | 65,9 | 56 | 70,9 | 43 | 65,2 | 159 | 67,4 |
| Pessimism | 60 | 65,9 | 57 | 72,2 | 55 | 83,3 | 172 | 72,9 |
| Guilt, worthlessness, anxiety or fear | 66 | 72,5 | 57 | 72,2 | 51 | 77,3 | 174 | 73,7 |
| Low self-esteem | 65 | 71,4 | 66 | 83,5 | 59 | 89,4 | 190 | 80,5 |
| Inability to concentrate and make decisions | 51 | 56,0 | 51 | 64,6 | 42 | 63,6 | 144 | 61,0 |
| Thoughts of death and suicide | 48 | 52,7 | 54 | 68,4 | 40 | 60,6 | 142 | 60,2 |
| Unstable appetite, weight fluctuations | 44 | 48,4 | 42 | 53,2 | 36 | 54,5 | 122 | 51,7 |
| Dyssomnia | 67 | 73,6 | 67 | 84,8 | 59 | 89,4 | 193 | 81,8 |
| **Symptoms** | **B1** | | **B2** | | **B3** | | **Total** | |
| Low mood | 81 | 97,6 | 64 | 98,5 | 41 | 100 | 186 | 98,4 |
| Anhedonia | 62 | 74,7 | 53 | 81,5 | 29 | 70,7 | 144 | 76,2 |
| Severe fatigue | 68 | 81,9 | 51 | 78,5 | 32 | 78,0 | 151 | 79,9 |
| Pessimism | 68 | 81,9 | 55 | 84,6 | 29 | 70,7 | 152 | 80,4 |
| Guilt, worthlessness, anxiety or fear | 66 | 79,5 | 50 | 76,9 | 37 | 90,2 | 153 | 81,0 |
| Low self-esteem | 64 | 77,1 | 47 | 72,3 | 27 | 65,9 | 138 | 73,0 |
| Inability to concentrate and make decisions | 54 | 65,1 | 49 | 75,4 | 32 | 78,0 | 135 | 71,4 |
| Thoughts of death and suicide | 57 | 68,7 | 46 | 70,8 | 30 | 73,2 | 133 | 70,4 |
| Unstable appetite, weight fluctuations | 50 | 60,2 | 42 | 64,6 | 22 | 53,7 | 114 | 60,3 |
| Dyssomnia | 80 | 96,4 | 61 | 93,8 | 35 | 85,4 | 176 | 93,1 |

| Symptoms | Level of statistical significance of differences (p) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Age groups | | | | | | | | |
| | A1-B1 | A2-B2 | A3-B3 | A1-A2 | A1-A3 | A2-A3 | B1-B2 | B1-B3 | B2-B3 |
| Low mood | 0,465 | 0,451 | 0,617 | 0,535 | 0,666 | 0,455 | 0,591 | 0,446 | 0,613 |
| Anhedonia | 0,304 | 0,381 | 0,008 | 0,225 | 0,036 | 0,197 | 0,215 | 0,396 | 0,146 |
| Severe fatigue | 0,013 | 0,200 | 0,114 | 0,300 | 0,562 | 0,288 | 0,374 | 0,387 | 0,572 |
| Pessimism | 0,013 | 0,055 | 0,098 | 0,240 | 0,011 | 0,080 | 0,419 | 0,118 | 0,072 |
| Guilt, worthlessness, anxiety or fear | 0,185 | 0,324 | 0,071 | 0,546 | 0,314 | 0,305 | 0,427 | 0,104 | 0,066 |
| Low self-esteem | 0,284 | 0,077 | 0,004 | 0,045 | 0,005 | 0,220 | 0,315 | 0,132 | 0,311 |
| Inability to concentrate and make decisions | 0,145 | 0,111 | 0,087 | 0,165 | 0,215 | 0,523 | 0,120 | 0,101 | 0,472 |
| Thoughts of death and suicide | 0,023 | 0,449 | 0,131 | 0,027 | 0,207 | 0,212 | 0,463 | 0,383 | 0,485 |
| Unstable appetite, weight fluctuations | 0,078 | 0,112 | 0,543 | 0,319 | 0,273 | 0,501 | 0,355 | 0,306 | 0,179 |
| Dyssomnia | 0,022 | 0,292 | 0,370 | 0,354 | 0,011 | 0,287 | 0,366 | 0,035 | 0,133 |

by a decrease in the specific gravity of "classical" vital forms of depression with an increase in depressions with asthenic, anxious, and somatovegetative symptomatology. At the same time, the dynamics of pathomorphisis is most evident in the age group up to 30 years; among modern young patients vital and anesthetic forms of depression were significantly less frequently detected, and more often are asthenia phenomena in the form of increased fatigue, decreased performance, pessimism, thoughts of death or suicide, as well as dyssomnia, mainly in the form of postsomnic disorders. Among young patients, we have observed an increase in vegetative-somatic disorders and agitation. The trends in pathomorphosis are less evident in the age group of

**Table III.** Symptoms of depression in patients of different age groups who applied for psychiatric care in 1971–1995 and 2015-2018

| Option of depression | Age groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | abs. | % | abs. | % | abs. | % | abs. | % |
| | A1 | | A2 | | A3 | | Total | |
| Vital depression | 48 | 52,7 | 52 | 65,8 | 34 | 51,5 | 134 | 56,8 |
| Apathetic depression | 20 | 22,0 | 12 | 15,2 | 9 | 13,6 | 41 | 17,4 |
| Anesthetic depression | 23 | 25,3 | 15 | 19,0 | 23 | 34,8 | 61 | 25,8 |
| Somatic depressive disorders | 58 | 63,7 | 58 | 73,4 | 45 | 68,2 | 161 | 68,2 |
| Senesto-algic syndrome | 6 | 6,6 | 4 | 5,1 | 5 | 7,6 | 15 | 6,4 |
| Asthenic depression | 61 | 67,0 | 53 | 67,1 | 44 | 66,7 | 158 | 66,9 |
| Agitated depression | 24 | 26,4 | 21 | 26,6 | 26 | 39,4 | 71 | 30,1 |
| **Symptoms** | **B1** | | **B2** | | **B3** | | **Total** | |
| Vital depression | 34 | 41,0 | 29 | 44,6 | 18 | 43,9 | 81 | 42,9 |
| Apathetic depression | 20 | 24,1 | 14 | 21,5 | 12 | 29,3 | 46 | 24,3 |
| Anesthetic depression | 19 | 22,9 | 10 | 15,4 | 5 | 12,2 | 34 | 18,0 |
| Somatic depressive disorders | 66 | 79,5 | 50 | 76,9 | 31 | 75,6 | 147 | 77,8 |
| Senesto-algic syndrome | 8 | 9,6 | 10 | 15,4 | 4 | 9,8 | 22 | 11,6 |
| Asthenic depression | 68 | 81,9 | 51 | 78,5 | 32 | 78,0 | 151 | 79,9 |
| Agitated depression | 33 | 39,8 | 22 | 33,8 | 18 | 43,9 | 73 | 38,6 |

| Symptoms | Level of statistical significance of differences (p) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Age groups | | | | | | | | |
| | A1-B1 | A2-B2 | A3-B3 | A1-A2 | A1-A3 | A2-A3 | B1-B2 | B1-B3 | B2-B3 |
| Vital depression | 0,080 | 0,009 | 0,372 | 0,058 | 0,504 | 0,057 | 0,390 | 0,452 | 0,552 |
| Apathetic depression | 0,439 | 0,221 | 0,043 | 0,176 | 0,131 | 0,491 | 0,434 | 0,341 | 0,250 |
| Anesthetic depression | 0,425 | 0,366 | 0,008 | 0,213 | 0,131 | 0,024 | 0,176 | 0,118 | 0,438 |
| Somatic depressive disorders | 0,016 | 0,387 | 0,275 | 0,117 | 0,342 | 0,571 | 0,427 | 0,390 | 0,528 |
| Senesto-algic syndrome | 0,323 | 0,036 | 0,476 | 0,465 | 0,525 | 0,388 | 0,209 | 0,607 | 0,300 |
| Asthenic depression | 0,019 | 0,091 | 0,148 | 0,562 | 0,548 | 0,548 | 0,374 | 0,387 | 0,572 |
| Agitated depression | 0,043 | 0,222 | 0,397 | 0,556 | 0,060 | 0,072 | 0,286 | 0,401 | 0,202 |

45 years and older; they are manifested mainly in the reduction of anhedonia with a higher self-esteem and a decrease in the specific gravity of apathetic forms of depression. Clinical pathomorphosis is less expressed in the age group from 30 to 44 years; it manifests itself mainly in reducing the specific gravity of vital forms of depression and senesto-algic symptoms.

The results obtained allow determining the main trends of modern clinical pathomorphosis of depression in different age groups, which is important for the development of therapeutic, rehabilitation and preventive measures.

## CONCLUSIONS

The study of the specific features of modern clinical pathomorphosis of depressive disorders revealed its main tendencies, consisting in reducing the specific gravity of vital and anesthetic forms of depression with an increase in atypical anxiety, asthenic forms and forms with somatovegetative symptomatology. Clinical pathomorphosis is most apparent in young (up to 30 years) and older (over 45 years) patients, and less apparent in the middle age group (30-44 years).

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**Authors' contributions:**
*According to the order of the Authorship.*

**ORCID numbers:**
*Oleksandr O. Belov - 0000-0002-0156-0777*
*Nataliya G. Pshuk - 0000-0001-9857-2565*

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**CORRESPONDING AUTHOR**
**Oleksandr O. Belov**
Pirogova street, 109, 21100 Vinnitsa, Ukraine
tel: +380678636827
e-mail: oleksbelov@gmail.com

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ORIGINAL ARTICLE
PRACA ORYGINALNA

# IMMUNE STATUS OF PATIENTS WITH FRONTAL BASILAR TRAUMA HAVING BC "SYNTEKOST" APPLIED IN THE SURGICAL TREATMENT. REPORT 1. THE STATE OF THE SYSTEMIC CELLULAR AND HUMORAL IMMUNITY FACTORS OF PATIENTS WITH FRONTAL BASILAR TRAUMA IN THE ACUTE POSTTRAUMATIC PERIOD PRIOR TO SURGICAL TREATMENT

**Vasyl Kishchuk[1,2], Oleksandr Bondarchuk[1,2], Ihor Dmitrenko[1,2], Kateryna Lobko[1], Yaroslav Hrytsun[1,2], Maryna Timchenko[3], Oleksandr Datsiuk[1,2], Hennadii Bevz[1]**

[1]PIROGOV VINNITSA NATIONAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE
[2]PIROGOV VINNITSA REGION CLINICAL HOSPITAL, VINNYTSIA, UKRAINE
[3]INSTITUTE OF OTOLARYNGOLOGY NAMED AFTER PROF. O.S.KOLOMIYCHENKO UKRAINE, KYIV, UKRAINE

## ABSTRACT

**Introduction:** At present biocomposite materials are used in the surgical treatment of frontal bone fracture. They improve osteogenesis, reduce the number of complications. Immunologic aspects of application of these materials are studied insufficiently, therefore this report presents the results of immunoassay of patients with frontal bone fracture in the proximate posttraumatic period before implanting preparation "Syntekost".

**The aim:** To define the role of immune mechanisms in the realization of the biocomposite material's positive influence on the development of effective posstraumatic rehabilitation schemes.

**Materials and methods:** 16 patients with frontal bone fracture (FBF) were examined on admission to the Otolaryngology Clinics of Vinnitsa Region Hospital. Additionally, 10 patients of the similar age were examined as a control group. The content of cells with markers of surface antigens-CD3,14,16,20,25, concentration of immunoglobulins of classes M,G,A,E, $C_4$ complement component and lactoferrin was determined in blood. Immunoenzyme methods were applied. Nonparametric Wilcoxon — Mann — Whitney test, computer programme WIN Pepi were used for statistical measurements.

**Results:** A decrease in the level of IgM in comparison with practically healthy donors and an increase in the concentration of lactoferrin were identified as humoral immunity factors of patients with frontal basilar trauma. The most significant deviation in the peripheral blood cellular makeup in CD-markers was an increase in cells with markers CD14 and CD16.

**Conclusions:** The level of cells and prodefensin-lactoferrin that maintain inborn immunity increases and the concentration of coarse defensive protein decreases in the initial period after frontal bone fracture, which must be taken into consideration during post-surgical treatment.

**KEY WORDS:** trauma, immunoglobulins, CD-markers, $C_4$ complement component, lactoferrin

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## INTRODUCTION

It is known that both in the initial and remote periods of skull fractures there is a significant immune response to trauma, which becomes apparent through changes in immune response level at initial stages after a trauma and possible development of autoimmune response at the late stage [1,2,3]. In the recent years synthetic compositions on the basis of hydroxyapatite (BC"Syntekost") that can accelerate osteogenesis and prevent the development of liquorrhea and other posttraumatic complications have been used in the surgical treatment of frontal bone fracture [4]. The present report offers results of immunoassay of patients with frontal bone fracture in the proximate posttraumatic period before implanting preparation "Syntekost".

## THE AIM

To define the role of immune mechanisms in the realization of the biocomposite material's positive influence on the development of effective posstraumatic rehabilitation schemes.

## MATERIALS AND METHODS

16 patients with frontal bone fracture (FBF) were examined on admission to the Otolaryngology Clinics of Vinnitsa Region Hospital. Additionally, 10 patients of the similar age were examined as a control group. Blood was drawn from an ulnar vein and divided into two parts: with heparin to get mononuclears and without it to get blood serum. Mononuclears were received from the heparinized blood by means of centrifugal sedimentation (120g, 10 min, cooling centrifuge NU 800R, Turkey) in the ficoll paque density gradient (1.077, Pan-Eco, RF), they were weighed in medium 199 being enriched (vitamins, aminoacids, embryonic calf serum, reagents Serva, Germany) up to density of 2 mln cells/ml. T-lymphocytes (CD3), B-lymphocytes

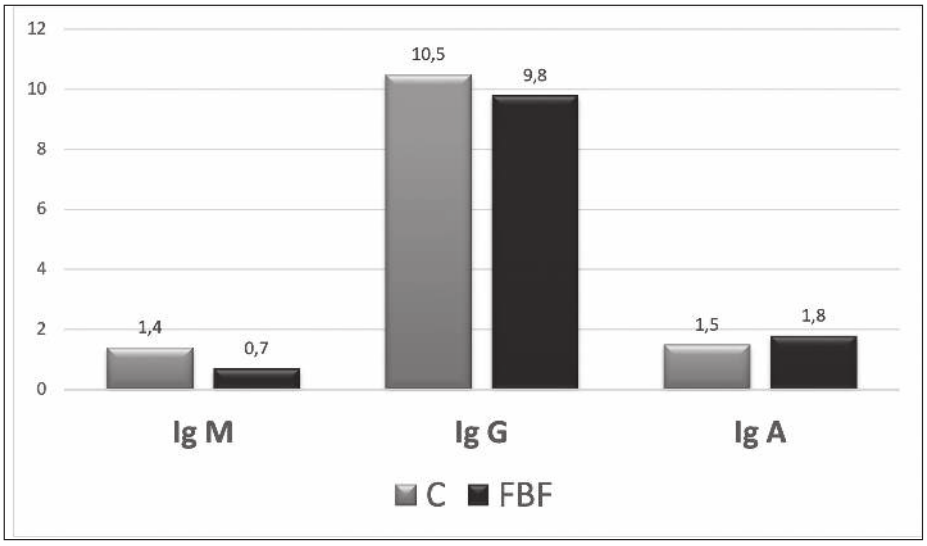


**Fig. 1.** The content (g/l) of immunoglobulins of M,G,A classes in the blood serum of the control group patients and of the patients with FBF.
C – control groupe
FBF – fracture of frontal bone
Ig M - Immunoglobulin M
Ig G - Immunoglobulin G
Ig A - Immunoglobulin A

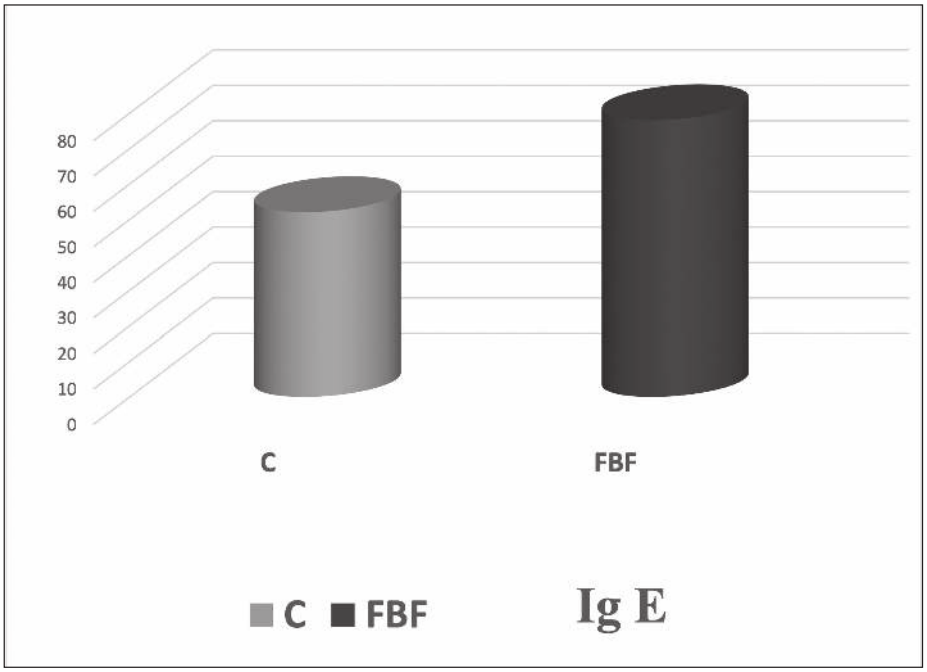


**Fig. 2.** The content of E class immunoglobulins (ME/ml) in the blood serum of the control group patients and the patients with FBF.
C – control groupe
FBF – fracture of frontal bone
Ig E - Immunoglobulin E

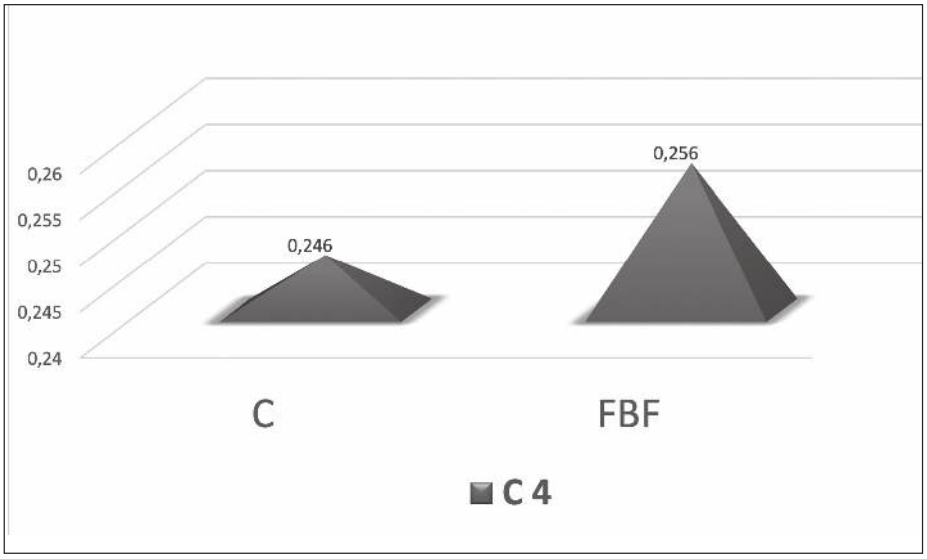


**Fig. 3.** The content of C4 complement component in the blood serum of both examined groups.
C – control groupe
FBF – fracture of frontal bone

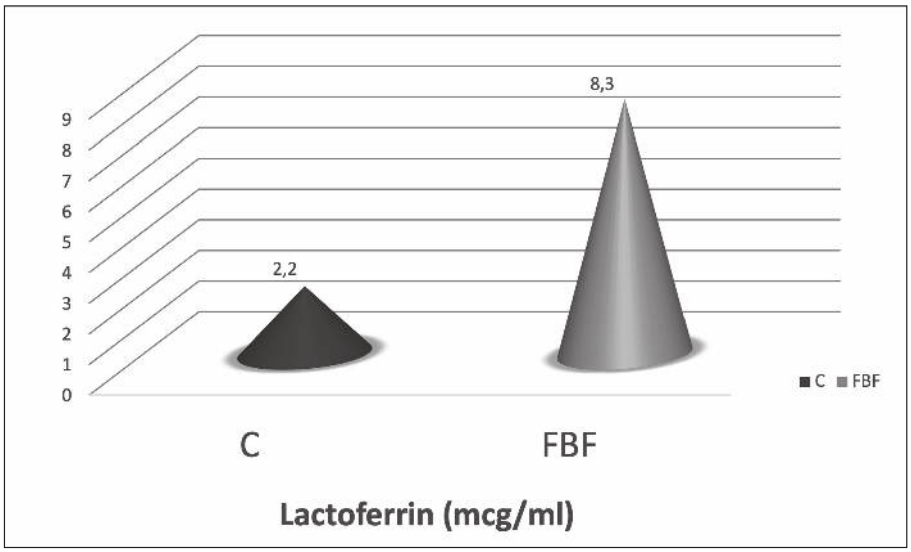


**Fig. 4**. Lactoferrin content in the blood of the examined groups.
C – control groupe
FBF – fracture of frontal bone

**Table I.** The content of different types of blood cells in the patients with FBF and in the control group patients (by mucous tunic).

| Groups and indices | Relative content (%) | | | | |
|---|---|---|---|---|---|
| | CD3 | CD14 | CD16 | CD20 | CD25 |
| C,M (min.max.) | 55,5 (40-65) | 6,5 (4-8,5) | 6,5(4-7,5) | 17,8(12-19) | 5,5(5-7) |
| FBF, M (min.–max.) | 48,2(38-55) | 12,5(7-16) | 13,5(6-17) | 15,5(10-15) | 8,5(5-12) |
| p | > 0,05 | < 0,05 | < 0,05 | > 0,05 | < 0,07 |

(CD20), monocytes (CD14), natural killer cells (CD16), activated lymphocytes (CD25) were detected applying monoclonal antibodies to cell surface antigens (CD) and using rosette method [5].

The content of immunoglobulins of M,G,A,E classes in the blood serum was analyzed using immunoenzyme method (reagents Xema-Medica Co.Ltd., RF and Lab line reader, Austria). Furthermore, the content of $C_4$ complement component (Microgen, RF) and prodefensin-lactoferrin, which is an indicator of an acute phase of any inflammation (Belamy e.a., 1989). Statistical analysis was undertaken using Nonparametric Wilcoxon — Mann — Whitney test as recommended by E.V. Gubler (1990) [6] according to Biostatistics-6 programme.

## RESULTS

Received data showed that the content of immunoglobulins of classes M,G,A,E in patients with FBF did not differ from the one in the control group patients, whereas the level of IgM was significantly lower than in the control group patients: 0,3 and 1,5 g/l correspondingly (figure 1,2). The content of $C_4$ complement component in the stated period after FBF did not differ from the one of the control group. (figure 3)

At the same time there was a significant increase ($p<0,02$) in lactoferrin – from 3 mkg/ml, which is the norm, to 10 in patients with FBF (figure 4).

When studying the content of cells of different types according to clasters of differentiation, significant deviations were identified in macrophages and natural cytotoxic cells, CD14 and CD16 correspondingly (table I), the content of which increased during the first 24 hours of FBF. The tendency towards the content increase was also noted while determining the number of activated cells that reflect to a certain extent the activation of regulatory T-cells [7]. The decrease in IgM concentration in the blood serum may relate to the usage of coarse proteins from blood as a plastic material in extreme situations [8]. The increase in cells with CD14 and CD16 markers proves that innate immunity factors take part in defense and adaptation processes as quickly responsing components of the immune system.

## CONCLUSIONS

1. A decrease in the IgM level and an increase in the lactoferrin concentration were noted in patients with frontal basilar trauma while determining systemic humoral immunity element.
2. The most significant deviation in the peripheral blood cellular makeup in CD-markers was an increase in cells with markers CD14 and CD16.

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**Authors' contributions:**
*According to the order of the Authorship.*

**ORCID numbers:**
*Vasyl Kishchuk - 0000-0002-3390-2401*
*Oleksandr Bondarchuk - 0000-0002-7636-9694*
*Ihor Dmitrenko - 0000-0002-1357-2847*
*Kateryna Lobko - 0000-0002-0045-2352*
*Yaroslav Hrytsun - 0000-0002-3541-3636*
*Maryna Timchenko - 0000-0002-7889-1152*
*Oleksandr Datsiuk - 0000-0001-6298-4891*
*Hennadii Bevz - 0000-0003-1257-4290*

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## CORRESPONDING AUTHOR
**Oleksandr Bondarchuk**
National Pirogov Memorial Medical University
Pyrogov str., 56, Vinnytsia, Ukraine
tel.: +380432570360
e-mail: eskulap20009@gmail.com

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ORIGINAL ARTICLE
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# SCREENING INVESTIGATION OF DISTRIBUTION OF MOOD DISORDERS IN ADOLESCENCE AND PECULIARITIES OF THEIR CURRENCY

**Larysa V. Pypa, Yulia N. Lysytsia, Ruslan V. Svistilnik, Maryna M. Murhina**
VINNYTSIA NATIONAL PYROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE

## ABSTRACT

**Introduction:**. The problem of mood disorders in adolescents has recently become acute due to the high frequency of encounter and social significance.

**The aim:** To investigate the screening of anxiety and depressive disorders and their manifestations in adolescent children to determine risk factors and to develop measures for their prevention.

**Materials and methods:** The study was attended by 189 students aged 16-17 years of the educational institutions of the Khmelnytskyi region. For study it was used: Spielberger questionnaire in adaptation A. Andreeva and questionnaire for child depression M. Kovacs, 1992.

**Results:** A high level of personal anxiety was detected in 44 adolescents (23,3%) and situational in 76 (40,2%) adolescents. In 48 (25,4%) adolescents there were signs of depression, in 11 (5,8%) - severe depression. The level of depression in girls was significantly higher compared to boys (95% CI, 2,6-8,8) ($p<0,0004$), which was manifested in the form of aggressive behavior (95% CI, 3,3-9,4) ($p<0,0001$) and anhedonia (95% CI, 1,7-7,0) ($p<0,001$). Signs of depression more often were appeared in adolescents who had an incomplete family (95% CI, 0,7-8,5) ($p<0,02$) and manifested in the form of aggressive behavior (95% CI, 0,6 ($p<0,02$), anhedonia (95% CI, 0,7-7,3) ($p<0,01$) and negative self-esteem with the presence of suicidal thoughts (95% CI, 0,3-7,5) ($p<0,03$).

**Conclusions:** Mood disorders are quite common among adolescents and require timely detection and correction in order to improve their social adaptation and prevent suicidal behavior. The main factors of mood disorders in adolescents can be an incomplete family and a female.

**KEY WORDS:** anxiety, depression, adolescents, mood, diagnosis

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## INTRODUCTION

According to WHO statistics, depression is one of the most common forms of mental illness today [1]. Child and adolescent depression has become one of the most popular themes of psychological research in the last 4 decades. First of all, this is due to the fact that more children and adolescents begin to suffer from depressive manifestations along with adults [2].

Depressive disorders are especially dangerous in the teenage period, when the subtle structures of the child's personality are unprotected to the destructive power of depression, which can have negative consequences in the form of asocial behavioral manifestations, the formation of unwanted character traits, deep internal conflicts, problems in communication, studying, personal self-determination and self-realization etc. [1].

Depressive disorders in adolescence can lead to the formation of bad habits (alcoholism, smoking) and even to encourage the use of narcotic substances. The development of depression at this age has a rather high risk of developing other mental disorders in adulthood [3, 4]. However, the most dangerous consequence of depression is a suicide. Suicide is one of the main causes of death among young people associated with depression, more than half of which occurs in the puberty period [5].

Suicidal behavior of adolescents, who has recently been increasingly threatening is most often due to internal-family circumstances, relationships with peers in school [6]. Suicide is the second leading cause of death in adolescents in Europe, so suicide prevention in these countries is a key public health goal [7].

Cluster analysis of depression symptoms in the age aspect allowed to establish that in the adolescents aged 15 years and older, anxiety (59,8%), apathy (20,8%) and behavioral (19,4%) variants of depression were formed [8].

Stresses of private life rank first among the factors that affect the mental state of adolescents [9]. Among other key risk factors for depression, women's gender, heredity, other mental and physical disorders as well as obesity should be noted [4, 10].

Anxiety negatively affects not only the emotional state of a person but also further violates the functional capabilities of the psyche, inhibiting its development as a personality and in most cases into pathopsychological disorders [11].

Anxiety disorders are quite common disorders of the psychics in children, which, according to literature, occur in 9% and 32% of children and adolescents [12].

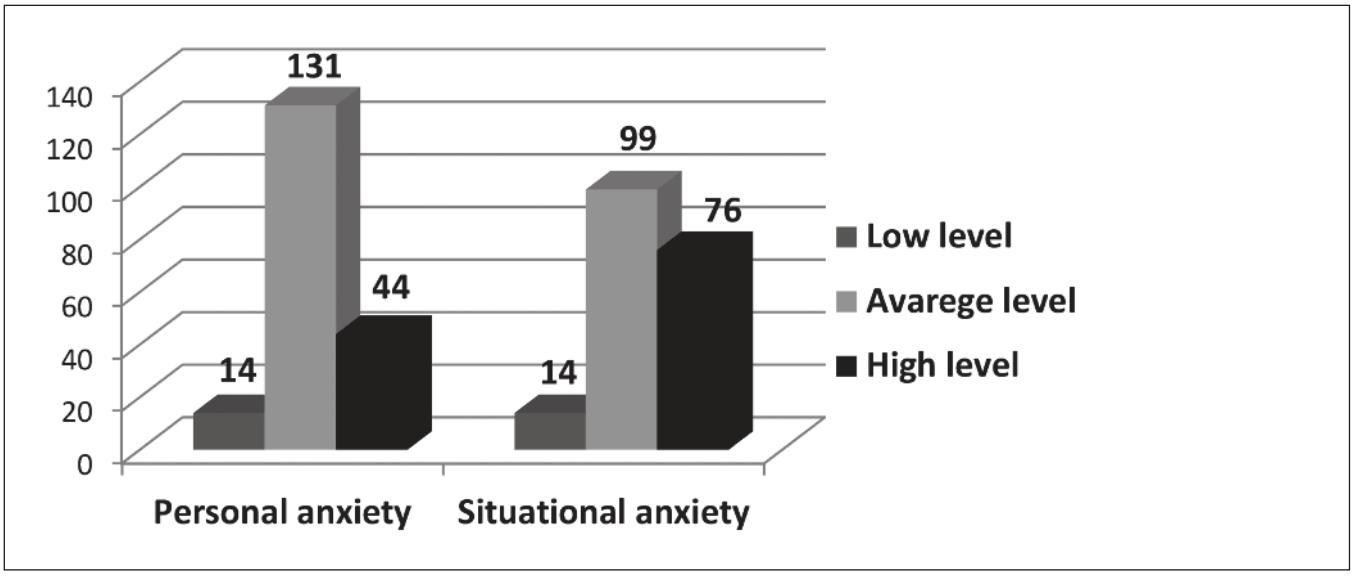


**Fig. 1.** Levels of anxiety in adolescents by the questionnaire of Spielberger's anxiety modified by A. Andreeva.

It should also be noted that anxiety is an independent risk factor for the development of cardiovascular events in adolescents. High body mass index (50,8%), high blood pressure (50,8%) and physical inertia (50,0%) were the most common cardiovascular risk factors [13].

The presence of subclinical depressive symptoms and adolescence as a factor in the future risk of depression, as well as the negative effect of these symptoms on social adaptation indicates the importance of evaluating depressive symptoms in adolescence [14]. The American Academy of Pediatrics Bright Futures recommends an annual check of children and adolescents for emotional and behavioral abnormalities [4, 10].

Therefore, the mental health of adolescents requires careful monitoring and research that will help respond in a timely manner, detect and prevent and if necessary treat and detect emotional disorders that have an important social significance.

## THE AIM

To investigate the screening of anxiety and depressive disorders and their manifestations in adolescent children for the identification of risk factors and the development of measures for their prevention.

## MATERIALS AND METHODS

The study was attended by 189 students aged 16-17 years of the educational institutions of the Khmelnytskyi region. The study used Spielberger Test Questionnaire (STPI), modified by A. Andreeva (1988) and the Children's Depression Inventory, M. Kovacs, 1992.

The Spielberger test questionnaire was modified by A. Andreeva, which reveals the level of cognitive activity, anxiety and anger as an existing condition and as a personality trait. The scale consists of two parts. The minimum score for each scale is 10 points, the maximum is 40 points [15].

The Children's Depression Inventory was developed by Maria Kovacs (1992) and adapted by the staff of the Clinical Psychology and Psychiatry Laboratory. The method is intended for the study of children and adolescents 6-17 years and allows to appreciate the affective and cognitive symptoms of depression, somatic complaints, social problems and behavioral problems. The overall normal index for CDI can vary from 0 to 54, 50 is a critical value, after which the depth of symptoms increases [16]. The results were processed using Student's criterion to construct a 95% confidence interval (CI) for the difference in mean.

## RESULTS AND DISCUSSION

Our screening research on the presence of anxiety in adolescents both in general and in individual groups showed the presence of anxiety symptoms in children and its dependence on individual factors.

In general, according to the questionnaire of anxiety, in the study of the whole quantity of adolescents (n=189), the personal anxiety was 23,1±3,8 points and situational (reactive) anxiety was 22,4±3,5 points which is its average level. Such data testify to the need for a more detailed examination of this category of adolescents in school establishments to investigate and identify the main causes of its occurrence, as there are significant risks for the development of such anxiety disorders in the future such as panic disorder, obsessive-compulsive disorder, somatoform disorder, and others which has an important social significance.

We also separately counted the number of adolescents who had a high general score on the anxiety questionnaire indicating a high level of anxiety (Fig. 1).

The presence of elevated anxiety levels in a significant percentage of adolescents is associated with the study of E.A. Mikhailova et al. (2015), which revealed a significant increase in the alarming version of depression as the child

**Table I.** Indicators of anxiety of adolescents in normal life and during the studying

| | | Spielberger Questionnaire Modified by A. Andreeva (M ± σ) | | | | | |
|---|---|---|---|---|---|---|---|
| | n | Anxiety | | Cognitive Activity | | Negative emotional experiences | |
| | | Usual | Reactive | Usual | Reactive | Usual | Reactive |
| City | 82 | 23,0±3,5 | 21,8±3,1 | 25,7±3,6 | 24,9±3,3 | 23,3±5,0 | 17,7±5,0 |
| Village | 107 | 23,1±4,0 | 22,9±3,9 | 25,7±4,0 | 25,2±3,6 | 22,9±4,7 | 17,9±4,7 |
| p | | >0,05 | **<0,05** | >0,05 | >0,05 | >0,05 | >0,05 |
| Girls | 53 | 23,9±4,5 | 21,5±3,6 | 25,0±3,6 | 24,9±3,9 | 23,1±4,9 | 18,2±4,9 |
| Boys | 136 | 23,1±3,5 | 22,8±3,3 | 26,0±3,9 | 25,0±3,6 | 23,1±4,9 | 17,6±4,8 |
| p | | >0,05 | **<0,05** | >0,05 | >0,05 | >0,05 | >0,05 |
| Smoking | 47 | 23,1±3,3 | 22,2±3,1 | 25,7±3,5 | 24,7±2,3 | 23,9±4,9 | 18,1±4,8 |
| Non-smoking | 142 | 23,2±4,1 | 22,5±3,5 | 25,8±3,9 | 25,2±3,7 | 22,2±4,8 | 17,9±4,7 |
| p | | >0,05 | >0,05 | >0,05 | >0,05 | **<0,05** | >0,05 |
| Incomplete family | 31 | 22,7±4,2 | 21,6±3,3 | 26,0±4,3 | 24,9±3,1 | 26,2±4,2 | 17,7±4,4 |
| Complete family | 158 | 23,3±3,8 | 23,1±3,2 | 25,7±3,7 | 25,2±3,5 | 22,7±4,9 | 17,6±5,1 |
| p | | >0,05 | **<0,01** | >0,05 | >0,05 | **<0,0001** | >0,05 |
| Successful in studying | 59 | 23,2±4,4 | 22,4±3,4 | 26,7±2,8 | 25,1±3,8 | 24,3±5,3 | 17,9±5,2 |
| Unsuccessful in studying | 130 | 23,1±3,4 | 22,4±3,5 | 25,4±3,9 | 24,8±3,5 | 22,6±4,5 | 17,8±4,4 |
| p | | >0,05 | >0,05 | **<0,02** | >0,05 | **<0,02** | >0,05 |

grows, which is most pronounced in children older than 15 years and constitutes a significant percentage (59,8%) compared with non-alarming manifestations of depression [8].

A high level of personal anxiety was detected in 44 people (23,3%) and situational anxiety in 76 (40,2%) persons, which are quite high indicators for this category of children because they are a risk group for the development of emotional disorders and comorbid them depression The average level of personal anxiety was found in 131 (69,3%) and the average level of situational anxiety was in 99 (52,4%) persons, which constituted the vast majority of adolescents. And only in a small number of adolescents the level of both personal and reactive anxiety was low and accounted for 14 (7,4%) persons respectively.

Also the level of anxiety in adolescents was determined depending on sex, place of residence, fullness of the family, the presence of bad habits and the success of the school (Table I).

Thus, the level of situational anxiety was higher in rural adolescents (95% CI, 0,1-2,2) ($p<0.05$), which can be due to a lower level of education and adaptability than adolescents, who studied and lived in the city. The level of situational anxiety was also higher in boys than in girls (95% CI, 0,1-2,3) ($p<0,05$), that can be due to less successful and boys' activity in learning and, accordingly increasing anxiety in the process of studying the material and its control. It was found that the level of situational anxiety was clearly higher in adolescents who lived in a full family compared with adolescents living in an incomplete family (95% CI, 0,3-2,7) ($p<0,01$) In adolescents who lived in an incomplete family according to different circumstances they did not have a father in 19 (61,3%) and mother - in 12 (38,7%) adolescents. A higher level of situational anxiety in adolescents with full-family can be attributed to the greater responsibility and concentration of these adolescents over studying outcomes and possibly greater control by parents over the learning process. In adolescents with incomplete families have probably less attention due to life circumstances and less control over their personal life and education, which respectively, causes less anxiety.

Personality negative emotional experiences in general also had an average level of severity. However, they were clearly higher in children who smoked compared to adolescents who did not have this harmful habit (95% CI, 0,1-3,3) ($p<0,05$). Expressed personality anxiety is likely to induce adolescents to develop harmful habits as a means of possibly influencing anxiety.

The personal negative emotional experiences were quite pronounced and high in children living in an incomplete family compared with adolescents living in complete families, and overall had an average negative emotional experience (95% CI, 1,6-5,3) ($p<0,0002$). Thus it can be noted that the absence of one of the parents under different circumstances can lead to the formation of expressed negative emotional experiences that can affect the success of studying, social adaptation of the child in society, the emergence of bad habits, lead to the development of anxiety and depressive reactions. Such adolescents need special attention from the side of society as risk groups for the development of deviant behavior, the propensity to abuse drugs and the development of depressive reactions with their consequences in the form of suicide.

It should be noted that personal negative emotional experiences were clearly higher in adolescents who were

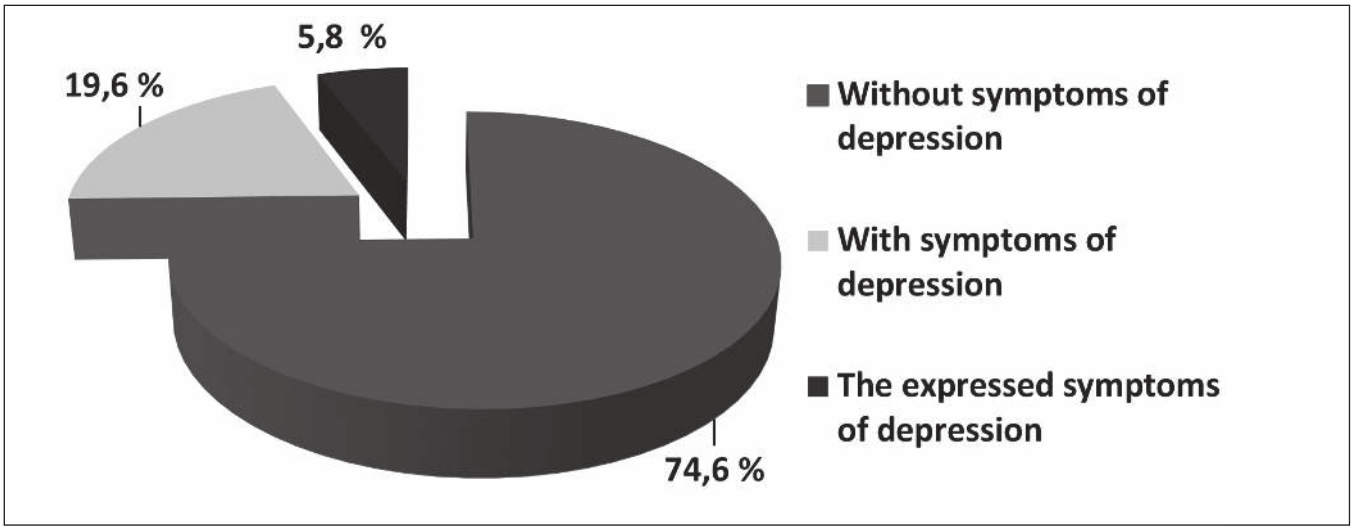


**Fig. 2.** Depressive symptoms were identified in adolescents according to the questionnaire for childhood depression (Maria Kovacs, 1992).

successful in the study (95% CI, 0,2–3,2) (p<0,02). Possibly, personal attitude to studying, more preoccupancy and mental stress and increased responsibility of such adolescents can be a reason for their negative emotional experiences. Such adolescents need have a look at the day's regime with more time for rest and reduction of mental load. At the same time the situational negative emotional experiences in these children had an average level of severity and did not differ from other groups of adolescents.

Pre-clinical manifestations of depression can accompany a child or adolescent for months and sometimes for years, causing devastating effects on intercourse with peers, studying and other life spheres. Therefore, high rates of repression even at the clinical level deserve close attention. The CDI method, developed by M. Kovach, is most commonly used worldwide for the diagnosis of repression in children and adolescents who are not diagnosed with depression (actually aimed at studying subclinical manifestations of depression) [2].

Our screening study on the presence of depressive symptoms in adolescents both in general and in individual groups showed the presence of depressive symptoms in adolescents and its dependence on individual factors.

In general in the study of the entire number of children (n=189) the total score on the CDI questionnaire was 50,5±10,1, which according to the interpretation of the questionnaire is a critical level in which it is possible to diagnose minimal depressive disorders and after which the depth of symptoms significantly is growing.

We also separately counted the number of adolescents, where the total score in the questionnaire exceeded the upper limit of the average of 55 points, their number was 48 (25,4%) persons (Figure 2).

Namely in 25,4% of all adolescents we examined showed clear signs of depression. In the general structure of adolescents signs of severe depression were found in 11 (5,8%) persons whose data significantly exceeded the average, that is, 70 and above points (maximum 84), which is quite substantial and requires appropriate attention, since they are precisely those the greatest risk of developing suicidal behavior.

Thus, the level of depressive symptoms practically did not differ among adolescents in rural areas from adolescents living in the city (Table II).

The overall level of depressive symptoms in girls was significantly higher in comparison with boys (95% CI, 2,6-8,8) (p<0,0004) and exceeded the critical level of indicators for the diagnosis of depression. According to the data of the subscale A, which characterizes the decrease in mood, in general, the girls tended to decrease while in boys it did not exceed the critical value and in general was within the norm (95% CI, 0,3-7,4 ) (p<0,03). In general the highest rate was observed in girls under the subclass B (59,4±11,4) compared to boys, clearly exceeding the critical values that can characterize the manifestations of depression in them, mainly in the area of interpersonal problems, negativism and aggressive behavior (95% CI; 3,3-9,4) (p<0,0001). In the subscales C, which characterizes the level of insecurity and inefficiency in the learning process, girls also showed a significant prevalence over the indicators in boys, who in general were within the normal range (95% CI, 3,9-9,6) (p<0,0001), that can indicate a significant influence of depressive symptoms on the effectiveness of teaching and relation with teachers and peers as shown in Table. 2

It should be noted that girls have a predominance of indicators on the subchapter D, which reached a critical level and indicated the presence of anhedonia (95% CI, 1,7-7,0) (p<0,001). Anemia is one of the key symptoms of depression and is characterized by a decrease or loss of satisfaction and therefore it is important in terms of detecting it from adolescents as a possible sign of depression in them.

A significant predominance of depressive disorders in girls over boys was also found in other studies that determined the female sex as a risk factor for the development of depression [7, 17].

Quite interesting were the data when analyzing the

**Table II.** Indicators of symptoms of depression in adolescents

| Child Depression Questionnaire (Maria Kovacs, 1992) (M ± σ) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **n** | **A** | **B** | **C** | **D** | **E** | **General** |
| City | 82 | 50,7±11,6 | 54,8±9,23 | 48,5±7,9 | 50,1±9,4 | 49,4±9,8 | 50,9±10,4 |
| Village | 107 | 50,2±10,9 | 55,2±10,4 | 49,9±10,3 | 47,5±6,7 | 49,0±9,2 | 50,4±9,8 |
| p | | >0,05 | >0,05 | >0,05 | **<0,03** | >0,05 | >0,05 |
| Girls | 53 | 53,1±12,7 | 59,4±11,4 | 54,3±11,8 | 52,5±8,5 | 50,0±9,3 | 54,5±11,0 |
| Boys | 136 | 49,3±10,4 | 53,1±8,7 | 47,6±7,4 | 48,1±8,2 | 48,6±9,3 | 48,8±9,1 |
| p | | **<0,03** | **<0,0001** | **<0,0001** | **<0,001** | >0,05 | **<0,0004** |
| Smoking | 47 | 47,2±8,0 | 53,2±8,5 | 46,8±6,5 | 47,7±8,4 | 47,9±7,9 | 47,8±7,5 |
| Non-smoking | 142 | 51,7±11,8 | 55,1±10,3 | 50,2±9,9 | 50,3±8,7 | 49,7±9,8 | 51,7±10,6 |
| p | | **<0,01** | >0,05 | **<0,03** | >0,05 | >0,05 | **<0,02** |
| Incomplete family | 31 | 52,2±10,4 | 58,3±13,7 | 53,0±12,1 | 52,9±9,4 | 52,5±10,5 | 54,5±10,8 |
| Complete family | 158 | 49,8±10,9 | 53,8±8,8 | 48,7±8,6 | 48,8±8,4 | 48,5±9,0 | 49,9±9,7 |
| p | | >0,05 | **<0,02** | **<0,02** | **<0,01** | **<0,03** | **<0,02** |
| Successful in studying | 59 | 52,8±12,3 | 55,5±12,0 | 50,3±9,2 | 52,2±8,5 | 50,1±9,3 | 52,6±10,7 |
| Unsuccessful in studying | 130 | 48,7±10,2 | 53,4±8,9 | 48,6±8,5 | 48,0±8,1 | 49,0±9,5 | 49,0±9,2 |
| p | | **<0,01** | >0,05 | >0,05 | **<0,001** | >0,05 | **<0,02** |

scales of adolescents who have harmful habits, including smoking tobacco. In general signs of depressive symptoms were not observed in adolescents who smoked (47,8±7,5 points), compared to those who did not smoke (95% CI, 0,5-1,7) (p<0,02) , whose indicators though were within the norm, however, reached critical values (51,7±10,6 points). Adolescents who do not smoke had a greater pronounced decrease in mood on the subchapter A compared with those who smoked (95% CI, 0,8-1,8) (p<0,01) and the level of uncertainty and inefficiency in the training of the underclass C (95% CI, 0,3-6,4) (p<0,03). However, according to preliminary data, teenagers who smoke are more likely to be more anxious than non-smokers (95% CI, 0,1-3,3) (p<0,05), which is likely to induce adolescents to the emergence of bad habits, as a means of possible effects on increased anxiety and possibly depression as a comorbid anxiety pathology.

In the study of adolescent depression a large number of internal correlations and external connections with anxieties in adolescents deprived of parental care have been identified [9].

Property divisions, social inequality, poverty and unemployment, marginalization and political alienation of the general population, the disintegration of family and group ties - these are the underlying preconditions for the formation of inadequate family relationships, provoking lack of attention to the adolescent, intense family atmosphere, deviant behavior of parents, etc.. These factors violate the social adaptation of adolescents and become the basis of suicidal behavior [6].

According to A. Consoli et al. (2013), 16,2% of adolescents who had depression reported suicidal thoughts over the past 12 months and 8,2% reported suicide attempts. The key factors that were associated with these conditions in adolescents were family factors and intra-family relationships [7].

In our observation according to the questionnaire there were signs of depression in adolescents who for various reasons had an incomplete family or orphanhood. The general meanings of depressive symptoms in such adolescents were significantly higher and the critical values over which depression was determined than in peers who lived in complete families (95% CI, 0,7-8,5) (p<0,02). In such adolescents there were manifestations of interpersonal problems, negativism, and aggressive behavior under the subscales B (95% CI, 0,6–8,2) (p<0,02) increased level of uncertainty and inefficiency in the process of training under the C (95% CI, 0,6-7,8) (p<0,02), the presence of anhedonia with the subscales D (95% CI, 0,7-7,3) (p <0,01). In adolescents living in a full family the relevant data on these subscales did not reach the critical level of such violations and were practically within the normal limits. It should be noted that it was precisely in adolescents from single-parent families that for the first time the critical level reached the value under the subscales E, which characterizes the presence of negative self-esteem and possible suicidal thoughts (95% CI, 0,3-7,5) (p<0,03).

Thus, the problem of an incomplete family has a very important social significance and requires a comprehensive study of social impact and education among the adult population as a pledge of prevention and prevention of the possible development of mental disorders in adolescents and their consequences, the formation of such children in society, the formation of stereotypes of behavior in adult life and their relation to family values.

The general level of the questionnaire's indices in adolescents with sufficient educational success was higher than that of adolescents who had low educational success (95%

CI, 0,5-6,5) (p<0,02). A similar tendency was observed in the subscales. Thus, for the subscales A, which characterizes the decrease in mood, in general, adolescents who had sufficient success in study there was a tendency to decrease it (95% CI, 0.7 - 7.5) (p <0.01).

It should also be noted that the prevalence of adolescents who were successful in studying, subscales D reached a critical level, indicating the possible presence of anhedonia (95% CI, 1,6-6,7) (p<0,001). According to other subscales there was no significant difference in the indicators. The obtained data is in agreement with the data in the study of anxiety in this group of adolescents.

It is possible that such emotional disturbances can arise on the basis of the characteristics of these teenagers and their upbringing, which forms a special attitude to studying, increased responsibility, integrity and diligence, which requires a separate study. It is also possible that such emotional disturbances can be generated as a result of excessive mental and emotional overload.

## CONCLUSIONS

In general among all the studied adolescents there was an average level of personal (23,1±3,8 points) and situational (22,4±3,5 points) anxiety. A high level of personal anxiety was found in 44 (23,3%), and situational anxiety in 76 (40,2%) adolescents, indicating the widespread anxiety among this category of children who need special attention and should be a risk group for the development of emotional violations and comorbid depression.

Personality negative emotional experiences were more pronounced in adolescents who smoke (95% CI, 0,1-3,3) (p<0,05) and were living in an incomplete family (95% CI, 1,6-5,3) (p<0,0002). Consequently, the presence of a incomplete family as well as other social factors is likely to violate the social adaptation of adolescents and become grounds for the development of anxiety and bad habits.

In the 48 (25,4%) among all studied adolescents there were clear signs of depression, of where 11 (5,8%) outlined signs of severe depression, indicating its widespread prevalence among this number of adolescents. Such adolescents need timely detection and special attention, as they should form a risk group for the development of suicidal behavior and other mental disorders, need timely help.

The overall level of depressive symptoms in girls was significantly higher in comparison with boys (95% CI, 2,6-8,8) (p<0,0004), which can indicate a female gender as one of the key risk factors for developing depression in adolescents. Depressive symptoms in girls were mainly manifested in the form of interpersonal problems, negativism, aggressive behavior (95% CI, 3,3-9,4) (p<0,0001) and anhedonia (95% CI, 1,7-7,0) (p<0.001).

Signs of depressive disorders were observed in adolescents who for various reasons had an incomplete family (95% CI, 0,7-8,5) (p<0,02). In such adolescents depressive disorders manifested in the form of interpersonal problems, negativism, aggressive behavior (95% CI, 0,6-2,8) (p<0,02), as well as anhedonia (95% CI, 0,7-7,3) (p<0,01) and negative self-esteem with the presence of suicidal thoughts (95% CI, 0,3-7,5) (p<0,03), which in any case was not observed in other subgroups of adolescents. Consequently, as in anxiety situations the presence of an incomplete family is one of the key factors in the development of depression and possible suicidal behavior in adolescents.

Given the high incidence of anxiety and depressive disorders in adolescents, their impact on social adaptation and behavior, periodic compulsory testing of children using simple questionnaires for the presence of emotional disorders should be introduced in order to detect and correct their correction in a timely manner, especially in children with existing factors risk (female sex, incomplete family), which will prevent further severe mental disorders, promote social adaptation and quality of life of the child.

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**Authors' contributions:**
*According to the order of the Authorship.*

**ORCID numbers:**
*Larysa V. Pypa - 0000-0002-4448-5308*
*Yulia N. Lysytsia - 0000-0003-0248-0338*
*Ruslan V. Svistilnik - 0000-0002-9378-7388*
*Maryna M. Murhina - 0000-0002-6324-8826*

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## CORRESPONDING AUTHOR
**Ruslan Svistilnik**
Department of Neurology and Neurosurgery,
Faculty of Postgraduate Education,
National Pyrogov Memorial Medical University
Vodoprovodnaya st, 8/1, 29001, Khmelnytskyi, Ukraine
e-mail: rus80ua@gmail.com

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# ANALYSIS OF SOCIAL AND MEDICAL PORTRAIT OF CHILDREN WITH PERTUSSIS, MENINGOCOCCAL INFECTIOUS, SCARLET FEVER AND ESTIMATION OF THEIR ASSIGNED PHARMACOTHERAPY

**Oryna Detsyk, Iryna Fedyak, Iryna Bilyk**
IVANO-FRANKIVSK NATIONAL MEDICAL UNIVERSITY, IVANO-FRANKIVSK, UKRAINE

## ABSTRACT

**Introduction:** The level of childhood bacterial diseases incidence does not have a downward trend.

**The aim:** Conduction of a sociological analysis of medical cards for children with pertussis, meningococcal infection (MI), scarlet fever, and evaluation of consumed pharmacotherapy according to real clinical practice in Ukraine.

**Materials and methods:** 1215 medical cards of inpatients; methods: sociological – document analysis, retrospective frequency.

**Results:** Among the cards of children with pertussis: 50.2% – female, 49.8%– male; by age children up to 1 year (49.3%) were prevailed. In 79.6% incidence – medium-hard form pertussis, 42.2% with complications. Among patients with MI by sex there were: 50.5 % – boys and 49.5% – girls; by age – children aged 1-4 (40.2%); the structure of generalized forms of MI: 40.2% – meningococcemia, 11.4% – meningitis, 48.4% – combination. Scarlet fever was more frequently: boys (56.4%), children aged 5-9 (44.7%), urban residents (79.7%); it was 93.4% of a medium-hard form. Most of medicines were prescribed to children with MI – 15.8 trade names per 1 person, it was prescribed 191 INN, most often – Sodium chloride (90.0%), Ascorbic acid (68.5%), Ceftriaxone (65.8%); patients with pertussis – 11.2, 196 INN (Chlorpromazine (69.1%), Dexamethasone (53.2%), Butamirate (51.8%)); scarlet fever – 9.3 medicines, 114 INN (local action Comb drug for throat diseases treatment (94.4%), Ceftriaxone (48.7%), Metamizole sodium (38.1%)).

**Conclusions:** Frequency analysis data of consumed pharmacotherapy in real pediatric practice in Ukraine shows the need for its further optimization in accordance with the principles of evidence-based medicine, the results of research on the socio-demographic characteristics of patients, forms and complications of course of the basic disease.

**KEY WORDS:** retrospective analysis, pertussis, meningococcal infection, scarlet fever, children

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## INTRODUCTION

The most widespread children bacterial infections (CBI) are pertussis, meningococcal infectious (MI), scarlet fever [1-4]. During the past ten years, there has been a significant increase in the pertussis incidence among children. Pertussis is a sharp infectious vaccine-controlled disease with airborne transmission mechanism. Its leading clinical symptom is protracted spasmodic cough [5-7]. Both in Ukraine and abroad, high incidence is registered among children of the first year of life, especially in infants who have not yet been vaccinated. At the same time young children have the highest risk of severe disease and complications. According to statistic data in Europe and North America, the prevalence of pertussis among high school children and adults is noted. The probability of getting sick after contact with a patient is very high – 90 % [8-13].

Unlike pertussis the MI belongs to uncontrolled infections and can cause both sporadic cases of the disease and epidemic outbreaks. This is an acute anthroponistic disease of the respiratory tract infections caused by meningococcus (Neisseria meningitidis) and is characterized by clinical polymorphism in the form of nasopharyngitis, purulent meningitis and sepsis [14-17]. In European region countries the mortality of MI is 9-12 %, in Ukraine the mortality rate varies from 14 to 17 %. It is generally accepted that the categories with the highest risk of MI development are newborns and children of the first year of life (since natural immunity against N. meningitidis is especially low), adolescents (due to their habits and behavior that promote interpersonal communication), travelers who have been staying for a long time in endemic regions. The susceptibility to MI is generally, the index of contagiousness is 10-15 % [18-23].

One of the known infectious children diseases with streptococcal etiology is scarlet fever. This is an acute anthropogenic infectious disease caused by β-hemolytic streptococcus group A and characterized by symptoms of general intoxication, sore throat and skin rash, susceptibility to septic and allergic complications. The main way of infectious transmission is airborne. It is possible contact way of infection through toys, things as well as through food. The lowest incidence rate is recorded in children of the first year of life (especially up to 6 months), in the blood of which antibodies that have been spread through the placenta are circulated. Contagiousness index of scarlet fever is 40 % [24-28].

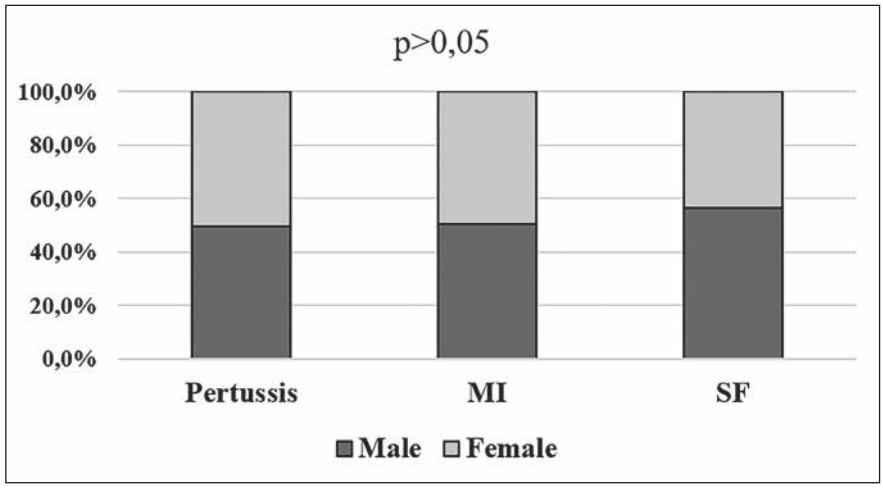


**Fig.1.** Gender distribution of children with bacterial infections

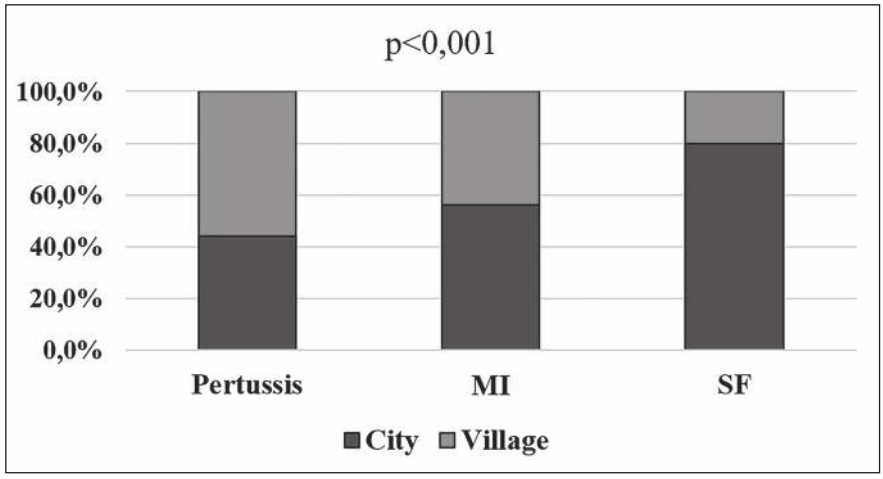


**Fig. 2.** Distribution of children suffering from children bacterial diseases by area of residence

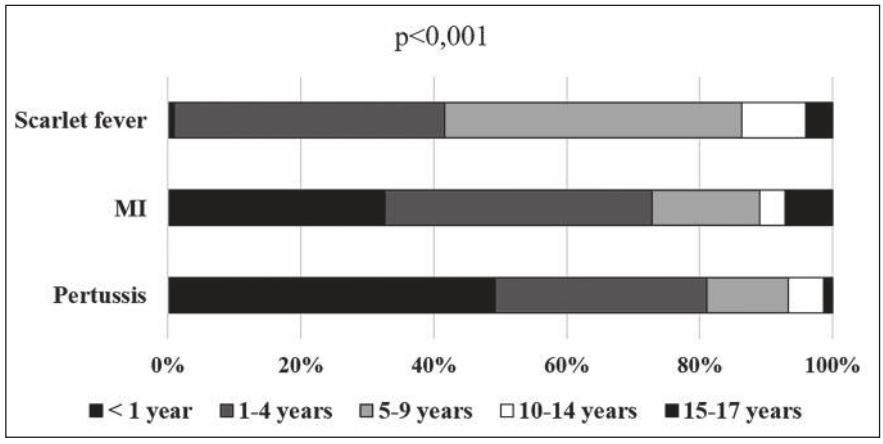


**Fig. 3.** Distribution of children suffering from children bacterial diseases by age

Since infectious diseases remain one of the main causes of worldwide children mortality, the study of the socio-demographic characteristics of children suffering from pertussis, MI, scarlet fever is relevant for optimizing the provision of effective medical and pharmaceutical aid.

## THE AIM

Conduction of a retrospective analysis of gender, age, social characteristics of children with pertussis, MI, scarlet fever at the age of 0-17; forms of diseases, complications, causes of patients discharge from hospitals; as well as the evaluation of drugs prescribed by doctors by frequency analysis based on real clinical practice in Ukraine.

## MATERIALS AND METHODS

The sample collection consisted of 1 215 medical cards of the form № 003/o stationary patients with pertussis (A 37), meningococcal infection (A 39), scarlet fever

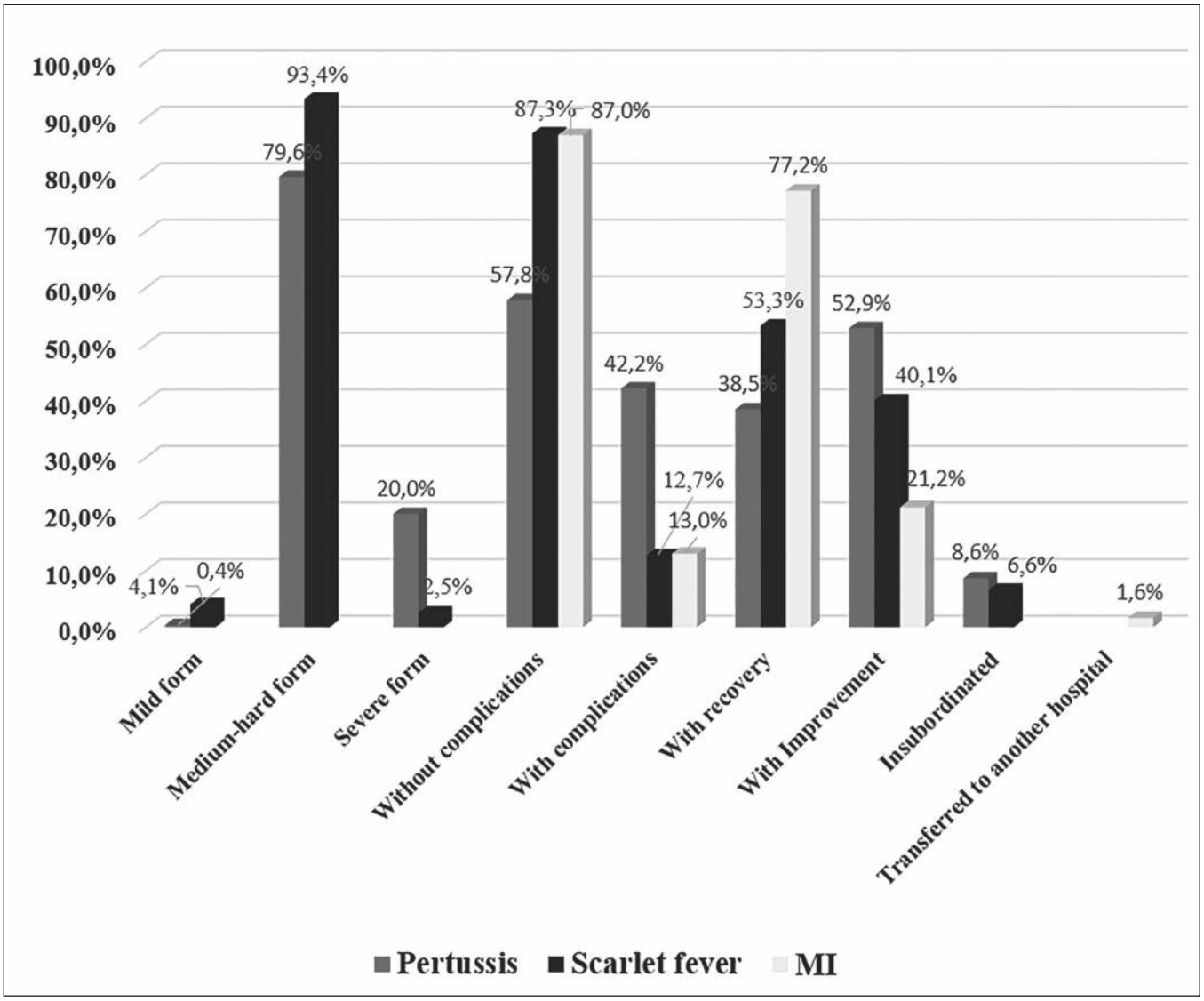


**Fig.4.** Distribution of medical cards of children with bacterial infections by criteria of severity, presence of complications, reason of discharge from hospital

(A 38) during 2009 – 2016, which were obtained by random selection from the archives of the 6 regional clinical children's infectious hospitals in Vinnytsia, Ivano-Frankivsk, Kiev, Odessa, Ternopil and Kharkiv oblast. To work with archival materials with the preservation of the confidentiality of personal data of children were obtained permits of the chief doctors of each health care institution. It was used the sociological method of documents analysis (medical cards): formalized (quantitative) and content analysis (qualitative and quantitative method, which allowed quantification of medical cards by categories with subsequent interpretation of data). In addition, to determine the appropriateness of pharmacotherapy prescribed for patients to clinical protocols, the frequency method of clinical and economic research was used, which consisted in ranking of the medicines consumed by them by the frequency of use – in the whole set of appointments and among the names of medicines by international non-proprietary names (INN).

## RESULTS

Among 1 215 analyzed medical cards, there were 834 children with pertussis disease history, 184 – MI (generalized forms of meningococcemia, meningitis or their combination), 197 – scarlet fever. On average, children with pertussis were treated in hospital for 15±7 bed-days, for MI – 14±7 bed-days, for scarlet fever – 11±5 bed-days. According to the medical cards, demographic characteristics of sick children were studied, first of all – gender and place of residence (Fig. 1, 2).

The distribution of patients by gender (Fig. 1) showed that there were more boys with MI and scarlet fever than girls ($p > 0.05$). The distribution by the area of residence (Fig. 2) showed that the children with scarlet fever (79.7 %) and MI (56 %) lived in cities and children with pertussis – in villages (55.8 %) ($p < 0.001$).

By the age children with pertussis were prevailed in two categories – up to 1 year (49.3%) and from 1 to 4 years (31.8 %). The most often MI was found in children at the

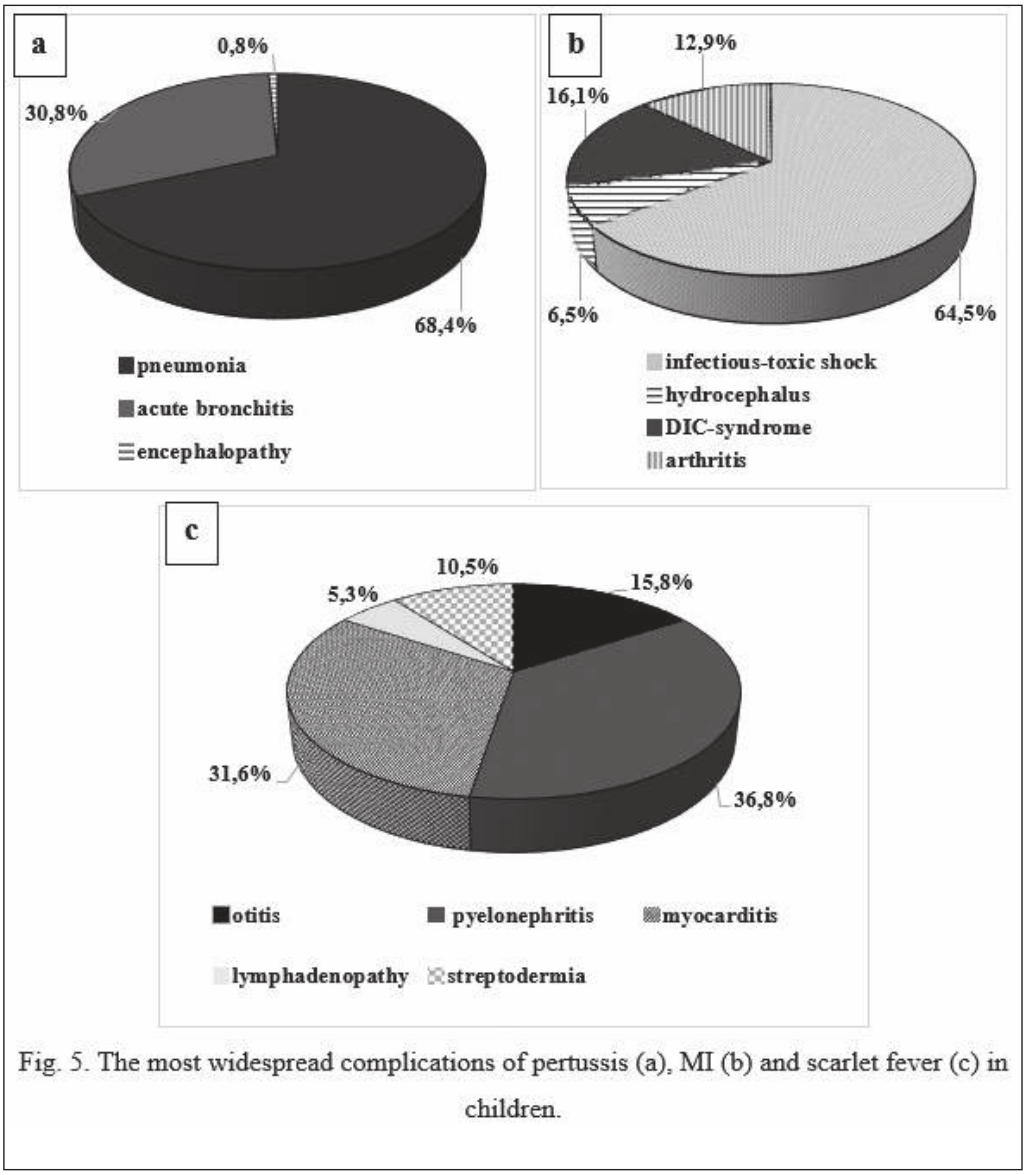


Fig. 5. The most widespread complications of pertussis (a), MI (b) and scarlet fever (c) in children.

**Fig. 5.** The most widespread complications of pertussis (a), MI (b) and scarlet fever (c) in children

age of 1-4 (40.2 % of the sample). Among children with scarlet fever, patients aged 5-9 (44.7 %) and 1-4 (40.6 %) were prevailed. Thus, according to the research girls up to 1 year, which mostly were residents of villages got sick by pertussis more often. MI was prevailed in boys aged 1-4 years, and scarlet fever aged 5-9 years, both mostly city residents ($p < 0.001$) (Fig. 3).

By the severity criteria both pertussis and scarlet fever in contrast to the MI are divided into mild, medium-hard and severe forms (Fig. 4). The analysis showed that most of patients were with pertussis (79.6 %) and scarlet fever (93.4 %) of a medium-hard form. In the structure of meningococcal infection among generalized forms 40.2 % had meningococcal disease, 11.4 % – meningitis, and 48.4 % – their combination.

It was found that MI (87 %) and scarlet fever (87.3 %) were undergone without complications, 42.2 % of pertussis was complicated. 77 % of patients with MI were discharged with recovery and 3 persons were transferred to another hospital. 52.8 % of patients with pertussis and 40.1 % with scarlet fever left the hospital with an improvement. Unfortunately, 8.6% of children with pertussis and 6.6 % of children with scarlet fever did not continue their treatment in a hospital (Fig. 4).

Among the most widespread pertussis complications there were pneumonia (68.4 %), acute bronchitis (30.8 %). 10.8% of MI cases were complicated by an infectious-toxic shock, which made 64.5 % of the total complications, and 2.7 % – DIC-syndrome (16.1 %). The most widespread complications of scarlet fever were pyelonephritis (36.8 %), myocarditis (31.6 %), otitis (15.8 %) (Fig. 5).

According to the concomitant diseases rating which were discharged in medical cards of children with bacterial infections, the most common for three nosologies was such comorbidities as anemia (Table I).

The next stage of the research was to conduct a retrospective clinical and economic analysis of intended pharmacotherapy for children with pertussis, MI and scarlet

**Table I.** TOP-10 concomitant diseases that accompanied the diagnosis of pertussis, MI, scarlet fever in children aged 0-17 years

| | Pertussis | MI | SF |
|---|---|---|---|
| 1. | Anemia | Anemia | Anemia |
| 2. | Foramen ovale (heart) | Pneumonia | Urinary tract infection |
| 3. | Diseases of the digestive system | Herpesviral infections | Adenoiditis |
| 4. | Thymomegaly | Angiopathy of eye retina | Biliary dyskinesia |
| 5. | Ascariasis | Gastroenteric fermentopathy | Ascariasis |
| 6. | Pinworm infection | - | Pinworm infection |

**Table II.** TOP-10 drugs (INN) by the frequency of appointments

| Pertussis | | | MI | | | Scarlet fever | | |
|---|---|---|---|---|---|---|---|---|
| INN | % patients that have taken drugs | % in total summation of appointments | INN | % patients that have taken drugs | % in total summation of appointments | INN | % patients that have taken drugs | % in total summation of appointments |
| Chlorpromazine | 69.1 | 6.2 | Sodium chloride | 90.0 | 5.5 | Comb drug | 94.4 | 10.2 |
| Dexamethasone | 53.2 | 4.8 | Ascorbic acid | 68.5 | 4.3 | Ceftriaxone | 48.7 | 5.3 |
| Butamirate | 51.8 | 4.6 | Ceftriaxone | 65.8 | 4.2 | Metamizole sodium | 38.1 | 4.1 |
| Drotaverine | 49.9 | 4.5 | Lactic acid producing organisms | 62.0 | 3.9 | Loratadine | 35.0 | 3.8 |
| Ceftriaxone | 49.5 | 4.4 | Electrolytes in combination with other drugs | 61.4 | 3.9 | Glucose | 32.5 | 3.5 |
| Procaine | 45.8 | 4.1 | Furosemide | 60.9 | 3.9 | Ibuprofen Lactic acid producing organisms | 30.5 | 3.3 |
| Comb drug | 45.7 | 4.1 | Dexamethasone | 54.4 | 3.4 | Sodium chloride | 29.4 | 3.2 |
| Clemastine | 45.5 | 3.9 | BAS | 46.7 | 3.0 | Ascorbic acid Cocarboxylase | 28.9 | 3.1 |
| Magnesium sulfate | 42.8 | 3.8 | Heparin | 46.2 | 2.9 | Desloratadine | 27.4 | 3.0 |
| BAS | 34.7 | 3.1 | Cocarboxylase | 45.7 | 2.9 | Diphenhydramine BAS | 26.9 | 2.9 |

fever. The results of the frequency analysis show that 9 317 prescriptions of 196 drugs according to international non-proprietary names (INN) were prescribed for children with pertussis, which was 11.2 per patient. Totally, patients with MI were assigned 191 names of drugs by the active substance. The total number of appointments is 2 908, and the number of appointments per patient is 15.8. For children with scarlet fever, 1 824 appointments were prescribed by 114 drugs (INN), for one patient – 9.3. Table II shows the TOP-10 drugs by the frequency of use for the treatment of each studied bacterial infections.

As indicated by the results of the frequency analysis, Ceftriaxone was included in TOP-5 INN antibacterial drugs that were most commonly used. In addition, children with scarlet fever (48.7 %) and MI (65.8 %) were most often taken this drug. In the pharmacotherapy of the pertussis this drug was the fifth (49.5 %). The analysis data indicate that patients with MI received a lot of infusions, and with pertussis – drugs for the cough attacks reduction and prevention (Chlorpromazine). Comparison of the results of real clinical practice with the Ukrainian protocol was evidenced by the absence of an effective formulary approach to the appointments of drugs to patients in Ukraine, since the list of actually consumed drugs is wider than legally recommended. Thus, the order of the Ministry of Health of Ukraine № 354 from 09.07.2004 "On approval of the Protocols for the diagnosis and treatment of children infectious diseases" [29] for the treatment of children suffering from pertussis it is recommended to use antibacterial medicines and aminazine. TOP-10 INN analysis for the treatment of patients with MI showed that according to the protocol for treatment of patients with MI (Ministry of Health of Ukraine Order № 737 from 12.10.2009 "The Protocol for the Treatment of Meningococcemia in Children" [30]), the following INN were prescribed: ceftriaxone, electrolytes in combination with other drugs, furosemide, dexamethasone, heparin. At the same time, the

auxiliary therapy drugs (vitamins, probiotics, and dietary supplements) are not included in the recommendations of the regulatory document. The same applies to regulatory approaches to scarlet fever therapy which also contain no vitamins, probiotics, but also contain local antiseptic agents that accounted a significant proportion of Comb drug in accordance with the protocol requirements [29].

## DISCUSSION

According to the Guidelines for the public health management of pertussis in England (2018) macrolides (azithromycin and clarithromycin) are recommended to treat patients with pertussis. A number of researchers, namely: Marchant JM, Petsky HL, Morris PS, Chang [30], Altunaiji SM, Kukuruzovic RH, Curtis NC, Massie J [32], Cherry JD [11] have experimentally confirmed the advisability of using macrolides for pharmacotherapy of pertussis in children. Simultaneously, the results of real clinical practice analysis in Ukraine revealed the prevalence of cephalosporins, namely Ceftriaxone in the doctors' prescriptions. On the other hand, a qualitative analysis of antibiotic therapy in patients with MI in Ukraine showed the same approach to its practice with evidence-based medicine. Since the use of Ceftriaxone or Cefotaxim is advisable in the treatment of patients with MI according to Zalmanovici Trestioreanu A, Fraser A, Gafter-Gvili A, Paul M, Leibovici L [34] and National Collaborating Center for Women's and Children's Health [15] publications, which show the results of this study. And for the treatment of patients with streptococcal infection, penicillins are drugs of choice, despite the more than 60-year period of their application [35]. Cephalosporins in the treatment of patients with scarlet fever are used while penicillin allergies and macrolides are also second-line drugs [36]. At the same time, the results of the analysis of the practice of prescribing antibiotics to patients with scarlet fever in Ukraine also showed the priority of Ceftriaxone over other antibacterial agents.

Consequently, data of the actual clinical pediatric practice for treatment of children with pertussis, MI, scarlet fever in Ukraine indicate the need for its further optimization both in relation to evidence-based therapy and pharmacoeconomics. The next stage of our research will be conducting of ABC- and VEN-analyzes.

## CONCLUSIONS

The results of the study showed that 50.2 % of children's medical cards belonged to women, 49.8 % to men; by age, children over 1 year were significantly more prevailed (49.3 %); the share of rural residents (55.2 %) was higher than urban (44.2 %). In 79.6% pertussis had a medium-hard form and 42.2 % had complications in the form of pneumonia (68.4 %) or acute bronchitis (30.8 %). The distribution of patients with meningococcal disease also did not reveal any gender differences: 50.5 % were boys and 49.5 % were girls, and there were more urban residents (56.0%); by the age there was predominance of children aged 1-4 years (40.2 %). In the structure of meningococcal infection among generalized forms 40.2 % had meningococcal disease, 11.4 % had meningitis, 48.4 % had a combination of them; 13 % of patients had complications among which the leader was an infectious-toxic shock (64.5 %). Scarlet fever was more widespread in boys (56.4 %) and children aged 5-9 years (44.7 %), among patients a significant prevalence of urban residents was found (79.7 %). This disease was 93.4 % in medium-hard form, among its complications pyelonephritis (36.8 %) and myocarditis (31.6 %) were predominated.

It was found that the largest number of medicines by INN was taken by children with MI – an average of 15.8 trade names of drugs, and in general this set of patients was assigned to 191 INN, among which Sodium chloride as a solvent (90.0 %), Ascorbic acid (68.5 %), Ceftriaxone (65.8 %) were leaders. The second place by the number of consumed drugs was taken by patients with pertussis (11.2, 196 INN), which were most commonly prescribed by Chlorpromazine (69.1%), Dexamethasone (53.2 %), Butamirate (51.8 %). One child with scarlet fever consumed on average 9.3 drugs (114 INN totally), whose ranking was led by the local route Comb drug for the treatment of throat (94.4 %), Ceftriaxone (48.7 %), Metamizole sodium (38.1 %).

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**Authors' contributions:**
*According to the order of the Authorship.*


**ORCID numbers:**
*Oryna Detsyk - 0000-0003-3979-9455*
*Iryna Bilyk - 0000-0002-4048-2820*


**Conflict of interest:**
*The Authors declare no conflict of interest.*


## CORRESPONDING AUTHOR
**Iryna Bilyk**
The Chair of Organization and Economics of Pharmacy and Drug Technology
Ivano-Frankivsk National Medical University
2 Galytska str., Ivano-Frankivsk, 76000, Ukraine
tel: +380987242088
e-mail: bily4ka@ukr.net



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# PREPARATION CONTENT UPDATING OF FUTURE DENTISTS TO PROFESSIONAL INTERACTION

**Borys I. Palamar[1], Volodymyr V. Proshkin[2], Nataliia P. Volkova[3], Oksana O. Rezvan[4], Lidiia P. Tkachenko[5]**
[1] BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE
[2] BORYS GRINCHENKO KYIV UNIVERSITY, KYIV, UKRAINE
[3] ALFRED NOBEL UNIVERSITY, DNIPRO, UKRAINE
[4] O.M. BEKETOV NATIONAL UNIVERSITY OF URBAN ECONOMY IN KHARKIV, KHARKIV, UKRAINE
[5] H.S. SKOVORODA KHARKIV NATIONAL PEDAGOGICAL UNIVERSITY, KHARKIV, UKRAINE

## ABSTRACT

**Introduction:** One of the most important indicators of the professional training of future dentists, their competitiveness is the development of professional interaction.

**The aim** of the article is to update the content of the training of future dentists to engage in professional interaction.

**Materials and methods:** The study, completed during 2015-2018, was attended by 292 students of the specialty "Stomatology". The research uses the following methods: theoretical – analysis, synthesis, systematization and synthesis of scientific literature; empirical – testing, survey, monitoring, pedagogical experiment to find out the effectiveness of the developed content of training future dentists; methods of mathematical statistics.

**Results and conclusions:** For realization of the research purpose it was specially developed a discipline "Professional interaction of dentists" which is aimed at the realization of the tasks: the acquisition of future dentists theoretical knowledge on problems of communication and interaction; increasing the need for communication, implementing a variety of interactions; the formation of future dentists readiness for the implementation of professional interaction, positive communicative attitude to team interaction and receiving satisfaction from it. The program results of the study of the indicated discipline are presented, content of its modules is disclosed. Interactive forms which are used in the process of training future dentists (trainings, business games, problem situations, etc.) and teaching methods (dialogue-discussion, polygon, brainstorming, method of ideas generation, situational dialogues, etc.) are described.

The components of future dentist's readiness for professional interaction are developed: motivational, cognitive, operational and personal. The results of the pedagogical experiment, which proved the effectiveness of the implementation of the special course "Professional Interaction of Dentists», are presented. Statistical analysis of the results of the study made it possible to establish that after studying the special course in the experimental group there was a noticeable significant increase in the number of students assigned to the high level, in addition, the number of future dentists with a low level was significantly reduced.

**KEY WORDS:** future dentists, professional training, content, professional interaction

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## INTRODUCTION

In today's conditions of economic and socio-cultural transformation, dynamic development, technologicalization and commercialization of the medical industry, including dentistry, the quality of medical care, and hence, the level of professional training of dentists, their competitiveness, the key indicator of which is the effective professional interaction. This requires special attention to the training of dental practitioners who, having performed various roles (therapist, surgeon, orthopedist, orthodontist, children's dentist, dental hygienist, dental technician, etc.), would be able to successfully interact with different groups of patients, colleagues, managers, nurses and other professionals, cooperate on the basis of trust, support, understanding, tolerance, compassion, respect for each other.

The problem of the professional interaction of a doctor, in particular a dentist, has recently become the subject of studies of a lot of scientists. Researchers pay attention to the communicative preparation of doctors, in particular dentists (A. Hroisman, I. Kontsevych, I. Hardy), the formation of their professional competence (Ya. Kulbashna), professional-personal culture (M. Tararyshkina), communicative (V. Kipiani) and speech competence (M. Musokhranov), ethical and deontological culture (O. Gwyldis), readiness for interaction (S. Poplavska), tolerance (P. Babenko) and etc. The research emphasizes that in order to establish effective interaction with patients, the doctor should have a high level of professional speech (A. Korobkov, M. Lisovii), foreign language (G. Yepifantseva, L. Krysak) and intercultural communicative competence (N. Kalashnik). Scientists are united in the fact that the art of interaction between a dentist and a patient is a very complex, multifaceted and versatile process, where the doctor acts not only as a specialist who uses his knowledge and experience for the treatment, rehabilitation and maintenance of the patient's health, but also as a person, which analyses the

patient's treatment process in the context of moral, ethical, cultural, and religious values.

A significant number of scholars (I. Aartman, A. Almeida, K. Arnrup, M. Berman, M. Clarke, S. Cohen, B. Schouten, S. Wilson, etc.) emphasized that in conditions of growing competition among medical institutions of the stomatological profile, the quality of dental treatment, in particular the organization of professional interaction, prevention of initiation of conflict situations is influenced by the level of organization of their special communicative, conflictological, deontological training, mastering the knowledge of ethical and legal regulation of the daily work of a dentist. At the same time, the researchers singled out the communicative aspect of training as a leading one.

## THE AIM

The purpose of the article is to uncover the updating of the contents of the training of future dentists to engage in professional interaction.

## MATERIAL AND METHODS

The study, completed during 2015-2018, was attended by 292 students of the specialty "Stomatology" at the Dnipropetrovsk Medical Academy, Dnipropetrovsk Medical Institute for Traditional and Alternative Medicine, Lviv Medical Institute, Zaporizhzhia State Medical University, of which 148 people are experimental (EG), 144 - control (CG) groups, as well as 28 teachers of the above mentioned universities.

In the process of research, the following methods have been applied: theoretical – analysis, synthesis, systematization and synthesis of scientific literature; empirical – testing, survey, monitoring, pedagogical experiment to find out the effectiveness of the developed content of training future dentistry; methods of mathematical statistics to assess the statistical significance of positive changes in the results of experimental work.

## RESULTS AND DISCUSSION

As A. Fastivets correctly notes, the level of health of the population and its preservation is a medical problem that requires the optimal solution and the need to improve the management of the system of measures to achieve the goal [1, p. 781]. But we are confident that the solution to this problem is also in the field of higher medical education. To achieve the purpose of the study, we have developed a discipline "Professional interaction of dentists", which is aimed at solving the following tasks: the acquisition of theoretical knowledge of the problems of communication and interaction by future dentists; increasing the need for communication, implementing a variety of interactions; the formation of future dentists readiness for the implementation of professional interaction, positive communicative attitude to team interaction and receiving satisfaction from it.

After studying the discipline students ***must know***: styles, tactics and strategies for professional interaction; principles of interaction between the client and the dentist; the peculiarities of complex, conflicting relationships between the dentist and the client; classification of barriers of professional interaction; the essence of dentist's readiness for professional interaction; the formation of an individual style and the problem of professional deformation; types, features of verbal means of professional communication; ***be able to***: provide practical work in different models, styles, tactics and strategies of professional interaction; have the mechanisms of attracting customer attention in the process of interaction; to create a positive emotional background of interaction; solve complex situations in professional interaction; apply different strategies to prevent and overcome barriers to professional interaction; have different ways of influencing people during interaction; apply an individual style of professional dentist behavior in the process of interaction with different clients and employees. During developing the programed results of the discipline "Professional interaction of dentists" we were guided by the results of the study by S. Wang [2], K. Bond [3].

Modeling the content of the special course was based on the fact that students must, during their study, realize knowledge as their own value. Researchers argue that the content presented to students should "reflect the connections and relations of subjects, the phenomena of objective reality, and include the personal views of the one who speaks, his assessment, the relation to the objective connections of the outside world, ... emotions ..." [4, p. 185]. At the same time, comparing the new knowledge with his own - "a process of contradictory and ambiguous, peculiar discussion, dialogue (mainly internal), which results in the formation of an emotional attitude to the proposed knowledge and their initial acceptance or rejection" [5, c. 152]. It is the emergence of "cognitive dissonance" (L. Festinger) encourages man to overcome it. In an effort to reduce dissonance, the subject changes, overestimates the "source information" or changes his and his own behaviour [4, p. 242].

The program of the discipline is designed for 120 hours: lectures – 15 hours, seminars – 10 hours, practical classes – 15 hours, individual work – 24 hours, independent work – 56 hours.

The special course consists of two modules. The first module "The basis of professional interaction of the dentist" contains the following topics: Historical sources of professional interaction of the dentist; Professional interaction – the leading component of the professional activity of the dentist; Interaction of a dentist and a client, basic deontological norms; Interaction with complex clients. Barriers to interaction; Conflict designs of professional interaction. The second module "Readiness of the dentist to engage in professional interaction" involves the study of the following topics: Types and forms of behaviour of the dentist in the process of interaction with different people; Professional language and speech – the basis of the professional interaction of the dentist; Non-verbal means of

professional communication of a dentist; Computer tools for professional dentist communication. The topics of the seminar include: Professional roles of the dentist and the peculiarities of their interaction; Speech technique as the basis of the skill of professional interaction of the dentist; Individual style of dentist's professional behaviour; Methods and forms of conflict management in a trade organization. Strategies for resolving professional conflicts; Means and methods of self-regulation in professional interaction.

During the lectures and seminars, the following interactive teaching methods were used: dialogue-questioning (patient in the doctor's review, anamnesis), dialogue-arrangement, dialogue-sharing of impressions, dialogue-discussion (communicative partners are trying to work out a certain decision, to reach certain conclusions, give arguments and evidence), conversation polygon, "brain attack" ("brainstorming"), method of generating ideas (stimulates the activity and intuitive thinking of students in the process of finding ideas, suggestions, promoting integration at the information gathered, considerably increases the efficiency of the decisions making), the method "borrow a position" (aimed at working out discussion questions, subject to the presence of two opposite views), situational dialogues ("Dentist - patient", "Review patient dentist"), which is expedient to implement in dyads: teacher – student, student – student, student – doctor, student – ill, student – medical staff, student – group, student – patients relatives, student – doctor – mentor, student – junior medical staff.

The following forms of discussion, such as the Tree of Solutions, Talk Show, and the Round Table, which were aimed at developing the skills of public speaking as a possible form of professional communication had shown its effectiveness. The most interesting were the following discussions: "How to reach psychological contact with a patient?", "Why do we need to build relationships and build a collaborative communicative space at the patient-patient level?".

During the seminars, the students' activities were intensified through dialogue interaction (polylogue), which allowed the student's subject experience to be used, and, consequently, to make the investigated material personally significant.

It was expedient to simulate problem situations. The following methods of simulation of the problem situation were singled out: the method of analogy (based on life experience, or actualization of previously obtained knowledge to solve new problems), inductive, analytical and synthetic way (students independently study phenomena and facts and make the necessary scientific conclusions), the nomination of problem question (it is expedient to solve the problem and master the new knowledge). Among the situations that were discussed during the classes, we can distinguish the following: "At the reception of the dentist," "Visit a dentist in the house for the elderly", "Conflict of the dentist and patient", "Explain, please, the doctor, how do you see the process of treatment" and others.

Students were invited to participate in role-playing and business games with division into teams with different functions (two teams conduct a discussion where the first team submits a certain opinion to the discussion, and the second attempts to refute it). Interesting were the game-polls: "Pass the next", "Ask a friend", "You – me, I – you", "Competition teams". Its value is that they seek to ascertain the level of the learned lecture material by the teacher (students themselves raise questions and define the defendant, which requires more thorough preparation for classes; the control mechanisms of consciousness, which constrain the flow of ideas under the pressure of the usual, stereotyped forms of adoption, disappear decisions, decreases fear of failure, fear to seem ridiculous, uncertainty in their knowledge and skills).

Games, as a model of interpersonal communication, provided the development of skills for professional interaction, and also shaped the ability of students to play the role of a doctor (dentist-therapist, dentist-orthopaedist, and dentist-surgeon), a patient, and a relative of a patient, to see oneself from the position of the subject of interaction. During exercises, trainings ("Interaction of a doctor and a patient", "Children's stomatology reception", "Long-term contact with patient's parents") were widely used.

Important role was assigned to trainings. The trainings selected for the study included training exercises that future dentist performed according to the model, instruction, tasks, without a sample, and detailed instructions from the teacher: "Questioning" (aimed at developing skills to ask questions in the course of communication between the dentist), "Infinite Chain" (involves the wording an alternative position on a discussion problem, forecasting the consequences of individual professional positions and decisions for individuals), "Arguments "for" and "against" (the goal is to develop the skills of the counter-argumentation), "Organization of the argument" (aimed at understanding the process of uniting opinions on the creation of a logical, understandable and convincing argument), "Explanation on the cards" (elaboration of the skills of the selection of arguments ), "Adjustment of Emotional Stress" (aimed at developing the skills of verbal regulation of emotional stress during professional communication).

The components of future dentist's readiness for professional interaction are: motivational (the need to increase the skill of professional interaction, the presence of the motivation of achievement the desire for success, self-improvement), cognitive (completeness and strength of knowledge of the professional interaction of the dentist), operational (level of mastery of a set of skills of professional interaction: communicative-speech, interactive, moral-ethical, attitude to the modelling of professional interactions), personal (the degree of formation of empathy, reflection, emotional intelligence, tolerance). The effectiveness of the implementation of the special course reflects the dynamics of levels of formation of components of readiness of students to professional interaction (Table I).

Comparison of data on the level of formation of components of readiness for professional interaction of students of control and experimental groups suggests significant positive changes at all levels.

**Table I.** Changes in the indicators of levels of formation of readiness components for professional interaction among students of the control and experimental groups

| The level of formation | A group of students | | | |
|---|---|---|---|---|
| | CG (144 people) | | EG (148 people) | |
| | Experiment Stage | | | |
| | Constitutive | Control | Constitutive | Control |
| **Motivational component** | | | | |
| High | 20,8 | 22,3 | 21,6 | 38,9 |
| Sufficient | 38,2 | 41,7 | 39,9 | 46,9 |
| Low | 41,0 | 36,0 | 38,5 | 15,5 |
| **Cognitive component** | | | | |
| High | 13,9 | 17,4 | 12,8 | 43,2 |
| Sufficient | 47,9 | 40,9 | 54,7 | 41,9 |
| Low | 38,2 | 41,7 | 32,5 | 14,9 |
| **Operatinal component** | | | | |
| High | 18,1 | 19,4 | 20,2 | 41,7 |
| Sufficient | 41,7 | 41,7 | 39,9 | 48,0 |
| Low | 40,2 | 38,9 | 39,9 | 10,3 |
| **Personal component** | | | | |
| High | 17,4 | 18,8 | 18,1 | 39,1 |
| Sufficient | 41,7 | 45,8 | 41,9 | 47,1 |
| Low | 40,9 | 35,4 | 40,0 | 13,8 |

Analysing the levels of formation of the motivational component of future dentist's readiness for professional interaction, it should be noted that during two years in the control group there were some changes. However, the dynamics were insignificant. The number of students with a high level increased by 1.5%. Some changes occurred in students who had a low level of motivation component formation (from 41.0% to 36.0%). The results obtained regarding the presence of minor changes in the control group indicate that there is no deliberate work on the formation of future dentist's readiness for professional interaction. As for the experimental group, the data of the table show that after studying the special course in the level of formation of the motivational component there were significant positive changes. The indicators were: for the high level - (+ 17.3%), for the low level - (- 23.0%).

Regarding the dynamics of levels of formation of the cognitive component of the readiness of future dentists to professional interaction, the findings suggest a rapid positive change. After the research in the experimental group, the number of students who we attributed to a high level (from 12.8 to 43.2%) significantly increased. Growth was + 30.4. Qualitative analysis of the results showed that future dentists are free to have profound and effective knowledge about the essence, peculiarities of the professional interaction of dentists. They have stable perspectives on the peculiarities of the interaction between the dentist and the client (assistant, colleague, and leader), the barriers of interaction, types and forms of behaviour of the dentist in the process of interaction with different people. Significantly, the number of faithful full answers grows, as evidenced by the effectiveness of the developed special course, the nature of the established methods of training, which ensure the formation of students' willingness to engage in professional interaction.

The number of students with a low level (from 32.5 to 14.9%) significantly decreased. Growth was (-17.6). Regarding the control group, we have found some changes, but insignificant: high (from 13.9 to 17.4%), sufficient (from 47.9 to 40.9%), low (from 38.2 to 41.7 %) Growth accordingly was (+3.5; -7; +3.5). Changing motives led to the launch of internal mechanisms of self-development, self-realization and self-improvement of the individual in the types of professional interaction, awareness of the need for personal restructuring as future dentists.

With regard to the dynamics of levels of the formation of the operational component of the readiness of future dentists to professional interaction, we can state the following. In the process of diagnosis it was found that if in the control group the number of students with a high level is 19.4% (compared with 18.1%), then in the experimental one – 41.7% (compared with 20.2%). The increase was accordingly (+1.3 and +21.5). This is associated with the inclusion of interactive learning methods in the learning process, which required future dentists to justify their own views on the problem and ways to solve it; game teaching methods, which, based on professionally directed situations, provided a manifestation of the personal position of future dentists during the interaction in the systems "student – student", "teacher – student".

A low level was found in 38.9% of control group students. As to the experimental one, significant positive changes were found in each of the studied levels, namely: high level – positive changes +21.5; sufficient – changes +8,1; low - (-29.6). By comparing the results obtained, we note that after studying the special course in the experimental group there is a noticeable significant increase in the number of students who are attributed to a high level: the percentage of students in the experimental group with a high level has changed from 18.1 to 39.1. It is significantly reduced the number of future dentists who showed a low level (from 40.0 to 13.8%). In the control group, changes occurred, but insignificant: the high level – from 17.4 to 18.8%, sufficient – from 41.7 to 45.8% and the low level – from 40.9 to 35.4%.

## CONCLUSIONS

The article presents a solution to the problem of preparing future dentists for professional interaction. The educational discipline "Professional interaction of dentists" is developed and aimed at realization of the tasks: acquisition of theoretical knowledge of the problems of communication and interaction by future dentists; increasing the need for communication, implementing a variety of interactions; the formation of future dentists readiness for the implementation of professional interaction, positive communicative attitude to team interaction and receiving satisfaction from it. The program results of the study of the indicated discipline are presented, content of its modules is disclosed. Interactive teaching methods used during lectures and seminars are described.

The components of future dentist's readiness for professional interaction are developed: motivational, cognitive, operational, personal. The results of the pedagogical experiment, which proved the effectiveness of the implementation of the special course, are presented. After studying the special course in the experimental group, a significant increase in the number of students who were assigned to a high level, in addition, significantly reduced the number of future dentists who showed a low level.

The development of a methodology for preparing future dentists to engage in professional interaction will be the subject of further scientific research.

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5. Passov Ye. Communicative method of teaching foreign language speaking. Education, Moscow, 1991, 223 p.

**Authors' contributions:**
*According to the order of the Authorship.*

**ORCID numbers:**
*Borys I. Palamar - 0000-0003-2510-0713*
*Volodymyr V. Proshkin - 0000-0002-9785-0612*
*Nataliia P. Volkova - 0000-0003-1258-7251*
*Oksana O. Rezvan - 0000-0002-7371-3605*
*Lidiia P. Tkachenko - 0000-0002-6375-3558*

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*The Authors declare no conflict of interest.*

**CORRESPONDING AUTHOR**
**Borys I. Palamar**
Bogomolets National Medical University
Kyiv, Ukraine
tel: +380672387654
e-mail.: palamar.bi@ukr.net

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# CORRUPTION IN MEDICAL SPHERE OF UKRAINE: CURRENT SITUATION AND WAYS OF PREVENTION

**Vladislava S. Batyrgareieva[1], Andriy M. Babenko[2], Sandra Kaija[3]**
[1]ACADEMICIAN STASHIS SCIENTIFIC RESEARCH INSTITUTE FOR THE STUDY OF CRIME PROBLEMS NATIONAL ACADEMY OF LAW SCIENCES OF UKRAINE, KHARKIV, UKRAINE
[2]ODESA STATE UNIVERSITY OF INTERNAL AFFAIRS, ODESA, UKRAINE
[3]RIGA STRADINS UNIVERSITY, RIGA, LATVIA

## ABSTRACT

**Introduction:** All social life spheres in Ukraine are influenced by corruption. Ukrainian citizens were inquired in order to determine corruption rate in various social spheres. It was conditioned by reforming criminal justice and administrative management, which is directed, particularly, for liquidation of corruption in the state. Special emphasize is stressed on corruption rate in the medical sphere.

**The aim** of the article is to determine: 1) population's attitude towards to corruption, in particular, in the medical sphere; 2) the most corruptive social spheres; 3) efficiency of anti-corruption measures; 4) readiness of population to participate into struggle with corruption.

**Materials and methods:** The study is grounded on dialectical, comparative, analytic, synthetic, sociological (special-purpose inquiry form, interview), statistic and comprehensive research methods. The study group consisted of 1 120 citizens and 513 medical and pharmaceutical professionals of Ukraine. Questions were related to: 1) citizens' contact with corruption; 2) corruption expansion rate in state authorities, self-governing authorities, in various infrastructure spheres, particularly, in healthcare; 3) awareness about struggle with corruption in the state and in the region and determination of citizens' readiness to cope with corruption.

**Results:** Corruption contact level of citizens remains steadily high. Corruption in the medical sphere is the most widespread: during the previous year before the inquire 63% respondents were involved into corruptive schemes. Corruption in the medical sphere can be subdivided in the following levels: from patient to doctor; inside the hospital – from a healthcare institution employee to the executive hospital staff; on state level concerning state procurements of medications. A bribe to health care professionals was given for: receipt of a sick leave certificate and various references (for example, about unfitness for military service, fitness for driving a car or fulfillment of particular works); high-quality conduct of an operation, medical servicing rendering; writing out a "necessary" prescription; approval or hiding of any bodily injuries; falsification of a true cause of death. All health care professionals have come across different corruptive practices, among which the following payments are widespread: for employment in a hospital, license for private medical practice or establishment of private clinics, "avoidance" of checks of healthcare institutions' activity. The largest bribes are given state officials for participation in tenders for medical drugs supply by pharmaceutical companies. All health care professionals have come across different corruptive practices, among which the following payments are widespread: for employment in a hospital, license for private medical practice or establishment of private clinics, "avoidance" of checks of healthcare institutions' activity.

**Conclusion:** Corruption on the sphere of medical practice is complex phenomenon. The conducted poll made it possible to structure the corruption problem, to see its various levels and levels. In respondents' opinion, a scrupulous information campaign is a positive tendency: 45% consider this is a guarantee of anticorruption. Nevertheless, only 5% respondents assume personal notification of anticorruption bodies about receipt of a bribe by medical staff.

**KEY WORDS:** health care, patient, patients' rights, defects in medical care

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## INTRODUCTION

The fight against corruption has always been and is now in the attention focus of the Ukrainian state. It is sufficient to say that there are numerous national and regional problems in the fight against corruption that have acted or continue to operate at present [1–6]. However, society, in the broadest sense of the word, is not yet ready to end this shameful phenomenon. Moreover, during the years of Ukraine's independence, corruption and its core - corruption crimes- have become a systemic negative phenomenon of social reality that is widespread in all economic sectors and the activities of state and local government bodies along the entire vertical of public administration [7]. Corruption as a social corrosion constantly erodes state structures [8]. From the criminological point of view, corruption is a social phenomenon, a kind of legal cynicism, the content of which is the system of negative attitudes, instructions and actions aimed at satisfying personal, group or corporate interests through the use of power or official position by some officials in spite of the state's and society's interests [9]. Therefore, the preventing corruption problem for Ukrainian society, unfortunately, remains traditionally acute. And this is despite the fact that Ukraine is moving towards the development of numerous anti-corruption measures, their normative documentation and implementation. But, according to indicators of entities' work of anticorruption activity, the implementation of normative prescriptions in law-enforcement activities remains extremely ineffective.

The fight against corruption is complicated by the corruption spread at all levels of government. It covers the various spheres of our society, affects more and more new social institutions. Corruption penetrates the everyday life of different segments of population. The effectiveness of anti-corruption decisions taken at the highest state level is offset by their deliberate blocking and neglect. According to non-governmental international anti-corruption organization and study of its level called Transparency International, in 2017, the index of corruption perception in Ukraine was 30 points from 100 possible, which is 1 point higher than in 2016 [10]. In 2018, the index even improved by 2 points (from 30 to 32), which allowed it to rise from 130 to 120 in the overall ranking, but Ukraine remains in the red zone of countries with a high level of corruption perception [11].

According to data-polling perfomed by the Kyiv International Institute of Sociology with the support of the United States Agency for International Development (USAID), which was conducted from 2007 till 2015, every year about 66% of Ukrainians are exposed to corruption, becoming participants in corruption relations [12]. That is, two-thirds of Ukrainian citizens are involved in corruption, most of them in some way recognize the need for this illegal activity, because corruption, in their opinion, is necessary to solve many problems.

It is alarming that corruption affects practically any sphere of public life and is twice as horrible when it is infected with the healthcare sector, because according to all-Ukrainian sociological survey conducted in 2018, 69% of Ukrainians believe that paying for medical services that are free and guaranteed by the state are corruption [13]. As a result, corruption acts repeatedly and repeatedly, becoming an approved way of behavior. So, of particular relevance is the corruption phenomenon in the field of health care [14]. In order to be effective, reforms to combat corruption must be informed by the theory, guided by evidence and adapted to the context [15].

## THE AIM

The purpose of this study is to find out, based on the authors' own sociological research in Kharkiv (Ukraine), and an analysis of published sociological surveys of corruption real state in the medical sphere for the period from 2007 till 2018, to identify levels of corruption and certain types of medical practices that are the most vulnerable as well as developing ways to prevent this negative social phenomenon.

## MATERIALS AND METHODS

This study was conducted during 2013-2018 and is based on the results of public opinion polls on corruption in medicine in Kharkiv (Ukraine), which was conducted in 2014-2015, the results of other sociological opinion survey conducted in Ukraine from 2007 till 2018, the national regulatory acts, the data of the Corruption Perceptions Index 2016, 2017 and 2018 from International Organization Transparency International, research papers and opinions of progressive people in the field. The inquiry was conducted using a sociological method (special-purpose inquiry form and interview). In general, about twenty questions were put to respondents. They concerned: 1) experience of direct contact with corrupt practices; 2) degree of corruption prevalence in the authorities, local self-government, in different spheres of service of the population, in particular, in the medical sphere; 3) establishment of the most corrupted institutions; 4) awareness of combat corruption in the state and the region, as well as the elucidation of citizens' willingness to counteract corruption.

Respondents' distribution by key demographic parameters coincided with the population make-up registered by official statistics. Doctors and pharmacists were asked about the existence of corruption practices in the medical sector and their types. Besides, the study is grounded on dialectical, comparative, analytic, synthetic, statistic and comprehensive research methods.

## RESULTS

Several years ago, with the support of the Kharkiv Regional State Administration, the creative team of the V.V. Stashys Scientific Research Institute for the Study of Crime Problems of the National Academy of Law Sciences of Ukraine with the involvement of scientists from other Law educational institutions of the country conducted a large-scale public opinion survey on corruption in Kharkiv city – a particularly large Ukrainian city. This study was carried out in 2014-2015 within the framework of the implementation of the Regional Program for Prevention and Counteraction of Corruption in the Kharkiv Oblast for 2013-2015, approved by the decision of the XXI Session of the VI convocation of the Kharkiv Regional Council on April 25, 2013.

Necessity for such a survey was predetermined by the reform of criminal justice and administrative governance, which was aimed, as well as, at overcoming corruption in Ukraine. The main purpose of the survey was to clarify the following issues: 1) attitude of pointed cities' inhabitants to the phenomenon of receiving unlawful benefits (bribes); 2) level and structure of experience of urban population about collision with corruption, as well as reasons for participating in corruption practices; 3) assessment of the effectiveness of existing anti-corruption measures in the state and the city; 4) readiness of population to engage in anti-corruption activities. After conducting a pilot study and establishing a high level of perceived corruption in the medical sector, the idea emerged to analyze separately the state of corruption in medicine. In addition, the study aims were to determine the impact of various social factors on the effectiveness of activities in the field of combating corruption and to develop recommendations for their consideration during formulating the principles of the national anti-corruption mechanism functioning; to work out the methodology of carrying out social and legal research which allows to increase the complexity and

comprehensiveness of the analysis of existing problem and substantiate recommendations of practical orientation.

Tendencies in the science development and effectiveness of its impact on law-making and law enforcement largely depend on its methodological principles [16]. Public opinion polls on the level of prevalence of corruption practices, including the medical sphere, were conducted using the appropriate toolkit - a specialized questionnaire posted on the Institute's service in the Internet, in the online poll, as well as through the distribution of this printes questionnaire form among the staff and patients of medical institutions of state, of communal and private property, as well as pharmaceutical imployers of Kharkiv city.

It should be noted that, by this time in Ukraine, there is practically no research on anti-corruption in medicine based on clear ideas about the extent of spreading of this negative phenomenon precisely in this area of society's life.

The materials of the conducted public opinion poll showed clearly that almost all branches of public life are permeated with corruption. At the same time, the corruption level remains stable in the Kharkiv region and does not differ from similar indicators of nationwide research. Thus, 63% of respondents in Kharkiv stated that during the last year, before the survey, they were personally involved in corruption relations or were informed about it by other persons. Corruption, according to the respondents, is necessary for solving many problems. Therefore, one third of Ukrainians find justification for corruption in solving personal cases [17]. That is, citizens perceive corruption as an acceptable mechanism, a kind of auxiliary tool for solving these problems, as "service" that allows you to save time, avoid extra worries and guarantee a good result that has its own market price.

The distribution of survey respondents by key demographic indicators coincided approximately with the population composition of the region, recorded by official statistics. Among the total number of respondents in Kharkiv, 48% were women, 52% were men [18]. The predominant segment of the respondents was persons of employable age (91%). Respondents belonged to different educational levels.

Approximately the same number of affirmative answers regarding the corruption of educational institutions, the police and the State Auto Inspection, which was eliminated at the end of 2015 (29%, 28%, and 24% respectively). Corruption in other areas (for example, in the servicing population of local self-government sector, as well as in judiciary and prosecutor's offices) is lower (about 20%). According to the respondents' opinion the lowest level of corruption was recorded among the employees of the Ministry of Emergencies (3%) and the State Registration Service of Ukraine (12%) (functions of this service were transferred to the Ministry of Justice of Ukraine in 2015). At the same time, almost half of the respondents (47%) personally witnessed the mercenary actions of medical professionals. Thus, in the Kharkiv region corruption is one of the first in the medical sphere among corruption practices. For comparison, it should be noted and the survey data conducted by the Ilka Kucheriva Foundation Democratic Initiatives, presented on December 7, 2017, at press conference in Kyiv. Over recent years, citizens personally or their relatives, acquaintances, most often gave a bribe precisely in medical institutions. 51% of respondents noted this (for comparison: 35% of respondents feed in higher education institutions or 15% in local authorities, and in patrol police (about 11%). In total, 2,000 respondents were interviewed according to a sample representing the adult population of Ukraine (except for the occupied territories of Crimea and certain territories in Donetsk and Luhansk oblasts). The sampling error does not exceed 2.3% [19].

By the way, a similar study has been conducted during a long time in some post-Soviet countries. For example, monitoring of the corruption's state in the medical sphere, carried out in the Republic of Latvia, found, that in 2005 41.3% of respondents had to pay informally, make gifts or use acquaintances in case of treatment in medical institutions. In 2007 the quantity of such persons significantly decreased (33.7%). In 2011 33.3% of the respondents used the corruption schemes in the medical sphere [20]. However, as it was noted in the Bureau for the prevention of corruption of the Republic of Latvia, the situation with corruption in the field of medicine doesn't change dramatically for the better, because the real measures for combating with this phenomenon aren't effective [20].

In connection with the above, one of the areas in our study was to find out the specifics of corruption in this area and the reasons for its dissemination. It is known that corruption impact can be grievous and critical, especially when such corrupt practices are gaining ground and can lead to patients' mortality [21].

The authors recall that the survey was attended by both ordinary citizens and directly medical professionals of private clinics and institutions of state and communal ownership, as well as pharmaceutical sector' ones.

Corruption in the field of medicine can be conditionally divided into the following main levels:

- the first: from patient to doctor or other health professional;
- the second: within hospital - from medical professionals to hospital administration;
- the third: at the state level in regard to public procurement of medicines [22] and equipment.

As it stated in the special literature, forms of corruption in healthcare and medicine may include (but not be limited) the following: bribes and "kickbacks" characterized as corruption indicia, bribes and "kickbacks" can be paid by individuals and firms for (I) procure government contracts, leases or licenses for construction of healthcare facilities, and for medicines supply, goods and services, as well as ensure their contracts' conditions; (II) preferences and fabrication (frame up) of bidding process; (III) manipulate and falsify records, and evidence alteration, giving the conformity appearance of procedures carried out to enactments of regulatory bodies; (IV) speed up of permission procedure to carry out legal activities, (e.g. obtaining institutional affiliation, company registration

or construction permits); (V) influence or change legal outcomes so as to avoid punishment for wrong acting [23].

Here are some of the most widespread types of services for which the healthcare professionals were given improper advantage by the Ukrainian population (the so-called first level of corruption in the medical sector). Thus, improper advantage, according to the study results, was provided by:

- for receipt of certificate of sickness and various references (for example, certificates of invalidity, certificates of driving eligibility, admission to certain works' fulfillment, permission to engage in certain sports, attend sports facilities, exemptions from physical education and etc.) (about 75% of the respondents indicated that they answered positively on corruption);
- for the quality of surgery conducting for a patient or providing medical services: consultations, scheduled or unscheduled inspections (that is, not "as everyone", but with a special individual approach). In this case, patient is guaranteed high-quality pre-operative and post-operative care, use of the best medical products, sutures, dressing materials, anesthetic agents, out-of-the-box testing, better conditions for staying in medical hospital, etc. Approximately 50% of the citizens who received affirmative answers attracted this practice.
- for extracting the "desired" recipe (about 10%);
- for confirmation or concealment of certain medical facts (most often - assaults and other bodily injuries) (less than 10%);
- for pre-discharge of patient from hospital or, conversely, for prolonging patient's stay in hospital (about 5%);
- for issuance of "necessary" certificates about the patient's mental state (up to 15%);
- for distorting the true death cause. In the latter case, the size of such bribes is one of the largest in medicine, since it is possible to conceal criminal death in these cases (but, fortunately, few such cases - only a few responded units answered "yes");
- separately, citizens indicated "charitable donations" in money or any goods, purchase of medicines, medical instruments, other medical materials in certain pharmacies or specific dealers indicated by doctors (more than 70%).

Similarly, the survey was conducted among the medical and pharmaceutical professionals. The main question was: "Are you aware of existence of corruption practices in the medical sphere? If known, then please, indicate what types do you know?"

Answers to these questions gave us an idea of the corruption of so-called the second and the third levels (let's remind that corruption of the second level is: the improper advantage transfers from doctor to medical institution chief, the third – in regard to state procurement of medicines and equipment).

Absolutely all respondents answered affirmatively. The most common practices were:

- payment for the post (a doctor, a nurse, a nurse, etc.) in hospital;
- fee for obtaining a license for private medical activities;
- payment to officials of the Ministry of Health of Ukraine and its territorial bodies for the "avoidance" of unnecessary inspections of medical institutions;
- fees for opening of private clinics operating on the basis of public hospitals, that is, using the equipment and capacity of the latter.

Finally, the third level of corruption in the medical field. For this level, some explanations need to be given. The fact is that the state purchases drugs at its own expense through tenders from certain pharmaceutical manufacturers. These purchases' volume depends on the population's needs in certain medicines. These needs from the regions are brought to the Ministry of Health of Ukraine, which organizes the medicines procurement process. It is in this procurement process that there are many corruption risks for determining the winners of the competitive bidding and purchasing the "right" dosages that are produced by the "necessary" pharmaceutical manufacturers. In addition, during long time, the same companies participate in the tender without allowing other companies to participate in this process. However, to prevent this fact becoming public, the said pharmaceutical companies create satellite companies belonging to the same business groups [22]. As stated in the Law of Ukraine "On the Principles of State Anti-Corruption Policy in Ukraine (Anticorruption Strategy) for 2014-2017", losses from corruption arrangements during the conduct of public procurement procedures amount to 10-15% (35-52.5 UAH billion) of the expenditure part of the State budget every year [4].

Not disclosing the details of these corruption schemes' essence, all respondents from medical and pharmaceutical professionals have shown that there are problems of so-called "rollback" to the Ministry of Health of Ukraine for tenders for a state order for the drugs supply by certain pharmaceutical companies. That is, in this case, they are forced to give bribes to pharmaceutical companies so their products can be accessed by consumers, including in hospitals. It is well known to everyone about this practice, but the analysis of the State Register of Judicial Decisions of Ukraine over the past year has not revealed any court decisions in this category of cases. Researchers are quoted as saying that in the field of health corruption actions include the same as tampering with data on the results of medicines clinical trials, misuse of pharmaceuticals and other resources, imposition of overestimated accounts to insurance companies [24]. In addition, it is noted that the fight against corruption in the health sector is a complex problem, because at one end of the scale are doctors and nurses, who charge small non-formal payments to patients to supplement inadequate incomes; at the other end, and far more pernicious, are the corrupt suppliers who offer bribes, and health ministers and hospital administrators who accept bribes, or siphon millions of dollars from health budgets, skewing health policies and dwindling funds that should be spent on building hospitals, buying medicines or employing staff [25].

During the poll, the Ukrainian public spoke about the main causes of corruption spreading in the medical sphere. At the same time, ordinary citizens' opinion and medical sphere

professionals was different. Some differences of opinion are determined primarily by the level of corruption practices in which they participate. Yes, ordinary citizens are aware of corruption as patients or relatives, that is, these persons are aware of the corruption causes the first conditionally designated level of corruption, which means "patient-doctor". As far as doctors and pharmacists are concerned, they are aware of corruption in the medical sphere, so to speak, from the inside, often speaking directly to participants (the second and the third levels of corruption practices).

We analyze the existence reasons of the corruption phenomenon at the first level. The corruption spread contributes to: underfunding of the medical sector (82% of respondents); low professional level of doctors (71%); low quality provision of free medical services as a norm for patient care and patients' fears that a doctor without bribes will not provide adequate assistance (54%); use of the medical institutions' facilities first of all in the interests of privileged patients (49%); provision of unlicensed or unlicensed medical services outside of medical institutions (40%); the tradition to thank the doctor for the best conditions of stay in medical hospital, "good attitude", etc. (39%); lack of appropriate drugs and the spread of counterfeit drugs that do not meet accepted standards or are completely counterfeit, which is a direct threat to the life and health of patient (27%). As it is rightly noted in the special literature on the traditions of "being grateful", the corruption that was an integral part of "shadow" economies of the communist countries has left a legacy of corruption throughout the region, especially in the health sector [26].

With regard to the corruption causes at the second and the third levels, the following are: practice of protectionism in obtaining workplaces, posts, and any other preferences (92%) (this practice implies the continued presence of doctors in illicit proceeds that would allow them to compensate for the expenditures for bribes); high competition in the market of services related to the state order for medicines (85%); bureaucracy that is in the health sector (80%); Organized criminal business controlling the areas of drug redistribution (42%); concealing the facts of embezzlement and theft of public funds allocated for public health, violations of public procurement rules, use of public health facilities for private business in the field of medicine (39%); high cost of raw materials for drugs manufacture of (32%); unjustified taxes (31%).

During conducting the questionnaires, respondents (the patients of medical institutions) were interrogated: who was a bribe initiator? To this question 41% of respondents answered that medical staff was an initiator of "remuneration" for the received medical services; half of the respondents (50%) showed that they had given the bribe allegedly on their own initiative, but in a situation where it was clearly possible to understand that such a step was necessary. And only a small part of respondents didn't answer this question (9%). We give data on this and foreign researchers of the post-Soviet countries. Thus, according to the results of Russian scientists, 32.4% of the respondents who fell into the situation when they needed a reward for solving any medical health problem showed that medical institution staff was a bribe initiator; 6.4% of interrogated persons didn't answer this question; the rest ones - 61.2% respondents showed that they themselves initiated corrupt actions [27].

A public opinion poll conducted by the Center "Democratic Initiatives" in Ukraine from September 18 to October 3, 2017 showed that medical institutions are leaders in everyday corruption practices. When asked if you paid medical workers, 16% of respondents replied that they do it regularly, 42% did it occasionally [19].

Due to the fact that public both as ordinary citizens and specialists whose professional interests are related to the sphere of medical care of population, are active participants in corruption processes, the fundamental task of the state anti-corruption policy is the radical transformation of public consciousness. This breakthrough will be witnessed by the formation of firm rejection climate of corruption in society. In Ukraine civil society, despite the growth of passionarity, patriotism is still at the stage of its formation. That is why the main subject of corruption prevention today, including in the field of medicine, is not society and public, but mostly criminal prosecution bodies that naturally react to corruption, but do not eliminate the problem roots. Therefore, it is erroneous to believe that corruption can only be curtailed by means of legal and administrative measures. These measures will provide support for anti-corruption spirit in society, and not vice versa.

Thus, the provision of further means and methods, as well as preventive strategies that would help eradicate corruption practices in many areas of public life, including the health sector, is a priority task of domestic legal science. Such strategies should include at the same time three distinct links of corruption practices existence.

It is needed the solution and the issue of working out concrete measures for combating corruption in the medical sphere. At the same time, concrete measures to be taken in order to significantly reduce the corruption level in the public health sector can be modeled on the basis of an analysis of respondents' responses on this issue. The majority of respondents from ordinary citizens consider that an effective measure of combating corruption is to bring the perpetrators of corruption into criminal responsibility while denying access to medical practice (92%). Many respondents argue that an important measure to counteract the corruption shameful facts in medicine will be wages increase for medical professionals and medical sector financing in necessary volumes. Another 12% of respondents rely on introduction of transparent health insurance schemes in the country, which is intended, in particular, to reduce the corruption level in the analyzed area. Regarding the anti-corruption measures proposed by healthcare professionals and pharmacists, among them, the following prevails: decent pay for their work and proper state policy to support the relevant sphere of society (87%); overcoming general disorder in the state (54%); fighting corrupt practices in bureaucratic apparatus (36%) (here refers to persons involved in state orders' formation for drugs, medical equipment, machinery, etc.); introduction of full payment of medical services - 21%; introduction of compulsory health insurance system of Ukraine - 19%.

And only 9% of the respondents indicated the necessity of bringing to justice the corrupted physicians.

A hypothesis is needed to prove that corruption in the medical sector is very difficult to regulate, since citizens are worried about their own health and their relatives' health. Therefore, they all perceive any hint of a bribe from medical professionals very seriously, considering it to be a norm.

In addition to the aforementioned, the conducted research has shown that positive, in the opinion of a considerable number of respondents, is the phenomenon of integrity informing about corruption offenses. Thus, 45% consider such a possibility as a guarantee of counteraction to the specified criminal act; however, only 5% of them assume a personal message to anti-corruption authorities on a free or paid basis on the facts known to them about receiving unlawful benefits by medical professionals. In this regard, it is necessary to find out the reasons for such a low readiness of the population to expose the corruptors while performing the function of virtuous informant.

In order to find out the complete picture of corruption in the medical sphere in Ukraine, the results of regional study should be compared with relevant studies in other regions of Ukraine. In addition, such studies will turn problems into periodic ones, and their results should be brought to general public attention in order to create an atmosphere of acute rejection of any corruption facts in society.

## CONCLUSIONS

Corruption is an extremely complex phenomenon. Therefore, solving this problem requires an integrated approach. It is impossible to overcome corruption in the medical sphere without paying serious attention to preventing corruption in other areas of public life. But in order to effectively implement certain anti-corruption strategies, one needs to have a clear idea of corruption state in the country. In this regard, a reliable tool for ascertaining this condition is the survey of ordinary citizens and doctors and pharmacists on anonymity conditions.

Health care of the nation, without a doubt, is priority area of the social policy of the Ukrainian state. The conducted poll on the sphere of medical practice of the country made it possible to structure the corruption problem, to see its various levels. Currently, there are clearly three levels of corruption practices in the field of medical care of the population of Ukraine: the first level, conventionally designated as corruption "from patient to doctor or other medical professional"; the second - "from an employee of medical institutions to hospital management" and, finally, the third - corruption at the level of state purchases of medical products and equipment.

The study of the reasons for corruption existence in the medical services' sphere leads to the disappointing conclusion that the tradition of retaliation for medical aid to doctors, on the one hand, has deep historical roots, and, on the other one, is supported by the established psychology of a person seeking for such a help, which is not paying a doctor, you cannot receive a qualitative and timely medical service. Subsequently, this tradition based on the psychology of "gratitude" is transformed from the format of direct contact "patient - bribe physician" to the format of "thanks" of a patient in the form of charitable contributions to the hospital, but not all medical staff understands the further appointment of these funds, that is what needs they are going further. It is very likely to assume that this money is deposited in some doctors' pockets. At the same time, numerous facts of enrichment at the expense of public funds in the healthcare sector have the most serious impact on the quality and accessibility of medical services in Ukraine, turning first and foremost into free-of-charge medical care on the predatory practice of withdrawal of funds from indigent citizens of our country.

Regarding the most likely and effective ways of overcoming corruption in the medical sphere, respondents from ordinary citizens are mainly in favor of repressive measures restricting corruption practices, and medical and pharmaceutical professionals are inclined to consider solving the problem of overcoming corruption practices in appropriate state support for the development and functioning of the medical sector.

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## CORRESPONDING AUTHOR
**Vladyslava Batyrgareieva**
Academician Stashis Scientific Research Institute
for the Study of Crime Problems of the
National Academy of Law Sciences of Ukraine, Kharkiv, Ukraine
tel: +380505830788
e-mail: vladis2229@yandex.ru

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PRACA POGLĄDOWA
REVIEW ARTICLE

# EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) – IN THE TREATMENT OF SEVERE, LIFE-THREATENING RESPIRATORY FAILURE

**Krystian Ślusarz[1], Paulina Kurdyś[1], Paul Armatowicz[2], Piotr Knapik[3], Ewa Trejnowska[3]**
[1]STUDENTS' SCIENTIFIC SOCIETY, DEPARTMENT OF CARDIAC ANESTHESIA AND INTENSIVE THERAPY, SILESIAN CENTRE FOR HEART DISEASES, MEDICAL UNIVERSITY OF SILESIA, ZABRZE, POLAND
[2]DEPARTMENT OF GENERAL, ENDOCRINE AND VASCULAR SURGERY, MEDICAL UNIVERSITY OF WARSAW, WARSAW, POLAND
[3]DEPARTMENT OF CARDIAC ANESTHESIA AND INTENSIVE THERAPY, SILESIAN CENTRE FOR HEART DISEASES, MEDICAL UNIVERSITY OF SILESIA, ZABRZE, POLAND

**ABSTRACT**

Extracorporeal membrane oxygenation (ECMO) is a technique involving oxygenation of blood and elimination of carbon dioxide in patients with life-threatening, but potentially reversible conditions. Thanks to the modification of extracorporeal circulation used during cardiac surgeries, this technique can be used in intensive care units. Venovenous ECMO is used as a respiratory support, while venoarterial ECMO as a cardiac and/or respiratory support. ECMO does not cure the heart and/or lungs, but it gives the patient a chance to survive a period when these organs are inefficient. In addition, extracorporeal membrane oxygenation reduces or eliminates the risk of lung damage associated with invasive mechanical ventilation in patients with severe ARDS (acute respiratory distress syndrome). ECMO is a very invasive therapy, therefore it should only be used in patients with extremely severe respiratory failure, who failed to respond to conventional therapies. According to the Extracorporeal Life Support Organization (ELSO) Guidelines, inclusion criteria are: $PaO_2$ / $FiO_2$ < 80 for at least 3 hours or pH < 7.25 for at least 3 hours. Proper ECMO management requires advanced medical care. This article discusses the history of ECMO development, clinical indications, contraindications, clinical complications and treatment outcomes.

**KEY WORDS:** acute respiratory distress syndrome, extracorporeal membrane oxygenation, acute respiratory failure, acute cardiac failure, critical care

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## INTRODUCTION

Severe respiratory failure and cardiac failure are the result of many diseases. They can also be a direct threat to the patient's life. All procedures that temporarily support the respiratory and/or cardiac system, which failed to respond to conventional therapies and treatment, are included under the term extracorporeal life support (ECLS). When ECLS is implemented in intensive care units among critically ill patients to improve respiratory and/or cardiovascular efficiency, it is referred to as extracorporeal membrane oxygenation (ECMO) [1]. Currently accepted indications for the use of ECMO are: acute respiratory distress syndrome (ARDS), cardiogenic shock, pulmonary embolism, myocarditis, and in cardiac surgeries (as a bridge for heart transplantation). Recently, the widespread use of ECMO in people after sudden cardiac arrest is also postulated [2, 3].

ECMO can keep the patient alive, substituting the function of the heart and/or lungs for up to several weeks. However, it is essential to note, that ECMO does not cure an inefficient or damaged organ, but gives the time needed for regeneration and recovery. ECMO should only be considered in the exhaustion of other conventional methods, as it is a very invasive technique. Conventional methods include advanced respiratory therapies, drugs improving respiratory and cardiac efficiency, gases affecting the pulmonary circulation, and *prone position* used to improve the ventilation in patients with ARDS.

In fact, the implementation criteria illustrate how severe the patient's condition must be in order to start this support. The basic one is meeting the criteria for the Berlin Definition of severe ARDS [4] and at least one of the following: (a) $P_aO_2$ / $FiO_2$ < 80 for at least 3 hours despite VT 6 ml/kg with PEEP ≥ 5 cm $H_2O$ and the use of alveolar recruitment; (b) pH <7.25 for at least 3 hours [5]. Chest radiographies of patients with severe ARDS often reveal diffuse ground glass opacities that result from partial loss of pulmonary alveolation (Fig. 1).

This review focuses primarily on ECMO – one modality of ECLS. It concerns the history of development, the types of ECMO, clinical indications, contraindications, clinical complications, predictive scales and treatment outcomes.

## HISTORY OF ECMO

The originator and first doctor operating with the use of ECMO prototype was Dr. John Gibbon. His idea was to

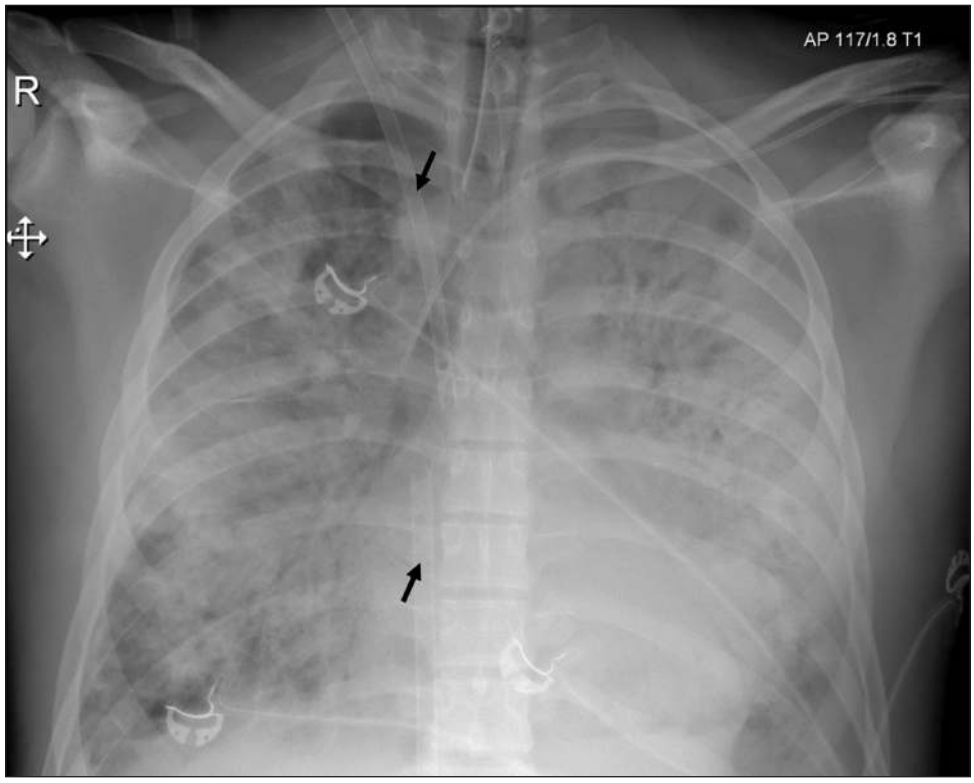


**Fig. 1.** Chest X-ray in a patient with severe ARDS – ground glass opacities. ECMO cannulas are inserted (black arrows) [authors' material].

create a device that would take deoxygenated blood from the body, oxygenate it, and return it to the body. In 1934, together with his wife, he began work on creating such a device. Initially, it was used for cat operations and because they ended successfully, 16 years later, he received support and started to build a more advanced machine. In 1953, he performed his first successful surgery with the use of extracorporeal circulation. The patient was an 18-year-old woman with congenital heart defects [6]. A few years later, the first prototype for bypass therapy was developed [7]. In the 1970s several cases were reported showing successful use of ECMO. In 1972 by Hill et al. for the treatment of ARDS with venoarterial ECMO and in 1977 by Barlett et al. for the treatment of cardiopulmonary failure [8-10]. In this decade, the use of ECMO began to increase significantly and further studies were conducted in order to use it not only in adults but also in neonates and children.

## WHAT IS ECMO?

ECMO is a technique of extracorporeal support that involves draining deoxygenated blood from the venous system, pumping it through an oxygenator, and reinfusing warm, oxygenated blood to the patient [11]. The dimensions of ECMO devices have been significantly reduced over the last years that they are now smaller than devices for renal replacement therapy.

The first component of the ECMO circuit is a venous cannula through which blood leaves the body. Then the blood goes to the pump, which gives the adequate pressure in the circulatory system. After passing through the pump, blood runs to the oxygenator, which acts as the lungs. The oxygenator is a device made of tiny tubes between which blood flows. The wall of the tubes is a semipermeable membrane through which oxygen and carbon dioxide can penetrate. Inside the tubes there is a space filled with gases, the concentration of which can be changed depending on the patient's condition. In modern oxygenators it is also possible to change the temperature of the patient's body thanks to built-in thermoregulators. The drains connect all ECMO elements into one closed system. The patient's body is connected to ECMO through cannulas. Blood leaves the body through the venous cannula and returns to it via the arterial cannula or the venous cannula. The type of return cannula determines the type of ECMO [12, 13].

## ECMO TYPES

There are two basic types of ECMO: venoarterial ECMO (VA ECMO) and venovenous ECMO (VV ECMO), however the combination of both types is also sometimes used. Schemes of both types of ECMO are shown in Fig. 2 and Fig. 3.

VA ECMO can be carried out using cannulas located peripherally or centrally. In the case of peripheral cannulation, blood is drained from a large vein (femoral vein or jugular vein) and returned to the aorta via access to the axillary, carotid or femoral artery. With central cannulation, blood is drained directly from the right atrium and reinfused to the ascending aorta [14]. It can also be used as a bridge for implantation of a device or heart transplantation. Pagani et al. reported that patients with ECMO as

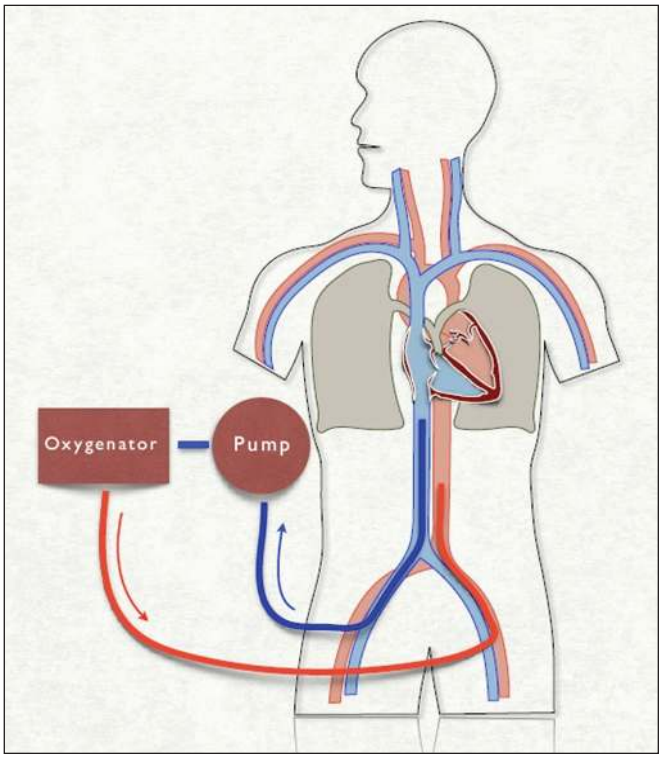


**Fig. 2.** Scheme of the VA ECMO circuit [Modified with the permission of www.ecmo.pl].

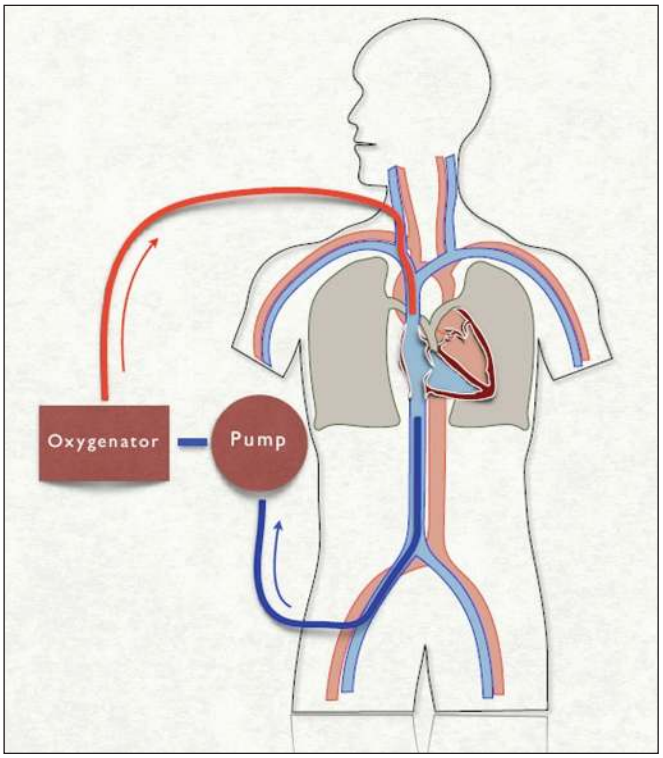


**Fig. 3.** Scheme of the VV ECMO circuit [Modified with the permission of www.ecmo.pl].

a bridge to implantable left ventricular assist device had a higher survival rate compared to patients without ECMO support [15].

The operating principle of the VV ECMO is similar to the one above, with the difference that oxygen-rich blood returns through the venous circulation (generally to the femoral or internal jugular vein) [16]. In the context of functions, extracorporeal carbon dioxide removal ($EC_{CO2}R$) is similar to VV ECMO, however $EC_{CO2}R$ only removes carbon dioxide without oxygenation of blood [17].

## WHEN TO USE ECMO SUPPORT?

Indications for ECMO support are cardiac and/or respiratory failure where despite the use of respiratory therapy and high oxygen concentrations, persistent hypoxemia and hypercapnia pose a threat to further deterioration of the patient's condition, with the possibility of death [5].

It is essential that ECMO should be considered only in cases where the cause responsible for respiratory and/or cardiac failure is potentially reversible [18]. Currently, most cases requiring ECMO support are for patients with cardiac failure and this population continues to rise compared to respiratory failure. In 2018, cardiac indications accounted for 44,5% of all cases (4636 out of 10 423 cases), respiratory indications were 39% (4068 out of 10 423 cases) and extracorporeal cardiopulmonary resuscitation (ECPR) was 16,5% (1719 out of 10 423 cases) (Fig. 4) [18]. ECPR might be a life-saving method in patients with cardiac rupture, in-hospital cardiac arrest or out-of-hospital cardiac arrest [19, 20].

## VV ECMO

VV ECMO provides only gas exchange without cardiac support. According to the Extracorporeal Life Support Organization (ELSO) Guidelines for Adult Respiratory Failure [21], the indications are listed below:

- In hypoxic respiratory failure due to any cause (primary or secondary) ECLS should be considered when the risk of mortality is 50% or greater, and is indicated when the risk of mortality is 80% or greater;

50% mortality risk is associated with a $PaO_2/FiO_2 < 150$ on $FiO_2 > 90\%$ and/or Murray score 2-3, AOI score 60, or APSS score;

80% mortality risk is associated with a $PaO_2/FiO_2 < 100$ on $FiO_2 > 90\%$ and/or Murray score 3-4, AOI > 80, APSS 8 despite optimal care for 6 hours or less; the best outcome in ECMO for adult respiratory failure occurs when ECMO is instituted early after onset (1-2 days);

- $CO_2$ retention on invasive mechanical ventilation despite high plateau pressure (>30 cm $H_2O$);
- Severe air leak syndromes;
- Need for intubation in a patient on lung transplant list;
- Immediate cardiac or respiratory collapse – pulmonary embolism (PE), blocked airway, unresponsive to optimal care.

The Polish recommendations for the use of VV ECMO

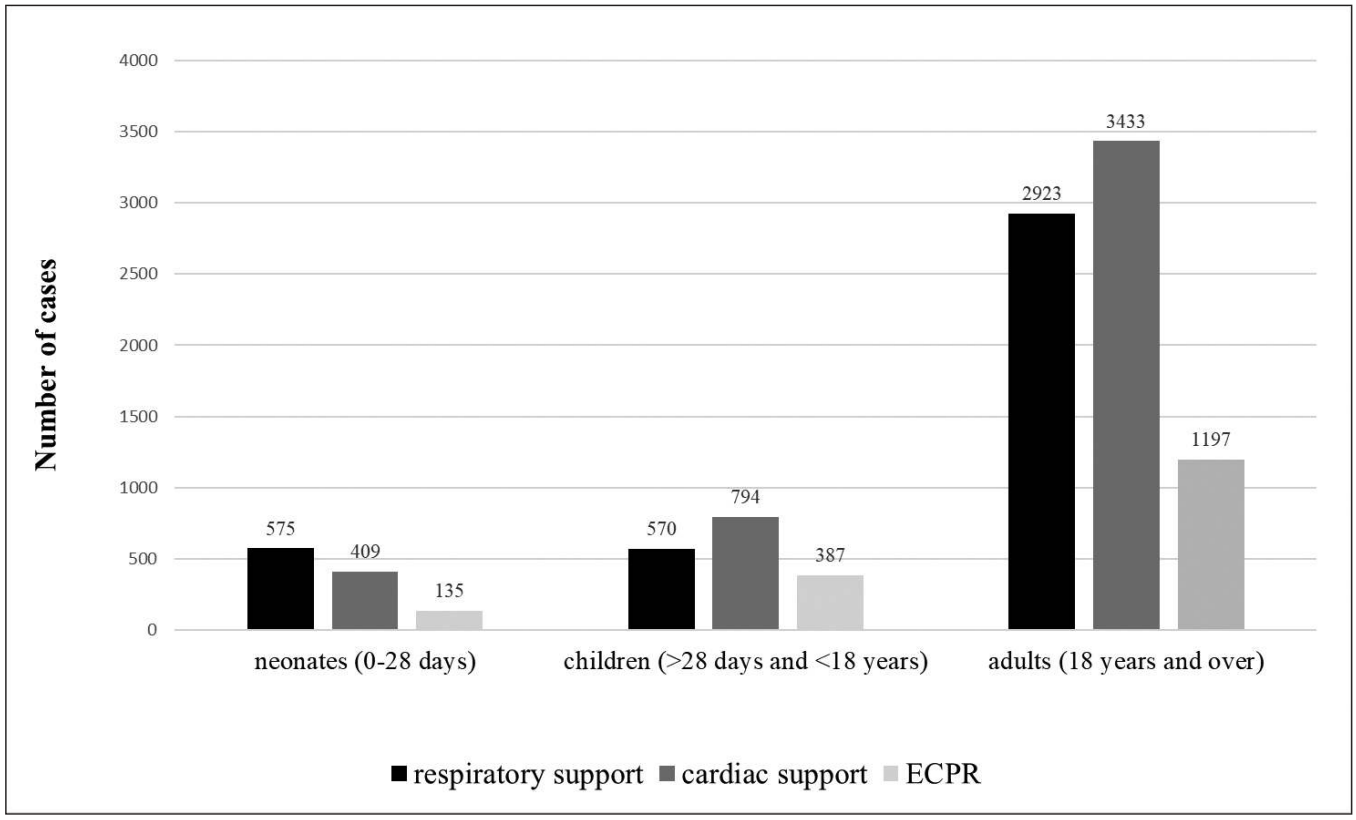


**Fig. 4.** The use of ECMO support in 2018. Based on ECLS Registry Report [18].

have been published by venovenous ECMO Expert Panel in *Anaesthesiology Intensive Therapy* in 2017 [5].

Certain causes of respiratory failure typically have a short acute phase and are associated with good recovery of pulmonary function. Therefore, the probability of a good response to ECMO therapy is high. Examples of these diseases are aspiration pneumonitis, asthma, near drowning, and granulomatosis with polyangiitis [22].

In the vast majority of cases, respiratory causes for the implementation of ECMO in the adult population between 2014 and 2018 have not been accurately classified in the ELSO report and are collectively described as "other" (7 203 cases; 58%). Among the classified causes, the most frequent are: ARDS (1 927 cases; 15%), acute respiratory failure (1 504 cases; 12%) and bacterial pneumonia (960 cases; 8%) [18].

## VA ECMO

Indications for cardiac failure are not as well defined as for respiratory failure. Cardiac indications for ECMO include failure to wean from cardiopulmonary bypass, life-threatening heart failure secondary to myocardial infarction or fulminant myocarditis, and as an adjuvant to conventional cardiopulmonary resuscitation [22].

The following indications are also relevant: support after cardiac surgery or cardiac transplant, acute myocarditis, myocardial infarction, non-ischaemic cardiogenic shock, cardiomyopathy, drug overdose, short-term bridge for heart transplantation or ventricular assist device insertion, support for cardiac catheterisation procedures in high risk patients, catecholamine crisis and circulatory collapse in pheochromocytoma [14, 16].

As in the case of respiratory causes, most of the cardiac causes for the implementation of ECMO in the adult population between 2014 and 2018 have not been accurately classified in the ELSO report and are collectively described as "other" (8 387 cases; 64%). Among the classified causes, the most common cause was cardiogenic shock (3 753 cases; 29%) [18].

## CONTRAINDICATIONS TO ECMO SUPPORT

With the introduction of ECMO therapy, it has raised questions of the ethical nature regarding the exact standards of use.

Contraindications for respiratory and cardiac patients are the same. The benefits and risks of such an invasive method should be considered. Absolute contraindications are severe systemic disease, use of immunosuppressants, intracranial bleeding and other absolute contraindications to anticoagulation. ECMO therapy cannot be used if the respiratory or cardiac disease process is irreversible. In addition, age above 65 is also a reason for disqualification for ECMO support [5, 21].

## MANAGEMENT OF ECMO

Treatment with ECMO support should be used with the close cooperation of anesthesiologists and cardiac surgeons with intensive care nurses and perfusionists [5, 23]. After

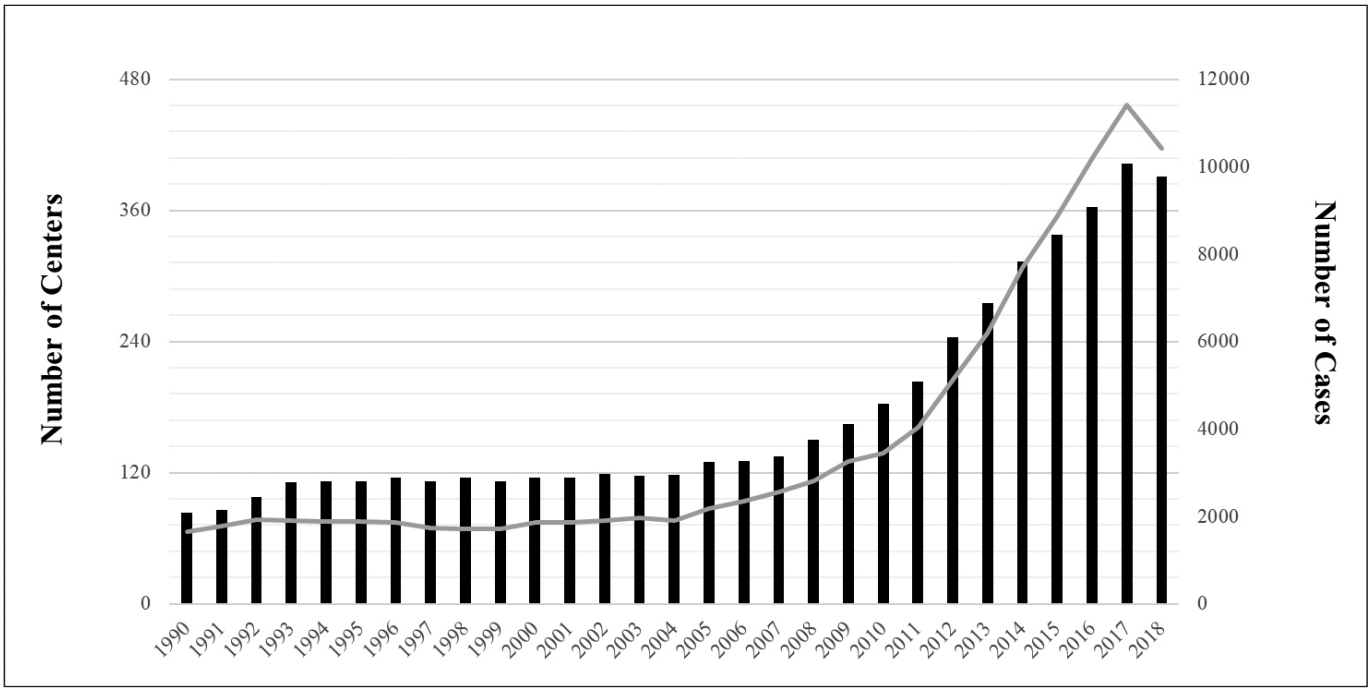


**Fig. 5.** Number of ECMO centers and ECMO cases by year. Based on ECLS Registry Report [18].

cannulation and obtaining the appropriate range of anticoagulation, ECMO is commenced by unclamping the circuit and slowly increasing flows to the target range [24].

The basic parameters that need to be monitored during ECMO treatment are [5]:

- pulse oximetry;
- acid-base balance of arterial blood (at least every 3 hours);
- invasive blood pressure measurement;
- parameters of renal function: creatinine, urea;
- ventilation parameters including ventilatory threshold (VT), respiratory rate (f), fraction of inspired oxygen ($FiO_2$), peak inspiratory pressure (PIP), static compliance, positive end-expiratory pressure (PEEP) – at least twice daily;
- lactate concentration;
- activated clotting time (ACT) or activated partial thromboplastin time (APTT) – no less than every 6 hours; heparin is a standard anticoagulant;
- International Normalized Ratio (INR), partial thromboplastin time (PTT), D-dimers, fibrinogen concentration, antithrombin concentration, number of platelets – once a day;
- chest X-ray – no less than every 3 days, and
- parameters related to the operation of the device should be recorded every hour.

ECMO therapy is interrupted in the following cases [5]: extensive ischemic focus in the central nervous system, massive intracranial bleeding, diagnosis during treatment of another progressive disease preventing the return of respiratory function, and no ability to improve the function of the respiratory system despite long-term therapy or brain death.

## COMPLICATIONS

Treatment outcomes are also linked to therapeutic complications that may occur during the course of ECMO. The most common complications are bleeding (29.3% V-V, 42.9% V-A), requiring transfusion of large amounts of blood products. The bleeding may occur from places where cannulas are inserted and from postoperative wounds. There are frequent internal bleeds to the lungs, digestive tract, mediastinum and abdominal cavity. However, the most dangerous is the bleeding to the central nervous system [25–27].

Infections are another very important complication. Most often they relate to the lower respiratory tract, blood and urinary tract infections. Infections increase the risk of death by 38-63%. They also prolong the stay in the intensive care unit and duration of ECMO therapy. The main causative pathogen is coagulase-negative staphylococci [28]. VA EMCO may result in hypoxia of the upper half of the body. Hypoxemia or electrolyte imbalances sometimes are the reason for arrhythmias. It should also be remembered that there is a risk of air embolism caused by a pump defect or cavitation [14]. In addition, there may be ischemia of the lower limb leading to amputation, the need for renal replacement therapy or neurological complications [25].

## PREDICTIVE SCALES

To reduce the probability of severe and life-threatening complications in patients, various predictive scales have been developed. Based on specific parameters, they help to assess whether the use of ECMO will result in a significant improvement in outcomes. The most common predictive scales used for VV ECMO are ECMOnet score, PRESERVE score, RESP score and PRESERT-Score [21]. All predictive models

were developed retrospectively, without the participation of a control group. The research groups were small and varied. Therefore, they should not be taken as a determinant in deciding whether a patient qualifies for ECMO therapy. Predictive scales should be used to assess the effects of treatment and risk of death. It has been proved that scales such as SAPS II, APACHE and SOFA, used daily in intensive care units, are not useful in the assessment of patients with VA ECMO to assess the severity of the patient's condition [29]. Therefore, there is a need to create a risk assessment model for this therapy. The most important scale is the SAVE score, which is based, like the RESP score, on the ELSO Registry [21].

## CURRENT DATA ON THE FREQUENCY OF USE AND CLINICAL TRIALS

According to the data from the international Extracorporeal Life Support Organization (ELSO) Registry Report, 112 231 patients received ECLS globally (up to January 2019). The majority of patients 40,3% were adults, 37,2% were neonates and 22,5% were paediatric [18]. The most commonly used type of ECLS was respiratory support 54% followed by cardiac support 35% and ECPR 11%.

In the following years, there was a significant increase in the use of ECMO support in adults due to improved equipment and growth of ECMO teams [30]. The global pandemic of the novel influenza A virus was also an important factor because of a higher incidence of ARDS [31, 32]. With the development and spreading of more detailed knowledge about ECMO, within several years in many countries the use of this therapy has increased several times. The number of ECMO centers and ECMO cases in the following years is shown in Fig. 5.

Multi-center randomized CESAR trial published in the Lancet in 2009 compared the use of conventional mechanical ventilation vs ECMO therapy as a treatment for acute respiratory failure. Patients were divided into two groups, the first was ventilated by conventional methods, the second was treated with ECMO therapy. In both cases, data about ICU stay, duration of hospitalization, ventilation parameters, prone position, administration of nitric oxide and steroids were collected. The results of the study showed that in the ECMO group, 6-month survival with good quality of life was higher (63%) compared to the control group (51%) [33].

The latest EOLIA trial, published in 2018, also examined the effectiveness of ECMO venovenous therapy compared to traditional ventilation methods in ARDS [34]. The main cause of acute respiratory failure was bacterial pneumonia (48%) and viral pneumonia (18%). 78% of patients had sepsis or septic shock. The primary end point of the study was mortality at 60 days. In this trial, 149 patients were randomized: 124 in the ECMO group and 125 in the control group. 35 patients in the control group crossed over to the ECMO group because of refractory hypoxemia. In both groups serious complications such as pneumothorax, pneumonia caused by ventilation and severe bleeding occurred. However, patients in the ECMO group had a significantly higher risk of thrombocytopenia and bleeding due to transfusion of packed red blood cells. The most important reasons for the death of patients in both groups were respiratory failure, multi-organ failure and septic shock. Demographic data, severity of ARDS and the center in which patients were treated did not affect mortality. In patients with very severe ARDS who received ECMO therapy early, there was no reduction in mortality within 60 days compared to the conventional mechanical ventilation group. In the ECMO group there was a lower frequency of therapy failure compared to the control group [34].

## CONCLUSIONS

Extracorporeal membrane oxygenation (ECMO) is a method for treating severe but potentially reversible states of cardiac and/or respiratory failure.

Therapy with the use of ECMO does not cure the pathogenic cause of the disease, but it gives the time necessary for the regeneration of inefficient organs. In addition, ECMO reduces or eliminates the risk of lung damage associated with mechanical ventilation in patients with severe ARDS (acute respiratory distress syndrome). ECMO is a very invasive therapy, therefore it should only be used in patients with extremely severe respiratory failure, who failed to respond to conventional therapies.

Initiation of ECMO should be performed in centers with the appropriate experience and requires an organized, coordinated effort.

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**ORCID:**
*Krystian Ślusarz - 0000-0002-7829-530X*
*Paulina Kurdyś - 0000-0001-8154-404X*
*Paul Armatowicz - 0000-0001-5793-0311*
*Piotr Knapik - 0000-0002-1058-1502*
*Ewa Trejnowska - 0000-0003-0279-4935*


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## CORRESPONDING AUTHOR

**Krystian Ślusarz**
Students' Scientific Society,
Department of Cardiac Anesthesia and Intensive Therapy,
Silesian Centre For Heart Diseases,
Medical University Of Silesia, Zabrze, Poland
e-mail: slusarzkrystian@gmail.com



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PRACA POGLĄDOWA
REVIEW ARTICLE

# ELIMINACJA USZKA PRZEDSIONKA LEWEGO W PREWENCJI POWIKŁAŃ ZAKRZEPOWO-ZATOROWYCH U CHORYCH Z MIGOTANIEM PRZEDSIONKÓW

# ELIMINATION OF THE LEFT ATRIAL APPENDAGE IN THE PREVENTION OF THROMBOEMBOLIC EVENTS IN PATIENTS WITH ATRIAL FIBRILLATION

**Urszula Gancarczyk, Tadeusz Przewłocki, Piotr Podolec, Monika Komar**
KLINIKA CHORÓB SERCA I NACZYŃ, INSTYTUT KARDIOLOGII UJ CM, KRAKOWSKI SZPITAL SPECJALISTYCZNY IM. JANA PAWŁA II, KRAKÓW, POLSKA

**STRESZCZENIE**

Migotanie przedsionków (AF) to najczęściej występująca tachyarytmia w populacji osób dorosłych. Powikłania zakrzepowo-zatorowe w przebiegu migotania przedsionków są jedną z przyczyn zwiększonej śmiertelności w tej grupie pacjentów. Doustne leczenie przeciwkrzepliwe istotnie zmniejsza ryzyko tych powikłań, jednak co dziesiąty pacjent ma przeciwwskazania do takiej terapii. Przezskórne zamknięcie uszka lewego przedsionka (LAA) jest skuteczną niefarmakologiczną metodą leczenia pacjentów poprzez eliminację źródła materiału zatorowego. Procedura ta jest wykonywana u pacjentów z wysokim ryzykiem powikłań zakrzepowych i współistniejącymi przeciwwskazaniami do leczenia przeciwkrzepliwego

**SŁOWA KLUCZOWE:** migotanie przedsionków, leczenie przeciwkrzepliwe, zamknięcie uszka lewego przedsionka

**ABSTRACT**

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the adult population. Thromboembolic events are one of the reson of increased mortality in this group of patients. Oral anticoagulation therapy significantly reduces the risk of complications, however every tenth patient has contraindications to this treatment. Percutaneous left atrial appendage occlusion (LAAO) is effective, non-pharmacological method of treatment through elimination the source of thromi. This procedure is dedicated to patients with high risk of thromboembolism events and contraindications to anticoagulation.

**KEY WORDS:** atrial fibrilation, anticoagulation therapy, left atrial appendage occlusion

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## MIGOTANIE PRZEDSIONKÓW

Migotanie przedsionków (AF) jest jednym z największych problemów współczesnej kardiologii, to najczęstsza tachyarytmia, która dotyka ponad 3% populacji osób powyżej 20. roku życia. Częstość występowania AF zwiększa się wraz z wiekiem oraz chorobami współistniejącymi, takimi jak: nadciśnienie tętnicze, choroba niedokrwienna serca, niewydolność serca, przewlekła choroba nerek oraz wady zastawkowe serca i wiąże się z zwiększoną umieralnością ogólną zarówno u kobiet, jak i u mężczyzn [1–3]. Jedną z głównych przyczyn zgonów pacjentów w przebiegu migotania przedsionków są powikłania zakrzepowo-zatorowe, w tym udar niedokrwienny mózgu. Według danych z piśmiennictwa AF jest przyczyną do 30% udarów mózgu, a zachorowania te związane są z gorszym rokowaniem niż w przypadku udarów mózgu o innej etiologii [4, 5].

Do oceny ryzyka wystąpienia powikłań zakrzepowo-zatorowych w przebiegu migotania przedsionków wykorzystywana jest skala CHA2DS2–VASc (***C****ongestive heart failure/ LV dysfunction;* ***H****ypertension;* ***A****ge ≥ 75;* ***D****iabetes mellitus;* ***S****troke;* ***V****ascular Disease;* ***A****ge 65-74;* ***S****ex category)* [6].

U pacjentów z niezastawkowym migotaniem przedsionków (tj. AF niezwiązane z ciężką wadą mitralną /stenoza/), którzy uzyskali w skali CHA2DS2–VASc co najmniej 2 punkty wskazane jest włączenie leczenia przeciwkrzepliwego (klasa I, poziom wiarygodności dowodów A). U osób z tylko jednym (poza płcią) dodatkowym czynnikiem ryzyka (mężczyźni, którzy uzyskali 1 pkt oraz kobiety – 2 pkt w skali CHA2DS2–VASc) należy rozważyć włączenie leczenia przeciwkrzepliwego, rozpatrując indywidualnie u każdego chorego ryzyko powikłań zakrzepowo-zatorowym w przebiegu AF, możliwe powikłania krwotoczne zastosowanego leczenia przeciwkrzepliwego, jak również osobiste preferencje danego pacjenta (klasa IIA, poziom wiarygodności dowodów B) [7]. W przypadku braku dodatkowych czynników ryzyka

(tj. mężczyźni – 0 pkt, kobiety – 1 pkt) leczenie przeciwkrzepliwe jest niezalecane (klasa III) [8].

Oprócz stratyfikacji ryzyka udaru u chorych z AF leczonych lekami przeciwkrzepliwymi należy oszacować ryzyko powikłań krwotocznych. Służą do tego odpowiednie skale, z których najszerzej stosowana jest skala HAS-BLED (***H**ypertension; **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR, **E**lderly, **D**rugs/alcohol*) [9]. Istotna jest przede wszystkim właściwa identyfikacja, a następnie modyfikacja czynników ryzyka powikłań krwotocznych. Sama, nawet wysoka punktacja w wyżej wymienionych skalach nie jest wskazaniem do zaprzestania leczenia przeciwkrzepliwego

W leczeniu przeciwkrzepliwym stosowane są doustne antykoagulanty (OAC – *oral anticoagulant*) do których należą antagoniści witaminy K (VKA – *Vitamin K Antagonist*) – warfaryna i acenokumarol oraz doustne leki przeciwkrzepliwe niebędące antagonistami witaminy K tzw. nowe doustne antykoagulanty (NOAC – *novel oral anticoagulant*) – dabigatran, apiksaban, rywaroksaban i edoksaban [10, 11].

Według wytycznych Europejskiego Towarzystwa Kardiologicznego lekami preferowanymi w grupie pacjentów z niezastawkowym AF, którzy rozpoczynają leczenie przeciwkrzepliwe są NOAC. W metaanalizie 4 badań klinicznych (RELY, ROCKET-AF, ARISTOTLE i ENGAGE AF-TIMI 48) wykazano, że NOAC w porównaniu z VKA (warfaryną) zmniejszają ryzyko zgonu, incydentu zakrzepowo-zatorowego (w tym udaru niedokrwiennego mózgu) oraz krwawienia wewnątrzczaszkowego, zwiększają natomiast ryzyko krwawienia z przewodu pokarmowego [11]. Pomimo możliwych powikłań leczenia OAC, właściwa terapia przeciwkrzepliwa jest podstawą leczenia pacjentów z AF.

## ELIMINACJA USZKA LEWEGO PRZEDSIONKA

Pomimo udowodnionej w wielu badaniach klinicznych skuteczności stosowania OAC w prewencji powikłań zakrzepowo-zatorowych u chorych z AF, przyjmuje się, że około 10% pacjentów ma przeciwwskazania do tego typu leczenia (m.in. z uwagi na przebyte zagrażające życiu krwawienia z przewodu pokarmowego lub do centralnego systemu nerwowego). Ponadto u znacznej grupy pacjentów, z uwagi na złą tolerancję leczenia, leki te nie są stosowane w ogóle lub zamiennie stosowane są leki przeciwpłytkowe, których stosowanie nie zapobiega występowaniu powikłań zakrzepowo-zatorowych, tym samym jest niezalecane (klasa III) [8, 12, 13].

Metodą stosowaną w prewencji powikłań zakrzepowo-zatorowych u pacjentów z AF jest eliminacja/zamknięcie uszka lewego przedsionka (LAA – *left atrial appendage*). LAA to zachyłek lewego przedsionka zlokalizowany przy jego bocznej ścianie, poniżej pnia płucnego (Ryc. 1). Stanowi on pozostałość z rozwoju embrionalnego przedsionka.

U pacjentów z niezastawkowym migotaniem przedsionków przyjmuje się, iż ponad 90% skrzeplin powstaje w LAA. Budowa uszka jest wysoce zmienna pod względem kształtu, wielkości i długości kanałów (*lobs*). W piśmiennictwie istnieje kilka klasyfikacji budowy uszka, z czego najczęściej stosowana jest klasyfikacja, która wyróżnia 4 morfologie:
1. skrzydełko kurczaka (*chicken-wing*),
2. kaktus (*cactus*),
3. rękaw (*windsock*),
4. kalafior (*cauliflower*).

Według danych z piśmiennictwa najbardziej trombogenne uszko ma kształt kalafiora [14–16].

Istnieje kilka sposobów eliminacji LAA m.in chirurgiczne wyłączenie (podwiązywanie) uszka w trakcie zabiegu kardiochirurgicznego lub chirurgicznej ablacji AF, zabiegi torakoskopowe, jak również zabiegi przezcewnikowe (przezskórne).

Metodą o udowodnionej skuteczności jest przezskórne zamknięcie uszka lewego przedsionka (LAAO – *left atrial appendage occlusion*). Zabieg polega na wprowadzeniu przez układ naczyń żylnych (dostęp najczęściej przez żyłę udową) do prawego przedsionka, a następnie przez nakłucie przegrody międzyprzedsionkowej do lewego przedsionka urządzenia (okludera) i jego implantacji w ujście LAA (Ryc. 2).

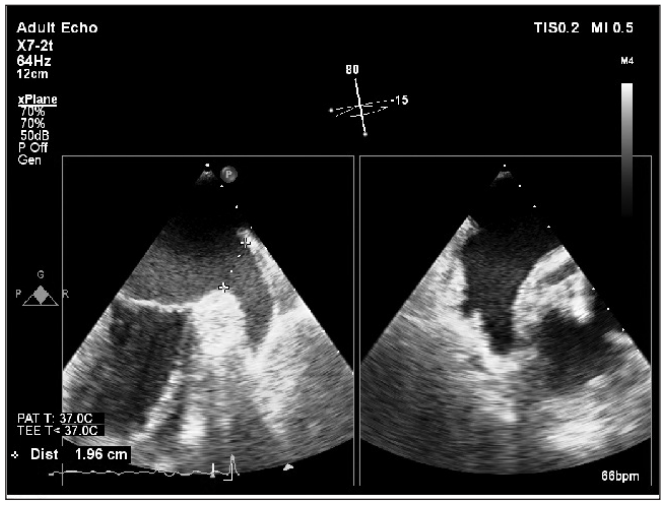
Kluczowym elementem przygotowania i kwalifikacji pacjenta do LAAO jest obrazowanie serca przy pomocy metod nieinwazyjnych, takich jak: echokardiografia przezprzełykowa (TEE) 2D i 3D, tomografia komputerowa z kontrastem (CT) oraz znacznie rzadziej stosowane badanie rezonansem magnetycznym (MR). Badania te służą do oceny morfologii uszka (kształtu, wielkości, położenia względem innych struktur serca), jak również są konieczne do wykluczenia obecności skrzepliny, która stanowi bezwzględne (najczęściej jednak czasowe) przeciwwskazanie do zabiegu. Najczęściej stosowanym badaniem w praktyce klinicznej jest badanie echokardiograficzne przezprzełykowe. Jego właściwe wykonanie pozwala na prawidłowe dobranie rodzaju, jak również wielkości urządzenia.

Zabiegi LAAO są wykonywane w ośrodkach, w których zapewniony jest dostęp do oddziału kardiochirurgicznego. Najczęściej procedura ta jest wykonywana w znieczuleniu ogólnym w trakcie której do monitorowania przebiegu zabiegu oprócz fluoroskopii wykorzystywane jest również badanie przezprzełykowe (Ryc.3).

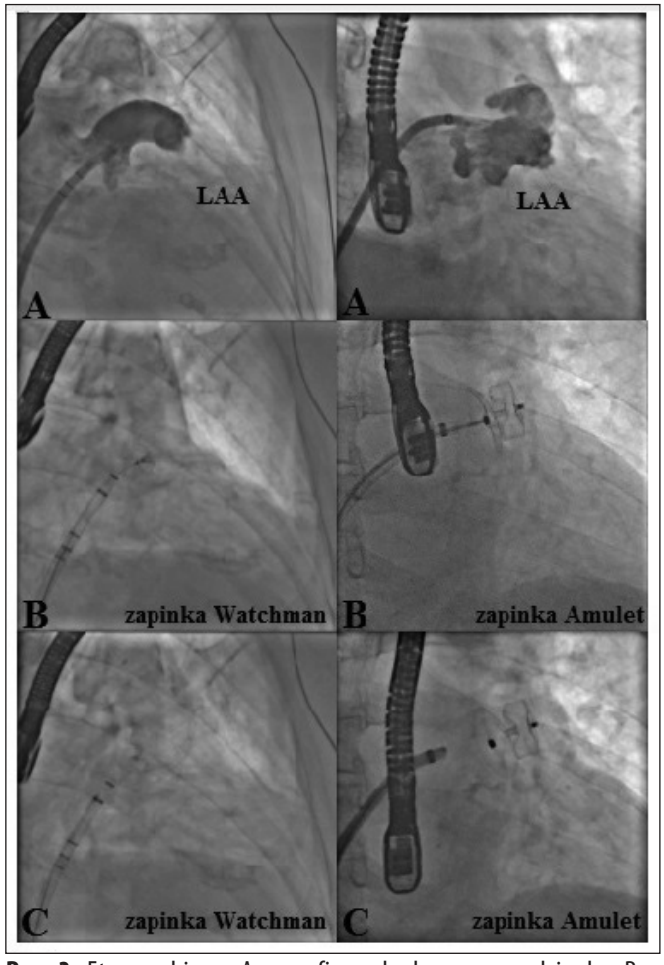
## SYSTEMY DO ELIMINACJI LAA

Istnieje kilka systemów (urządzeń) do tego typu zabiegów. Jedynym, jak do tej pory, systemem o udowodnionej skuteczności w randomizowanym badaniu klinicznym jest zapinka Watchman (Boston Scientific, USA). Urządzenie to zbudowane jest z siatki nitinolowej, której część zamykająca, od strony lewego przedsionka, pokryta jest przepuszczalną membraną z politetrafluoroetylenu.

Zabiegi z wykorzystaniem systemu Watchman są wykonywane w Europie od 2005 roku. W wieloośrodkowym prospektywnym, randomizowanym badaniu klinicznym PROTECT-AF oceniano skuteczność eliminacji LAA przy pomocy zapinki Watchman w porównaniu do warfaryny w prewencji powikłań zakrzepowo-zatorowych w przebiegu AF. Do badania włączono łącznie 707 pacjentów, u 463 implantowano urządzenie, pozostała grupa (244) należała do grupy kontrolnej. Złożony punkt końcowy zdefiniowa-

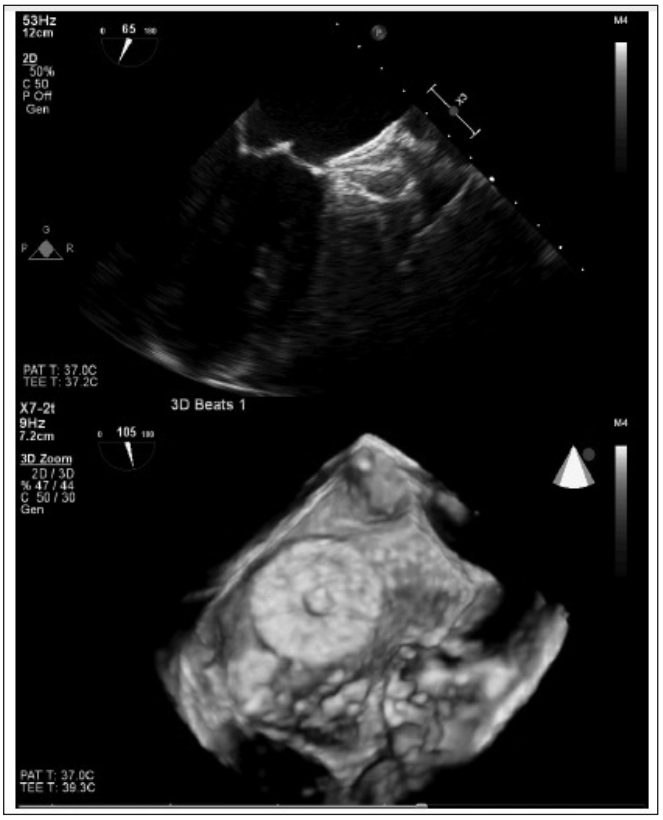



**Ryc. 1.** Uszko lewego przedsionka – badanie TEE.




**Ryc. 3.** Etapy zabiegu: A – grafia uszka lewego przedsionka; B – pozycjonowanie urządzenia w LAA; C – uwolnienie urządzenia.

no jako udar niedokrwienny, zgon nagły lub sercowy, udar krwotoczny oraz zator. W badaniu wykazano, iż eliminacja LAA przy pomocy urządzenia Watchaman jest leczeniem nie mniej skutecznym niż leczenie doustnym antykoagulantem (warfaryną) w zapobieganiu udarom, zatorom oraz zgonom sercowym. Dane z obserwacji odległej wskazują przewagę leczenia zabiegowego nad leczeniem farmakologicznym. Niemniej jednak w trakcie badania obserwowano istotnie wyższy odsetek poważnych powikłań, głównie okołozabiegowych w grupie pacjentów, u których wykonano procedurę (7,4% *vs.* 4,4%) w porównaniu do grupy leczonej zachowawczo [17, 18].




**Ryc. 2.** Badanie TEE – okulder wc uszku lewego przedsionka.

Badanie PREVAIL było kolejnym randomizowanym badaniem oceniającym skuteczność leczenia zabiegowego zapinką Watchamn *vs.* warfaryna. Również i w tym badaniu potwierdzono, iż skuteczne zamknięcie LAA przy pomocy urządzenia Watchman jest leczeniem co najmniej tak skutecznym, jak leczenie warfaryną i wiąże się z mniejszą częstością występowania powikłań krwotocznych u tych chorych w obserwacji odległej. Ponadto wykazano mniejszy odsetek istotny powikłań okołozabiegowych (4,2% w ciągu 7 dni od zabiegu), co wiązano z właściwym trybem szkolenia oraz coraz większym doświadczeniem operatorów [19].

Kolejnym systemem powszechnie stosowanym do przezskórnego zamknięcia LAA jest urządzenie Amplatzer Cardiac Plug oraz druga generacja urządzenia Amplatzer Amulet (Abbott, Abbott Park, IL, USA wcześniej St. Jude Medical, St. Paul, MN, USA). Zbudowany jest z 2 części połączonych talią: część pierwsza – dystalna tzw lobe jest implantowany w ujście uszka, część druga – proksymalna tj dysk pokrywa oraz zamyka wejście do uszka. Skuteczność oraz bezpieczeństwo stosowania systemu wykazano w wieloośrodkowym rejestrze do którego włączono w latach 2008-2013 łącznie 1047 pacjentów. Zabieg wykonano skutecznie u 97,3% osób. Ryzyko okołozabiegowego zgonu wyniosło 0,76%, ryzyko udaru mózgu – 0,86%. Poważne krwawienia wystąpiły u 1,24% pacjentów. W trak-

cie około rocznej obserwacji łączna częstość występowania zatorowości obwodowej wynosiła 2,3% [20]. Aktualnie trwa prospektywne randomizowane badanie kliniczne porównujące urządzenie Amplatzer Amulet i Watchman w zakresie skuteczności leczenia i bezpieczeństwa stosowania.

Metodą pośrednią pomiędzy zabiegiem kardiochirurgicznym a procedurą wewnątrznaczyniową jest zabieg eliminacji uszka lewego przedsionka systemem LARIAT (SentreHeart Inc. Redwood, California, USA). Polega on na założeniu na uszko, od zewnątrz, z dostępu przezosierdziowego pętli wykonanej z nierozpuszczalnego szwu chirurgicznego. Aby prawidłowo umieścić szew, w trakcie zabiegu do światła LAA wprowadza się drogą wewnątrznaczyniową czasowy cewnik z balonem, który ułatwia prawidłowe założenie pętli. Pierwsze zabiegi z użyciem systemu LARIAT zostały wykonane w Krakowie w Klinice Chirurgii Serca, Naczyń i Transplantologii Uniwersytetu Jagiellońskiego 2009 roku [21]. Skuteczność i bezpieczeństwo stosowania tej metody leczenia wykazano w licznych rejestrach i badaniach klinicznych [22, 23].

## WSKAZANIA DO ZABIEGU

W oparciu o aktualnie opublikowane wyniki badań Europejskie Towarzystwo Kardiologiczne zawarło w swoich wytycznych dotyczących leczenia migotania przedsionków zabieg przezskórnego zamknięcia uszka lewego przedsionka jako procedurę dedykowaną pacjentom z niezastawkowym migotaniem przedsionków i wysokim ryzykiem zakrzepowo-zatorowym w celu prewencji udarom mózgu przy współistniejących przeciwwskazaniach do leczenia przeciwkrzepliwego (klasa IIB, poziom wiarygodności dowodów B) [8]. Zalecenia te znalazły się również w dokumencie Asocjacji Interwencji Sercowo-Naczyniowych oraz Sekcji Rytmu Serca Polskiego Towarzystwa Kardiologicznego dotyczącym przezcewnikowego zamykania LAA [24].

W Polsce kwalifikowani do tego typu zabiegu są pacjenci z niezastawkowym migotaniem przedsionków, wysokim ryzykiem powikłań zakrzepowo-zatorowych (punktacja w skali CHA2DS2–VASc ≥3 pkt) ze współistniejącymi przeciwwskazaniami do przewlekłego leczenia przeciwkrzepliwego, którzy ponadto otrzymali pozytywną opinię zespołu sercowego (*Heart Team*) w skład którego wchodzą kardiolog inwazyjny, kardiolog zachowawczy, elektrofizjolog oraz kardiochirurg. Według opinii ekspertów istotną korzyść z wyżej wymienionych zabiegu mogliby odnieść chorzy, których nie uwzględniono w kryteriach refundacyjnych NFZ. Należą do nich m.in. pacjenci z wysokim ryzykiem zakrzepowo-zatorowym i wysokim ryzykiem krwawienia, chorzy którzy pomimo leczenia przeciwkrzepliwego przebyli epizod niedokrwienny (udar mózgu), chorzy z zaburzeniami krzepnięcia jak również z zaawansowaną niewydolnością nerek [24, 25]

## PODSUMOWANIE

Z uwagi na coraz większą częstość występowania AF w populacji ogólnej niezwykle ważne jest prawidłowe wykrywanie i właściwe leczenie pacjentów z migotaniem przedsionków. Kluczową rolę odgrywa tu profilaktyka powikłań zakrzepowo-zatorowych, w tym udaru niedokrwiennego mózgu. Pomimo niezaprzeczalnych korzyści stosowania leczenia przeciwkrzepliwego zarówno antagonistami witaminy K, jak i nowymi doustnymi antykoagulantami, istnieje spora grupa chorych, u których występują istotne powikłania tego leczenia. Zagrażające życiu krwawienia z przewodu pokarmowego czy przebyte krwawienie do centralnego systemu nerwowego istotnie uniemożliwia kontynuowanie stosowanie OAC. Wyniki badań klinicznych udowadniają, że leczenie niefarmakologiczne polegające na przezskórnej eliminacji uszka lewego przedsionka jest równie skuteczne i stanowi alternatywę dla pacjentów z przeciwwskazaniami do leczenia farmakologicznego.

Zabiegi przezskórnego zamknięcia uszka lewego przedsionka wykonywane są w Polsce z sukcesem, od wielu lat w wielu ośrodkach. W opinii ekspertów znacznie większa grupa pacjentów może odnieść potencjalne korzyści z zabiegu niż tylko grupa pacjentów objęta wskazaniami refundacyjnymi.

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**ORCID:**
*Urszula Gancarczyk - 0000-0003-2283-3356*
*Tadeusz Przewłocki - 0000-0002-9575-7270*
*Piotr Podolec - 0000-0001-6101-2935*
*Monika Komar - 0000-0001-5341-2947*



**Konflikt interesów:**
*Autorzy deklarują brak konfliktu interesów.*



## AUTOR KORESPONDUJĄCY

**Urszula Gancarczyk**
Oddział Kliniczny Chorób serca i Naczyń
IK CM UJ, KSS im. Jana Pawła II
ul. Prądnicka 80,31-202 Kraków, Polska
tel: 12 6142287
e-mail: ula.gancarczyk@gmail.com



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PRACA POGLĄDOWA
REVIEW ARTICLE

# OTYŁOŚĆ A OSTEOPOROZA – POWIĄZANIA MIĘDZY TKANKĄ TŁUSZCZOWĄ I KOSTNĄ

# OBESITY AND OSTEOPOROSIS-CONNECTIONS BETWEEN ADIPOSE TISSUE AND BONE.

**Joanna Głogowska-Szeląg[1], Marta Szeląg[2], Mateusz Stolecki[3], Marek Kudła[4]**
[1]ZAKŁAD PATOFIZJOLOGII, KATEDRA PATOFIZJOLOGII I ENDOKRYNOLOGII, ŚLĄSKI UNIWERSYTET MEDYCZNY, ZABRZE, POLSKA
[2]SKN III KATEDRA I ODZIAŁ KLINICZNY KARDIOLOGII, ŚLĄSKI UNIWERSYTET MEDYCZNY, ZABRZE, POLSKA
[3]KATEDRA I ODDZIAŁ KLINICZNY GINEKOLOGII, POŁOŻNICTWA I GINEKOLOGII ONKOLOGICZNEJ, ŚLĄSKI UNIWERSYTET MEDYCZNY, BYTOM, POLSKA
[4]KATEDRA I ODDZIAŁ KLINICZNY PERINATOLOGII I GINEKOLOGII ONKOLOGICZNEJ, ŚLĄSKI UNIWERSYTET MEDYCZNY, TYCHY, POLSKA

**STRESZCZENIE**

Wywodzące się z tej samej tkanki tkanka tłuszczowa i tkanka kostna pełnią zasadniczo różne funkcje, mimo to istnieje dosyć powszechny pogląd, że nadmiar tkanki tłuszczowej może ochronnie wpływać na masę tkanki kostnej zapobiegając utracie masy kostnej i chronić przed rozwojem osteoporozy. Tkanka tłuszczowa jest aktywną endokrynnie tkanką wydzielającą szereg czynnych biologicznie związków mających wpływ także na kość. Adipocyt i osteoblast wywodzą się z wspólnej komórki prekursorowej, w związku z tym zaburzenia wydzielania adipocytokin mogą odgrywać nie tylko rolę w patogenezie otyłości, ale wywierają również różnorodny wpływ na tkankę kostną. Sugeruje to, że otyłość może korzystnie oddziaływać na tkankę kostną kobiet po menopauzie poprzez zwiększenie obciążenia szkieletu osiowego oraz przez aktywność endokrynną tkanki tłuszczowej.

**SŁOWA KLUCZOWE:** otyłość, osteoporoza, tkanka tłuszczowa, kość, powiązania

**ABSTRACT**

The adipose and osseous tissue, although both derived from the connective tissues, perform different functions. In the common opinion, obesity might be a protective factor against bone loss and osteoporosis. The adipose tissue is a recognized major endocrine organ, producing a number of active biological substances, which affect the bone mass. Adipocyte and osteoblast are derived from the same mesenchymal stem cells. Therefore abnormal secretion of adipocytokines may play an important role not only in pathogenesis of the obesity, but also can influence the bone . It is supposed that obesity might have a protective effect on bone tissue in postmenopausal women, by increasing the load on the axial skeleton and because of its hormonal activity.

**KEY WORDS:** obesity, osteoporosis, adipose tissue, bone, connection

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## WSTĘP

Tkanka tłuszczowa i tkanka kostna pełnią zasadniczo różne funkcje, mimo to dość powszechnie uważa się, że nadmiar tkanki tłuszczowej może wpływać ochronnie na masę tkanki kostnej i zmniejszać zagrożenie osteoporozą [1–8].

Tkanka kostna jest wysoce wyspecjalizowaną odmianą tkanki łącznej, w której komórki otacza duża ilość zmineralizowanej substancji międzykomórkowej. Stanowi sztywną podporę kończyn oraz ochrania istotne dla życia narządy jam ciała. Kość jest miejscem dla przyczepu mięśni oraz dużym rezerwuarem niezbędnych do procesów życiowych pierwiastków, takich jak wapń, fosfor, magnez i sód.

Pogląd, iż tkanka tłuszczowa jest biernym magazynem zapasów energetycznych organizmu, zabezpieczającym także przed utratą ciepła [2, 9], zweryfikowało odkrycie w 1994 roku leptyny specyficznego dla tej tkanki peptydu o wielokierunkowych funkcjach biologicznych, należącego do adipocytokin [9]. Adipocytokiny nie tylko auto- i parakrynnie działają na adipocyty, ale także endokrynnie na odległe tkanki i narządy. Tkanka tłuszczowa jest więc organem endokrynnym, wywierającym również różnorodny wpływ na tkankę kostną [1, 2, 9–11]. Ostatnio coraz częściej mówi się też o możliwości zastosowania cytokin tkanki tłuszczowej w terapii osteoporozy [12].

Obecnie wiadomo, że obwodowa tkanka tłuszczowa, będąca tkanką hormonalnie aktywną, może regulować obrót kostny, wydzielając adipocytokiny m.in.: leptynę, adiponektynę czy rezystynę [1, 2, 9, 10, 12]. Ważną rolę we wzajemnej relacji między tkanką tłuszczową a kostną wydają się odgrywać czynniki genetyczne, gdyż zarówno skład tkanek miękkich, jak i niektóre cechy kości, jak: gęstość mineralna, geometria, tempo obrotu kostnego, a nawet ryzyko złamania, mogą mieć wspólne podłoże. Niektórzy badacze szacują wspólne uwarunkowanie genetyczne BMD

i BMI na 10-20% [13]. Za wspólne determinanty uważa się kilka genów kandydatów, w tym insulinopodobny czynnik wzrostu-I (IGF-I), leptynę, receptor dla leptyny, receptor dla estrogenów α oraz interleukinę 6 (IL-6) [14, 15].

Faktem jest, że po menopauzie częściej dochodzi do osteoporozy, jednak nie wszystkie kobiety w tym okresie są nią zagrożone. Spośród klinicznych czynników ryzyka największy wpływ na wielkość BMD mają wiek oraz BMI, z wiekiem bowiem częstość występowania osteoporozy wzrasta, niska zaś masa ciała już jest jej niezależnym czynnikiem [16, 17].

Sugeruje się, że otyłość może korzystnie oddziaływać na tkankę kostną po menopauzie przez zwiększenie obciążenia szkieletu osiowego i kości nośnych oraz endokrynną czynność tkanki tłuszczowej [1, 6–9]. Adipocytokiny wpływają zarówno na stan metaboliczny całego organizmu, jak i na destrukcję tkanki łącznej oraz dysfunkcję narządu ruchu. Menopauza i związane z nią zmiany hormonalne zaburzają funkcję komórek tłuszczowych, jest więc prawdopodobne, że menopauza istotnie wpływa na sekrecję adipocytokin. Wiadomo, że stężenia najlepiej poznanych adipocytokin – leptyny, adiponektyny i rezystyny – pozostają w ścisłej zależności od masy tkanki tłuszczowej i wykazują odmienności u kobiet i mężczyzn [18–21].

## TKANKA KOSTNA

W skład tkanki kostnej (BT – *bone tissue*) wchodzi istota międzykomórkowa zbudo-wana w 25% z części organicznej (osteoid), a w 60–70% z nieorganicznej (sole mineralne). Warstwa korowa, złożona z gęsto upakowanych warstw zmineralizowanego kolagenu, zapewnia sztywność i jest głównym składnikiem trzonów kości długich. Kość beleczkowa (gąbczasta) o porowatej strukturze, wpływa na wytrzymałość oraz zapewnia elastyczność szkieletu osiowego [22]. Dwie trzecie masy kości stanowią składniki mineralne (hydroksyapatyty i fosforany wapnia), resztę zaś woda i kolagen typu I. W tkance kostnej wyróżniamy trzy typy komórek; osteoblasty, osteocyty i osteoklasty, stanowiące tylko 5% jej masy [23]. Osteoblasty to komórki kościotwórcze, które pobudzają tworzenie masy kości i pośrednio pobudzają mineralizację kości. Powstają z komórek mezenchymatycznych. Syntetyzują kolagen typu I, proteoglikany, osteokalcynę i osteonektynę, hydrolazy, białka transportowe, glikoproteinę RANKL oraz osteoprotegerynę. Przez układ osteoprotegeryna–RANKL hamują resorpcję kości. Ponadto produkują czynniki wzrostu IGF-I i TGF-β. Na powierzchni błony komórkowej znajdują się receptory dla hormonów peptydowych, glikokortykosteroidów, czynników wzrostu, w tym IGF-I, witaminy D, serotoniny, leptyny. Dzięki funkcji wydzielniczej i obecności licznych receptorów uczestniczą w kościotworzeniu, a jednocześnie kontrolują proces kościoresorpcji, oddziaływując na dojrzewanie i aktywność osteoklastów [24]. Na czynność osteoblastów wpływają: witamina D, parathormon– (PTH), insulinowy czynnik wzrostu I (IGF –I).

Osteoklasty nazywane są komórkami kościogubnymi, należą do makrofagów wywodzących się ze szpiku kostnego. Nie mają receptorów dla parathormonu (PTH) i witaminy D oraz nie syntetyzują kolagenozy [24]. Są głównymi komórkami uczestniczącymi w resorpcji i remodelingu kości. Rozwój osteoklastów zależy od wielu czynników, w tym obecności ligandu dla czynnika stymulującego wzrost kolonii makrofagów (M-CSF) oraz receptorowego aktywatora czynnika jądrowego NF-κB (RANKL), produkowanego przez osteoblasty i limfocyty T i wiążącego się do swojego receptora (RANK), członka nadrodziny receptorów dla czynnika martwicy nowotworów. RANKL/RANK odgrywa dużą rolę w aktywacji i przeżyciu osteoklastów. Limfocyty B i inne komórki mogą produkować osteoprotegerynę (OPG), która jest antagonistą RANKL i zapobiega osteoklastogenezie [25, 26]. Osteoprotegeryna i RANKL odgrywają kluczową rolę w sprzężeniu między osteo-blastami i osteoklastami i mogą w przyszłości stać się podstawą terapii celowanych, opartych na farmakologicznym zahamowaniu resorpcji kości [27].

Osteocyty należą do ostatecznie zróżnicowanych osteoblastów wbudowanych w zmineralizowaną macierz kostną i stanowią 90% komórek kostnych szkieletu dorosłego człowieka. Odbierają i analizują mikrouszkodzenia oraz zmiany parametrów fizycznych tkanki kostnej, co pozwala na odpowiednie modelowanie kości i jej przebudowę. Podczas ruchu lub codziennego obciążenia hamują działanie osteoklastów i tym samym zachowują masę kostną, natomiast w odpowiedzi na brak obciążenia przekazują sygnał aktywujący osteoklasty, a tym samym resorpcję kości [27].

Główną rolę w patogenezie osteoporozy pomenopauzalnej odgrywa tkanka kostna gąbczasta. U dorosłych znajduje się w nasadach i przy nasadach kości długich oraz wypełnia wnętrze kości płaskiej, stanowiąc około 80% powierzchni kości. Struktura kości gąbczastej jest porowata i lżejsza od kości litej. Wytrzymałość zależy od ilości i grubości beleczek kostnych, szczególnie poziomych. Jej przebudowa przebiega szybciej niż kości litej, stąd zwiększony obrót kostny szybciej będzie powodował zmiany gęstości mineralnej kości, a tym samym szybciej i częściej po menopauzie pojawi się osteoporoza [23]. Drugi rodzaj to tkanka kostna lita zbudowana z blaszek kostnych, które wypełniają jej objętość, stwarzając warunki dużej wytrzymałości na oddziaływanie zewnętrznych sił mechanicznych. Kość zbita to przede wszystkim trzony kości długich, zewnętrzne warstwy nasad i kości płaskich. Zawiera około 80% całej masy mineralnej ludzkiego szkieletu. Spełnia funkcję ochronną i mechaniczną, jej wytrzymałość mechaniczna wzrasta proporcjonalnie do średnicy i grubości kości, a zmniejsza się ze wzrostem porowatości warstwy korowej, co zachodzi podczas procesu starzenia [23], doprowadzając do osteoporozy.

## OTYŁOŚĆ A OSTEOPOROZA

Ostatnie lata przyniosły wzrastające obciążenie społeczno-ekonomiczne dwoma istotnymi problemami – ogromnym rozpowszechnieniem otyłości na całym świecie oraz dużym odsetkiem ludzi dotkniętych osteoporozą w związku ze starzeniem się społeczeństwa. Dotychczas nie łączono występowania obu jednostek chorobowych, gdyż badania udowadniały ochronny wpływ dużej masy ciała na gęstość mineralną kości.

Według przeprowadzonych badań klinicznych, otyłość może korzystnie oddziaływać na tkankę kostną, szczególnie u kobiet po menopauzie [1, 6–9, 22]. Część autorów wręcz podkreśla, iż masa ciała jest głównym determinantem BMD (gęstości mineralnej kości) i tym samym ryzyka złamań, zaś tkanka tłuszczowa ma pełnić w tej relacji podstawową rolę [2].

Opisano rzadsze występowanie osteoporozy pomenopauzalnej u zdrowych, otyłych kobiet – grupę tę charakteryzuje wyższa wartość BMD w obrębie kręgosłupa lędźwiowego L2-L4, nasady bliższej kości udowej i kości promieniowej niż u kobiet szczupłych w zbliżonym wieku [6, 8, 22, 28]. Kobiety otyłe z wtórnymi chorobami powodującymi zwiększony obrót kostny mogą charakteryzować się spadkiem masy kostnej [1, 6, 8]. Większość badaczy wykazała istnienie korelacji między wskaźnikami BMI oraz BMD [4, 5, 6, 8], jednak nie wszyscy są zgodni co do występowania tych zależności oraz lokalizacji tej korelacji [8, 29].

Tkanka tłuszczowa jest aktywna endokrynnie i wydziela szereg czynnych biologicznie związków wpływających także na kość, zaś adipocyt i osteoblast wywodzą się ze wspólnej komórki prekursorowej, w związku z tym zaburzenia wydzielania adipocytokin mogą mieć znaczenie nie tylko w patogenezie otyłości [1, 10, 30]. Metabolizmy tkanki kostnej i tłuszczowej, mimo różnic między nimi, wiążą się za pośrednictwem takich czynników, jak leptyna i inne adipocytokiny [1, 2, 9, 31].

## POWIĄZANIA GENETYCZNE MIĘDZY TKANKĄ TŁUSZCZOWĄ A KOSTNĄ

Między tkanką tłuszczową a kostną istnieją ścisłe zależności, związane m.in. z mechanizmami regulującymi procesy różnicowania oraz dojrzewania adipocytów i osteoblastów. Podstawowym ogniwem łączącym obie tkanki jest wspólne pochodzenie adipocytów i osteoblastów z mezenchymalnej komórki zrębu szpiku kostnego [1, 32]. Osteogeneza i adipogeneza mają wiele wspólnych metabolicznych szlaków. Pobudzenie drogi Wnt/β-katnina hamuje adipogenezę i pobudza osteoblastogenezę, aktywacja zaś PPAR pobudza adipogenezę.

Na powiązania między obiema tkankami wpływają też czynniki genetyczne. Wykazano, że wspólne uwarunkowania genetyczne mają najprawdopodobniej masa tkanki tłuszczowej (BFM – *body fat mass*) oraz BMD – dwa główne, mierzalne wykładniki dwóch chorób cywilizacyjnych, otyłości i osteoporozy. Lokalizacje genomowe znajdują się na: 7p22-p21 (LOD 2.69) dla BFM i BMD kręgosłupa lędźwiowego, 6q27 (LOD 2.30) dla BFM i BMD szyjki kości udowej oraz 11q13 (LOD 2.64) dla BFM i BMD przedramienia [29]. Guerardel i wsp. dowiedli ponadto, że ośrodkowa ekspresja promotora SNP-3608 allelu C genu CART (*cocaine- and amphetamine-regulated transcript*) ma dwojaki charakter: z jednej strony chroni przed otyłością śmiertelną oraz miażdżycą, z drugiej zaś wykazuje korelację z BMD, szczególnie w kości korowej [33]. Kolejnym genem, który coraz częściej jest wymieniany jako czynnik plejotropowy wpływający na rozwój osteoporozy i otyłości, może być receptor aktywator głównego jądrowego czynnika transkrypcyjnego NF-κB – RANK (*receptor activator of nuclear factor-κB*). Może on regulować masę tkanki tłuszczowej i kostnej, ujawniając ekspresję w mięśniach szkieletowych, głównym miejscu wydatkowania energii, i pełniąc zasadniczą rolę w pobudzaniu osteoklastogenezy [34]. W niektórych doniesieniach sugeruje się, że rejon genomu kodujący powstawanie RANK jest także związany z genami kandydatami dla otyłości [34]; RANK ulega interakcji z ligandem (RANKL) i stymuluje osteoklastogenezę [35]. Według Bella, receptor aktywujący czynnik transkrypcyjny NF-κB wraz z ligandem RANKL zarówno pobudza proliferację, jak i hamuje apoptozę osteoklastów [36], co – w opinii innych badaczy – też może wiązać się z otyłością [34,37]. Aktywacja NF-κB jest ponadto manifestacją subklinicznego stanu zapalnego nie tylko w otyłości, ale i innych zaburzeniach metabolicznych (np.w nadciśnieniu tętniczym czy cukrzycy). Masa ciała jest głównym determinantem BMD, a tym samym ryzyka złamań, a masa tkanki tłuszczowej podstawowym elementem tego powiązania [2].

Zazwyczaj uważa się, iż otyłość chroni przed utratą masy kostnej i rozwojem osteoporozy [1, 2, 31], będąc również jednym z czynników redukcji złamań [2]. Niska masa ciała uznana już została za czynnik ryzyka osteoporozy [38]. Ryzyko złamania jest odwrotnie proporcjonalne do BMI, a sama wartość BMI jest wykorzystywana do metody FRAX, oceniającej 10-letnie ryzyko złamania [39].

## WSPÓLNE POCHODZENIE – KOMÓRKI MEZENCHYMALNE

Tkanka kostna powstaje w procesie osteogenezy, polegającym na różnicowaniu się progenitorowych komórek mezenchymy (pochodzenia mezodermalnego) w komórki kościotwórcze – osteoblasty. Różnicowanie jest aktywowane przez czynniki transkrypcyjne, kierujące komórki na dany szlak rozwoju z udziałem cytokin, białek morfogenicznych i hormonów. W różnicowanej komórce ma miejsce proces transkrypcji genów, charakterystyczny dla określonego typu komórki i wytwarzania białek budujących daną tkankę.

Multipotentne komórki mezenchymy mogą różnicować się w komórki pochodzenia mezodermalnego, w skład których wchodzą komórki tkanki kostnej i tłuszczowej – osteoblasty oraz adipocyty. Znajdują się one w szpiku kostnym i wielu tkankach, w tym kostnej i tłuszczowej, wpływając także na odpowiedź immunologiczną dzięki swojemu działaniu przeciwzapalnemu i hamowaniu proliferacji limfocytów [40].

## OSTEOGENEZA

Aktywacja i różnicowanie komórek w osteogenezie podlegają wpływom czynników transkrypcyjnych (TFs – *transcription factors*), cytokin i czynników wzrostu oraz układu endokrynnego [41]. Do głównych czynników transkrypcyjnych odpowiedzialnych za osteoblastogenezę należą Runx2 oraz Osx (Osterix) [42], natomiast PPARγ działa odwrotnie, hamując

osteoblastogenezę i pobudzając multipotencjalne komórki mezenchymalne do rozwoju w kierunku komórek tłuszczowych. Wydaje się, że proces ten może uczestniczyć w starzeniu tkanki kostnej [43]. Tworzenie tkanki kostnej zależy przede wszystkim od białek połączonych receptorem dla LDL5 i/lub LDL6, białka z rodziny *frizzled*, białka Wnts (agonista) i działających przeciwnie sklerotyny i białka Dickkopf). Za różnicowanie osteo-blastów do osteocytów odpowiadają głównie sklerotyna, periostyna oraz czynnik wzrostu fibroblastów [41, 42].

Osteoklasty podlegają kontroli nie tylko specyficznych białek TFs (PU.1, Fos) i czynnika jądrowego aktywowanych limfocytów, ale także obecności układu RANKL–OPG osteoosteoprotegeryna [44, 45]. Za procesy homeostazy tkanki kostnej odpowiada system RANK–RANKL (*receptor activator of NF-κB–receptor activator of NF-κB ligand*). Ligand RANKL jest cytokiną aktywującą osteoklasty, a tym samym wpływającą na kościoresorpcję. Białko OPG wiąże i tym samym neutralizuje RANKL, co skutkuje zahamowaniem kościoresorpcji [27, 45]. Istotną rolę w procesie osteogenezy odgrywają ponadto białka morfoge-niczne (BMPs – *bone morphogenic proteins*), które inicjują różnicowanie komórek mezenchymalnych w kierunku osteoblastów [41]. Do białek tworzących kość należą: osteopontyna, osteokalcyna, osteonektyna oraz kolagen.

Należy pamiętać, że warunkiem prawidłowego dojrzewania i mineralizacji tkanki kostnej są estrogeny, które działając na chondrocyty mogą wpływać na sekrecję zewnątrzkomórkowej macierzy chrząstki. Osoby z mutacjami receptorów estrogenowych bądź upośledzoną syntezą estrogenów charakteryzują się opóźnionym zamknięciem nasad kostnych i osteopenią. Również androgeny są niezbędne do normalnego wzrostu i mineralizacji kości długich [46]. Późniejszy wiek pierwszej miesiączki u kobiet zdrowych, wiążący się z krótszym wpływem estrogenów na tkankę kostną, objawia się uzyskaniem niskiej gęstości mineralnej kości i zmniejszeniem grubości dystalnej części kości promieniowej, co z czasem może predysponować do złamań [47, 48].

## PODSUMOWANIE

Dotychczasowe badania wykazały ochronny wpływ wysokich wartości BMI na tkankę kostną. Można więc przyjąć, że nadwaga i otyłość, z uwagi na zwiększenie obciążenia kości oraz produkty tkanki tłuszczowej są czynnikami chroniącymi przed osteoporozą i wynikającymi z niej złamaniami [1, 6, 8, 38, 49, 50]. Dodatnia zależność między masą ciała a BMD nie oznacza jednak, że otyłość chroni przed osteoporozą, ponieważ otyłość to przede wszystkim nadmierne nagromadzenie tkanki tłuszczowej, a nie tylko przekroczenie norm wartości BMI.

W piśmiennictwie doniesienia na temat zależności między BMD a masą ciała są rozbieżne. Część badań podaje, że już u kobiet premenopauzalnych masa tkanki tłuszczowej jest determinantą BMD [2, 51], w innych zależności takiej nie potwierdzono, a wręcz wskazano na zwiększenie ryzyka rozwoju osteoporozy i złamań niskoenergetycznych [52]. Także u kobiet po menopauzie nie określono jednoznacznie związku między tkanką tłuszczową a kostną oraz ich wpływu na rozwój osteoporozy [10].

Przytoczone wątpliwości dotyczące związków tkanki kostnej i tłuszczowej wymagają wyjaśnienia, tym bardziej, że okres pomenopauzalny charakteryzuje się odwrotną tendencją niż przedmenopauzalny, charakteryzując się spadkiem BMD i jednoczesnym wzrostem masy tkanki tłuszczowej. Poznanie zmian zachodzących w tym okresie wydaje się bardzo istotne.

Mimo niewątpliwego postępu w poznaniu etiopatogenezy oraz diagnostyki i terapii osteoporozy, nie rozwiązano jeszcze wielu niejasności. Najważniejszym celem postępowania nadal pozostaje redukcja częstości złamań, a w przypadku ich wystąpienia – zapobieganie kolejnym. Choć możliwości terapeutyczne są już dość szerokie, poszukuje się nowych kierunków, w tym coraz częściej wśród nowych terapii wymienia się hormony tkanki tłuszczowej – adipocytokiny [10].

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**ORCID:**
*Joanna Głogowska-Szeląg - 0000-0003-0949-322X*

**Konflikt interesów:**
*Autorzy deklarują brak konfliktu interesów.*

## AUTOR KORESPONDUJĄCY
**Joanna Głogowska-Szeląg**
Zakład Patofizjologii, Katedra Patofizjologii i Endokrynologii
Śląski Uniwersytet Medyczny
Pl.Traugutta2,41-800 Zabrze, Polska
e-mail:jglogowska-szelag@sum.edu.pl

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PRACA POGLĄDOWA
REVIEW ARTICLE

# LEGAL REGULATION OF PROFESSIONAL OBLIGATIONS OF PHYSICIANS IN UKRAINE

**Yuriy Baulin[1], Borys Rohozhyn[2], Inna Vyshnevska[1]**
[1]YAROSLAV MUDRYI NATIONAL LAW UNIVERSITY, KHARKIV, UKRAINE
[2]KHARKIV MEDICAL ACADEMY OF POSTGRADUATE EDUCATION OF THE MINISTRY OF HEALTH OF UKRAINE, KHARKIV, UKRAINE

## ABSTRACT

**Introduction:** It was identified that one of the priorities of medical reform in Ukraine is the establishment of an effective system of legal regulation of professional physician's obligations that meets European standards. However, the legal regulation of relations between actors in the field of health care lags behind the practice of their development.
**The aim** to find out the status of legal regulation of the professional obligations of health workers, to identify the gaps in this regulation, to formulate proposals for improving the legal framework for the issue under investigation.
**Materials and methods:** Legislation of Ukraine and certain European countries, international declarations and conventions, scientific works, 28 judgments of the European Court of Human Rights, 96 sentences of the practice of the national courts of Ukraine.
**Conclusions:** During the study, the stages of determining the professional physician's obligations were singled out, which would optimize the legislative process of regulation of obligations. One of the problems is the incorrect translation of protocols, which is assigned to a medical care institution. It was proposed to solve this problem by introducing a unified system of protocols and standards, the duty of translation and adaptation of which is entrusted to the central body of executive power in the field of health care. It is relevant to consolidate the duty of medical records management at the level of law, which will serve as a guarantee of ensuring the proper performance by the physician of a professional obligation to treat and diagnose a particular patient. In order to avoid cases of judgments, based on the results of the commission's assessment of the actions of a physician and to eliminate the number of cases of unjustified attraction of physicians to liability, it is necessary to consolidate a clear list of general professional physician's obligations in a single regulatory act.

**KEY WORDS:** medical law, physician, professional obligations

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## INTRODUCTION

The structural transformation of the health care system in Ukraine was initiated by the adoption by the Verkhovna Rada of the Law of Ukraine "On State Financial Guarantees for the legal and regulatory framework for governing the activities of physicians. In particular, the implementation of market relations caused significant changes in the interaction of patients, the state, medical institutions, namely, health-care providers and medical personnel, who offer medical services.

At the time of the medical reform in Ukraine in 2018, the autonomization of the primary health-care was implemented and a new list of primary health-care services and new requirements for the equipment of primary health-care services were approved.

However, the legal regulation of relations between actors in the field of health-care and, accordingly, the formalization of these relations substantially lags behind the practice of their development. This may be the basis for legal and social conflicts in the provision of health services.

The need for a high-quality legal regulation of the professional obligations of a health worker in Ukraine needs clear and precise legal regulation. Taking into account the path of Ukraine to the European Union, the experience of European countries in this area requires the bringing of Ukrainian national legislation to EU standards.

## THE AIM

To find out the status of legal regulation of the professional obligations of health workers, to identify the gaps in this regulation, to formulate proposals for improving the legal framework for the issue under investigation.

## MATERIALS AND METHODS

Laws of Ukraine, orders of Ministry of Health of Ukraine, legislation of certain European countries, Declaration of Helsinki of the World Medical Association (hereinafter - WMA), the Universal Declaration of Human Rights and Bioethics, the European Convention on Bioethics and Human Rights, scientific works, 28 judgments of the European Court of Human Rights, 96 sentences of the practice of the national courts of Ukraine.

This article is based on dialectical, comparative, analytical, formal-logical, statistical and complex research methods.

## REVIEW AND DISCUSSION

1. Provision of quality medical services is one of the most important components of a full-fledged life of society, which is why the activities of the doctor are subject to clear legal regulation. An analysis of the existing regulatory framework governing health-care services makes it appropriate to draw the conclusion that legal regulation covers the period from the training of a medical student to the direct provision of medical services as a doctor. This period can be divided into the following stages, which are subject to legal regulation: 1) acquiring the status of a doctor; 2) the admission of a physician to the provision of medical services; 3) establishment of professional obligations of a doctor; 4) the implementation of commitments by a doctor; 5) the responsibility for the non-implementation of the doctor's professional obligations. This article examines the stage of legal regulation of the establishment of professional obligations of a doctor.

The synthesis of 96 court's decisions regarding the non-provision of health-care to a sick person by a medical worker and improper fulfillment or non-fulfillment of professional obligations by a medical worker revealed that the main violations in the professional activity of a doctor are: 1) the absence of a corresponding certificate of a specialist physician in providing health-care services; 2) non-fulfillment of the professional obligation imposed on a doctor in providing health-care services; 3) delay and untimely provision of health-care services; 4) incorrect assessment of the patient's condition, which led to serious consequences in the form of deterioration of the patient's health or death; 5) the inattention of a physician during medical procedures or rapid medical intervention; 6) failure to comply the requirements of the standards and treatment protocols of diseases; 7) filling in the documentation regarding the state of health of a patient in violation of the requirements.

An analysis of the court practice has revealed that the violation of the standards for providing health-care services and job descriptions by a doctor is most common. As an example, the verdict of Cherkasy court can be mentioned, which found guilty an anesthesiologist of improper performance of professional obligations, which led to the death of the patient. During the resuscitation, the anesthesiologist did not carry out careful monitoring of the patient's condition and, due to his careless attitude to his professional duties, introduced into the body of the patient «Lidocaine», the introduction of which was not foreseen at that stage of treatment, which caused the death of the patient [2].

The overcoming of the problems that are currently taking place in the provision of medical care services by a doctor requires a clear definition in the national legislation of the professional obligations of a medical worker.

2. To apply for a doctor's post and to provide medical services in the future can a person, who has medical education, finished the internship and received a certificate of a specialist doctor. Following the implementation of these requirements, a person receives the right to practice medical activity by concluding an employment contract, in which one of the main conditions is the determination of the responsibilities of the medical officer, which are divided into general and special professional obligations.

G. Alcheva notes that the rights of patients and doctors are interdependent and give rise to obligations on both sides. This particular conformity of the rights and duties of doctors and patients supports the provision of medical care of the proper quality [3, p. 22].

General professional duties are mandatory for all doctors, regardless of their specialization, and provided for by national regulatory legal instruments and international instruments, namely: 1) by the laws of Ukraine, for example, the Fundamentals of Health Legislation of Ukraine (hereinafter - Fundamentals); «On Emergency Medical Aid», etc.; 2) by the international instruments, namely: the Lisbon Declaration on Human Rights, etc.; 3) by the subordinate regulatory legal instruments (decisions of the Cabinet of Ministers of Ukraine, orders and instructions of the Ministry of Health of Ukraine, etc.); 4) by the local regulatory legal instruments - acts adopted at the level of a medical institution.

The Lisbon Declaration on Human Rights and in the Clause 4 of the Helsinki Declaration of the WMA establish the basic principles of the work of the doctor, which should be aimed at supporting and protecting the health of a patient, taking into account the legal, ethical and practical norms of the country in which a doctor practices the medical activity [4, 5].

The International Code of Medical Ethics of the WMA divides professional duties of the doctor into general, concerning sick and in relation to others. According to the Code general responsibilities are as follows: to adhere the highest standards of professional activity; to provide competent medical aid with full technical and moral independence, etc.

The professional obligation of a physician for patients are as follows: to provide the patient with all the resources of his or her science; If the doctor is unable to conduct an examination or treatment, he must engage another physician, who has such facilities; to guarantee medical confidentiality and a number of other responsibilities.

The list of duties of the physician in relation to others includes the regulation of the relationship between doctors in the exercise of their professional activities and the obligation to adhere to the principles of the Geneva Declaration, adopted by the General Assembly of the WMA [6]. To a certain extent, these responsibilities have found their consolidation in the Fundamentals [7].

3. Particular attention should be paid to the professional obligation, holding any medical intervention with the implementation of professional requirements and standards, which is enshrined in Art. 4 of the Convention on the Human Rights and Dignity in connection with the Application of the Achievements of Biology and Medicine [8].

This obligation is enshrined in the Methodology for the development and implementation of medical standards of medical care on the principles of evidence-based medicine, which states that in the absence of a unified clinical protocol in the national system of standards, a health worker must apply a new clinical protocol if it is translated into Ukrainian and approved by the Ministry of Health. If the

protocol is set out only in English then its choice, translation and application are carried out in accordance with the order of the medical institution [9].

Analyzing the above-mentioned legislative provision, it is possible to distinguish several issues that arise in medical officers when establishing and fulfilling this duty. New clinical protocols are often not adapted for use in Ukraine, since there are difficulties with the use of medicine or their components when treated under a new protocol due to their absence on the territory of Ukraine. The same applies to technical support for the use of new methods and methods of treatment, since the level of technical equipment of health facilities in most areas is quite low. These circumstances may threaten the proper use of new protocols without their prior adaptation to Ukrainian realities.

When analyzing a medical error, O. Gornostay and other scientists note that one of the most important professional duties of a doctor is the implementation of protocols and standards for the provision of medical care, but the implementation of this duty in practice is complicated by the lack of translations of international protocols and standards; by the politicization and ideologization of national protocols, and by the primitivism of local protocols [10, p. 880].

Taking into account the experience of health care systems of foreign countries, it seems appropriate to create a regulatory framework that would include a system of quality assurance of medical care, an important element of which is the approval and implementation of national quality standards for medical care.

4. A medical officer's obligation is important in order to provide the patient with accessible information about the state of health, the purpose of medical treatment and the forecast of the possible development of the disease, in particular the risk to life and health. This duty is also enshrined in Art. 9 of Helsinki Declaration of the WMA, Art. 39 of Fundamentals, paragraph 3.6. The Ethical Code of the Doctor of Ukraine and other regulatory legal instruments.

Such violations became subject for consideration by the Constitutional Court of Ukraine, which in its decision noted that medical information in its legal regime belongs to confidential information, which the doctor is obliged not to disclose. However, there is an exclusion from this obligation, namely, the physician is obligated to provide such information in full and in an accessible form at the request of a patient, his family members or legal representatives [11].

The European Court of Human Rights assesses the refusal to provide the patient with medical records regarding his health as a violation of Art. 8 of the Convention for the Protection of Human Rights and Fundamental Freedoms. An example of the jurisprudence on this issue is the decision of the ECHR «K.N. and others against Slovakia». When establishing violation of Art. 8 of the Convention, the Court noted that the State has a positive obligation on the granting a person access to the documentation and records relating to the state of his or her health. The state is obliged to provide conditions for the copying of documents containing personal data, or, as appropriate, to provide compelling reasons for the refusal of such copying [12].

5. It is mandatory to obtain patient consent for any medical intervention for preventive, diagnostic or therapeutic purposes, which is enshrined in Article 6 of the Universal Declaration of Human Rights and Bioethics[13]. The mentioned professional duty of the doctor was embodied in Art. 43 of Fundamentals. As an exclusion from this rule, the article stipulates that consent of the patient is not required in the case of presence of signs of a direct threat to the patient's life, provided that it is impossible to obtain consent for such an intervention from the patient or his legal representatives for objective reasons.

M. Pashkovska notes that during the provision of medical services, some doctors violate the requirements for obtaining consent of the patient. Such violations are that: 1) doctors provide individual medical services without the consent or with consent of an incapacitated or partially capable person; 2) the consent is formalized without complying with the formal requirements; 3) the consent was given long before the provision of medical services, without proper informing of the patient about the order of providing such services or about the potential risks and consequences; 4) the consent was not given by the person voluntarily [14, c. 1241-1242].

In the decision of «M.A.K. and R.K. against the United Kingdom», the ECHR found the violation of Art. 8 of the Convention for the conduct of medical examination, blood sampling for the analysis and implementation of photo fixation of the wound of the child without the consent of the parents, as required by national law. Taking into account the circumstances of the case, the Court did not establish any justification because it was decided to take a blood test and make personal photos of a nine-year-old girl, contrary to the clearly expressed will of both of her parents, while she was in the hospital alone [15] .

6. The timely and proper filling (registration) of the medical card of the patient is also one of the general professional obligation of the doctor. The experience of consolidation such a duty at the regulatory level exists in Germany, where, in accordance with Clause 2 § 630f of the German Law on Patient Rights, it is foreseen that the physician who carries out the treatment of the patient is obliged to record in the patient's medical card all measures, processes and results, in particular, anamnesis, diagnosis, examination, results of examination, therapies and their consequences, interventions and their consequences [16].

In Ukraine, this obligation is enshrined in the Instruction on filling in the form of primary records «Medical card of the in-patient» [17]. Pashhkovskaya notes that the medical records that the physician records during the patient's treatment is one of the main evidence in the litigation against the doctor. That is why the doctor is obligated to keep records in compliance with the legal form and in accordance with the requirements of the law [18, p. 1621].

It is relevant to consolidate this obligation at the level of the law, since medical records are important in the provision of medical services to the patient, and is one of the guarantees of the proper implementation of the doctor's professional obligation to treat and diagnose a particular patient.

A prime example of the use of medical records as an evidence in criminal proceedings can be the verdict of Berdychiv City Court. The surgeon focused only on the disease of the lower extremities and did not pay attention to the physical state of the patient's health, namely, heart disease, which led to the death of the patient during treatment. During the inspection, it was discovered that the surgeon did not perform a daily review of the patient and did not fulfill the medical documentation. Taking into account the circumstances of the case, the court found the surgeon guilty of improper performance of professional duties and sentenced him to deprivation of the right to practice medical activity for 4 years [19].

On the basis of the human right to proper medical care, N. Gutorova, O. Zhitniy and O. Solovyov single out such a duty of the doctor as the use of safe and high-quality medicine in the provision of medical care, which is one of the obligatory components of an effective system of health protection I [20, p. 856].

7. Taking into account that the general professional duties of doctors in Ukraine are enshrined in normative legal acts of various legal force, in order to ensure legal certainty in the conduct of medical activities, it is relevant to establish in the Fundamentals an exhaustive list of professional duties of a medical officer, which include the following: 1) to contribute the protection and strengthening of human health, prevention and treatment of diseases, provide timely and high-quality medical care ; 2) to provide appropriate emergency medical care to citizens in the event of an accident and other extreme situations free of charge; 3) to carry out medical activities in accordance with the received certificate of a specialist doctor; 4) to conduct timely and qualified examination and treatment of the patient in accordance with the standards, instructions and protocols of diagnosis and treatment; 5) to explain to the patient in an accessible form the state of his health, the purpose of the proposed research and medical measures, a forecast of the possible development of the disease, including the existence of a risk to life and health; 6) to obtain the consent of the patient for medical intervention for preventive, diagnostic or therapeutic purposes; 7) to provide medical care in full to a patient who is in a state of danger to life; 8) to record the state of health and medical treatment of the patient, reflect the changes in the patient's condition (deterioration, improvement, complete recovery) and the whole process of medical treatment or rehabilitation during receiving inpatient care; 9) to adhere to the requirements of professional ethics and deontology, to keep confidential information, except the cases stipulated by the legislative acts, which became known in connection with the performance of professional or official duties about the disease, medical examination and its results; 10) to increase the level of professional knowledge and skills constantly, to study new methods of treatment; 11) to provide advisory assistance to the colleagues and other health care workers; 12) to disseminate scientific and medical knowledge among the population, to promote a healthy lifestyle.

8. Special professional obligations of a doctor are such obligations, the exhaustive list of which is individualized for each doctor depending on his specialty and the specific position he or she occupies in a medical institution. The list of special professional duties of a doctor of a certain specialty is provided by subordinate and local acts. In particular, these include the orders of the Ministry of Health of Ukraine regarding certain types of medical activities, as well as job descriptions, which specify the professional obligations of a specialist doctor on his or her position. By a guide to the qualification characteristics of professions of medical workers was established requirements for the level of knowledge of the specialist doctor, his or her tasks and responsibilities and qualification requirements [21].

## CONCLUSIONS

Creation of an effective system of legal regulation of professional physician's obligations that meets European standards is one of the priority directions of improvement of Ukrainian legislation in the field of health-care services.

The systematic approach to the legal regulation of the professional obligations of health-care officers makes it possible to balance public interest in the provision of high-quality treatment and the individual interest of a physician who is interested in clearly defined professional obligations.

According to the results of the analysis, the imperfect regulation of the procedure and standards of the provision of medical care and the lack of proper regulation of the physician's professional obligations not only impair the quality of the provision of medical services, but also lead to the unjustified attraction of the physician to liability.

In order to solve these problems, it is necessary, to systematize health-care service legislation, to establish a clear list of general professional obligations of the physician and criteria for the quality of the provided medical care, which can allow to avoid subjectivity in evaluating the actions of the physician during the provision of medical care services and will reduce the number of cases of unjustified attraction of physicians to liability.

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## CORRESPONDING AUTHOR
**Yuriy Baulin**
The Department of Criminal Law
Yaroslav Mudryi National Law University, Kharkiv, Ukraine
Pushkinskaya str., 77, 61024 Kharkiv, Ukraine
tel: +380951406024
e-mail: innavish12@gmail.com

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PRACA POGLĄDOWA
REVIEW ARTICLE

# KIŁA JAKO CHOROBA ZAKAŹNA – ASPEKTY PRAWNE

## SYPHILIS AS AN INFECTIOUS DISEASE – LEGAL ASPECTS

**Małgorzata Paszkowska**
WYŻSZA SZKOŁA INFORMATYKI I ZARZĄDZANIA W RZESZOWIE, RZESZÓW, POLSKA

**STRESZCZENIE**

Choroby zakaźne stanowią poważny problem społeczny. Od kilku lat w Polsce zauważalny jest wzrost zachorowań na kiłę. Jest to choroba zakaźna i jako taka podlega regulacjom prawnym. Kiły dotyczą ogólne(takie jak wszystkich chorób zakaźnych) oraz szczegółowe regulacje ustawowe. Przedmiotem artykułu jest przedstawienie polskich regulacji prawnych dotyczących kiły jako choroby zakaźnej. Celem szczegółowym artykułu jest przedstawienie i analiza obowiązków lekarza dotyczących rozpoznania(podejrzenia) kiły.

**SŁOWA KLUCZOWE:** choroba zakaźna, lekarz, obowiązki, przymus

**ABSTRACT**

Infectious diseases are a serious social problem. For several years, there has been an increase in syphilis in Poland. It is an infectious disease and as such is subject to legal regulations. Common (such as all infectious diseases) and detailed statutory regulations apply to syphilis. The subject of the article is the presentation of Polish legal regulations on syphilis as an infectious disease. The specific objective of the article is to present and analyze the doctor's duties regarding the diagnosis (suspicion) of syphilis.

**KEY WORDS:** infectious disease, doctor, duties, coercion

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## WSTĘP

Choroby zakaźne towarzyszyły człowiekowi od samego początku. W XX i XXI wieku w krajach rozwiniętych opanowano większość chorób zakaźnych, jednakże poważnym problemem stały się oporne na działanie antybiotyków szczepy drobnoustrojów, a także pojawiające się nowe schorzenia wywoływane przez nieznane lub nierozpoznane do tej pory patogeny. Rozprzestrzenianie się chorób zakaźnych stanowiło i stanowi poważne zagrożenie dla zdrowia całej populacji. Rozwój cywilizacji wpływa m.in. na upowszechnienie turystyki zagranicznej oraz migracje ludzi, a tym samym zwiększa się ryzyko rozprzestrzenienia chorób zakaźnych. Jedną z chorób, na której rozprzestrzenienie mają praktyczny wpływ także migracje transgraniczne jest kiła (łac. lues, syphilis) – ICD-10:A50-A53. Kiła występowała dawniej pod wieloma różnymi nazwami: syfilis, choroba francuska itd. Powszechnie przyjmuje się, że historia kiły wiąże się z wyprawami Krzysztofa Kolumba do Nowego Świata w 1492 roku podczas, których jego marynarze powszechnie współżyli z Indiankami. Po powrocie Kolumba do Barcelony, w roku 1495, wybuchła wielka epidemia nieznanej choroby i zdziesiątkowała wojska francuskie króla Karola VIII podczas oblężenia Neapolu [1]. Jednakże najnowsze(z 2015 roku) badania naukowców z Wiednia podważają tę teorię. Istnieje bowiem także kiła wrodzona, a ostatnio odkryto, że jej przypadki występowały już w 1320 roku. Pod koniec XV wieku kiła zaczęła szerzyć się epidemicznie. W Polsce pierwsze przypadki syfilisu zauważono już w tym samym czasie co w Neapolu (1495). W roku 1905 dwaj niemieccy mikrobiolodzy: Fritz Schaudin i Erich Hoffmann wyizolowali czynnik epidemiologiczny kiły tj. krętka bladego (*Treponema pallidum*), a rok później Wassermann opracował pierwsze serologiczne metody rozpoznawania zakażenia kiłowego (tzw. Odczyn Wassermanna) [2]. Na kiłę chorowali znani ludzie, m.in.: polscy królowie Jan Olbracht, Stefan Batory i Jan III Sobieski, malarze Henri de Toulouse-Lautrec i Paul Gauguin oraz pisarze Stanisław Wyspiański, Charles Baudelaire, Guy de Maupassant i Heinrich Heine. Obecnie obserwuje się stałe narastanie częstości nowych zachorowań w Polsce i na świecie, wzrasta także liczba przypadków kiły wrodzonej u noworodków.

Kiła to przewlekła ogólnoustrojowa choroba, wywołana przez drobnoustrój (bakterię Gram ujemną) krętek blady (łac. *Treponema pallidum*). Cechuje ją bogata symptomatologia kliniczna i wielofazowy przebieg [3]. Do zakażenia dochodzi głównie drogą kontaktu płciowego z osobą zakażoną lub przez łożysko. Do zakażenia krętkiem bladym może dojść przez: uszkodzoną skórę, uszkodzone błony śluzowe, bezpośrednio przez krwiobieg (przez ciężarną matkę na płód). Powszechnie wyróżnia się: kiłę wczesną (trwającą do 2 lat od zakażenia) oraz kiłę późną (powyżej 2 lat od zakażenia). Okres wylęgania choroby trwa średnio 2–4 tygodnie(w miejscu zakażenia tworzy się zmiana

**Tabela I.** Zachorowania na kiłę w latach 2009-2017 w Polsce.

| Nowo zarejestrowane zachorowania na kiłę na 100 tys. ludności | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **2009** | **2010** | **2011** | **2012** | **2013** | **2014** | **2015** | **2016** | **2017** |
| Kobiety | | | | | | | | | |
| 15-19 | 1,3 | 1,0 | 0,8 | 0,7 | 1,2 | 0,7 | 0,8 | 1,1 | 0,9 |
| 20-24 | 2,6 | 2,4 | 3,8 | 2 | 3,5 | 2,5 | 2,2 | 2,9 | 3 |
| 25-29 | 4,7 | 3,7 | 2,4 | 2,7 | 4,3 | 4,1 | 3,5 | 3,8 | 4,4 |
| 30-44 | 2,9 | 2,6 | 2,3 | 2 | 2,8 | 2,5 | 2,5 | 2,8 | 2,9 |
| 45+ | 0,6 | 0,5 | 0,5 | 0,5 | 0,7 | 0,6 | 0,5 | 0,5 | 0,5 |
| Mężczyźni | | | | | | | | | |
| 15-19 | 1,4 | 1,6 | 1,6 | 1,5 | 2,3 | 2,1 | 2,0 | 1,7 | 3 |
| 20-24 | 9,2 | 5,8 | 7,3 | 8,3 | 11,5 | 10,6 | 13,9 | 14,7 | 19,1 |
| 25-29 | 13,1 | 8,7 | 10,8 | 11,3 | 13,5 | 10,9 | 15,4 | 15,3 | 23,1 |
| 30-44 | 9,8 | 6,1 | 6,2 | 7,2 | 9,8 | 9,1 | 8,9 | 10 | 14,4 |
| 45+ | 2,5 | 2,0 | 1,9 | 2,0 | 2,6 | 2,2 | 2,2 | 2,3 | 2,4 |

Źródło: https://stat.gov.pl/obszary-tematyczne/zdrowie/zdrowie/zachorowania-na-niektore-choroby-zakazne,20,1.html dostęp z 22.04. 2019.

pierwotna-owrzodzenie). Choroba może trwać wiele lat z okresami występowania zmian klinicznych (kiła objawowa) i z okresami bezobjawowymi (kiła utajona). Kiła może być wrodzona (gdy do zakażenia dochodzi w życiu płodowym od chorej matki) lub nabyta. Objawy kiły później pojawiają po kilku, a nawet kilkunastu latach i mogą dotyczyć ośrodkowego układu nerwowego, układu krążenia, jak również innych narządów wewnętrznych oraz skóry i kości [4]. Kiła u kobiet w ciąży stanowi zagrożenie dla rozwijającego płodu. Diagnostyka serologiczna stanowi podstawę rozpoznania kiły. W leczeniu kiły stosuje się antybiotyki, najczęściej penicylinę. Brak lub zbyt późne wdrożenie leczenia prowadzi do nieodwracalnych uszkodzeń, a nawet śmierci pacjenta [5].

Kiła w świetle literatury przedmiotu oraz polskiego prawa należy bezspornie do chorób zakaźnych [6, 7]. Należy ona do grupy chorób tzw. wenerycznych. W 2017 r. zanotowano w Polsce 2,1 tys. przypadków zachorowań na choroby weneryczne. 40 proc. z nich zarejestrowano na Mazowszu (Tab. I). Najpowszechniejszą chorobą weneryczną w świetle statystyk jest kiła (i ją jako jedyną GUS wyróżnia z nazwy w swoich statystykach).

Według danych Narodowego Instytutu Zdrowia Publicznego – Państwowego Zakładu Higieny Zakład Epidemiologii Chorób Zakaźnych i Nadzoru zawartych w raporcie Choroby zakaźne i zatrucia w Polsce liczba zachorowań na kiłę w Polsce w roku 2017 wyniosła 1593 [8]. Najwięcej zachorowań było w województwie mazowieckim (525 przypadków). Dla porównania według tych samych danych na rzeżączkę zachorowało w 2017 w Polsce 321 osób. Wskaźnik zapadalności (na 100 tys. osób) na kiłę wyniósł w 2017 roku 4,15, podczas gdy w 2000 roku oscylował w granicach około 2,5. Według wstępnych danych Narodowego Instytutu Zdrowia Publicznego w 2018 roku na kiłę zachorowało 1450 osób [9]. Jak wynika z publicznych statystyk, od kilku lat obserwowany jest wzrost zachorowań na kiłę w Polsce i dlatego też postępowanie w przypadku jej podejrzenia/rozpoznania ma dla lekarzy coraz większe znaczenie praktyczne.

Na zapobieganie chorobom zakaźnym, a także na postępowanie w przypadku ich wystąpienia istotny wpływ ma prawo. Problematykę dotyczącą chorób zakaźnych w Polsce reguluje przede wszystkim ustawa z dnia 5 grudnia 2008 r. o zapobieganiu oraz zwalczaniu zakażeń i chorób zakaźnych u ludzi (t. jedn. Dz. U. 2018; poz.151) zwana w skrócie u.z.z.z. Przepisy powyższej ustawy stosuje się do zakażeń i chorób zakaźnych, których wykaz jest określony w załączniku do ustawy oraz biologicznych czynników chorobotwórczych wywołujących te zakażenia i choroby. Aktualnie wykaz obejmuje około 60 pozycji, w tym takich jak: bąblowica, błonica, borelioza z Lyme, choroba Creutzfeldta-Jakoba i inne encefalopatie gąbczaste, choroba wirusowa Ebola, czerwonka bakteryjna, gruźlica i inne mikobakteriozy, grypa, jersinioza, krztusiec, legioneloza, odra, ornitozy, ospa(prawdziwa i wietrzna), różyczka, rzeżączka, wirusowe gorączki krwotoczne, wirusowe zapalenia wątroby(A, B, C, inne), włośnica, wścieklizna, zakażenia żołądkowo-jelitowe oraz zatrucia pokarmowe o etiologii infekcyjnej lub nieustalonej, zakażenia szpitalne oraz zakażenia biologicznymi czynnikami chorobotwórczymi opornymi na antybiotyki kluczowe dla leczenia, zakażenie ludzkim wirusem niedoboru odporności (HIV) i zespół nabytego niedoboru odporności (AIDS), zimnica [10]. Na 25 pozycji wykazu znajduje się kiła. Jednakże w razie niebezpieczeństwa szerzenia się zakażenia lub choroby zakaźnej innych niż wymienione w powyższym wykazie Minister Zdrowia może ogłosić, w drodze rozporządzenia, zakażenie lub chorobę zakaźną oraz, o ile jest znany, wywołujący je biologiczny czynnik chorobotwórczy, a jeżeli to konieczne, szczególny sposób postępowania

świadczeniodawców i osób narażonych na zakażenie lub zachorowanie przez czas określony w rozporządzeniu.

Głównym celem niniejszego artykułu jest przedstawienie regulacji prawnych dotyczących kiły jako choroby zakaźnej. Celem szczegółowym niniejszego artykułu jest przedstawienie i analiza obowiązków lekarza dotyczących rozpoznania(podejrzenia) kiły, a także zwrócenie uwagi na aspekt społeczny związany ze wzrostem liczby zachorowań na kiłę w ostatnich latach. W niniejszej pracy dokonano analizy aktualnie obowiązujących norm prawnych w zakresie chorób zakaźnych, w tym dotyczących bezpośrednio kiły zawartych przede wszystkim w ustawie z dnia 5 grudnia 2008 r. o zapobieganiu oraz zwalczaniu zakażeń i chorób zakaźnych u ludzi(t. jedn. Dz. U. 2018; poz.151). W pracy zastosowano metodę analityczno-syntetyczną, a także wykorzystano dane statystyczne.

## DEFINICJA CHOROBY ZAKAŹNEJ

W Polsce pojęcie choroby zakaźnej od lat zdefiniowane jest normatywnie. Obecnie definicja choroby zakaźnej zawarta jest w ustawie z dnia 5 grudnia 2008 r. o zapobieganiu oraz zwalczaniu zakażeń i chorób zakaźnych u ludzi (art. 2 pkt 3). W świetle powyższej definicji ustawowej choroba zakaźna to choroba, która została wywołana przez biologiczny czynnik chorobotwórczy. Natomiast biologiczny czynnik chorobotwórczy to posiadające zdolność wywoływania objawów chorobowych drobnoustroje komórkowe lub wytwarzane przez nie produkty, zewnętrzne i wewnętrzne pasożyty człowieka lub wytwarzane przez nie produkty, cząstki bezkomórkowe zdolne do replikacji lub przenoszenia materiału genetycznego, w tym zmodyfikowane genetycznie hodowle komórkowe lub wytwarzane przez nie produkty. Szczególnym rodzajem choroby zakaźnej wyodrębnionym ustawowo jest choroba szczególnie niebezpieczna i wysoce zakaźna. Choroba szczególnie niebezpieczna i wysoce zakaźna to choroba zakaźna łatwo rozprzestrzeniająca się, o wysokiej śmiertelności, powodująca szczególne zagrożenie dla zdrowia publicznego i wymagająca specjalnych metod zwalczania, w tym cholera, dżuma, ospa prawdziwa, wirusowe gorączki krwotoczne (art.2 pkt 4 u.z.z.z.). Podejrzanym o chorobę zakaźną jest osoba, u której występują objawy kliniczne lub odchylenia od stanu prawidłowego w badaniach dodatkowych, mogące wskazywać na chorobę zakaźną. Natomiast zakażenie oznacza prawnie wniknięcie do organizmu i rozwój w nim biologicznego czynnika chorobotwórczego.

Art. 5 u.z.z.z. nakłada powszechne obowiązki w zakresie zapobiegania i zwalczania chorób zakaźnych. Zgodnie z powyższym artykułem osoby przebywające na terytorium Rzeczypospolitej Polskiej są zobowiązane na zasadach określonych w przedmiotowej ustawie do:

1. poddawania się:
a. zabiegom sanitarnym,
b. szczepieniom ochronnym,
c. poekspozycyjnemu profilaktycznemu stosowaniu leków,
d. badaniom sanitarno-epidemiologicznym, w tym również postępowaniu mającemu na celu pobranie lub dostarczenie materiału do tych badań,
e) nadzorowi epidemiologicznemu,
f) kwarantannie,
g) leczeniu,
h) hospitalizacji,
i) izolacji;
2. zaniechania wykonywania prac, przy wykonywaniu których istnieje możliwość przeniesienia zakażenia lub choroby zakaźnej na inne osoby – jeżeli są osobami zakażonymi, chorymi na chorobę zakaźną lub nosicielami,
3. stosowania się do nakazów i zakazów organów Państwowej Inspekcji Sanitarnej służących zapobieganiu oraz zwalczaniu zakażeń i chorób zakaźnych.

Szczególne obowiązki w przypadku podejrzenia lub rozpoznania choroby zakaźnej spoczywają m.in. na lekarzu.

## PODEJRZENIE/ROZPOZNANIE KIŁY

Ustawa z dnia 5 grudnia 2008 o zapobieganiu oraz zwalczaniu zakażeń i chorób zakaźnych u ludzi nakłada ogólne i szczegółowe obowiązki w zakresie zapobiegania i zwalczenia chorób zakaźnych na osoby fizyczne przebywające na terytorium RP, świadczeniodawców medycznych, oraz na Państwową Inspekcję Sanitarną. Zgodnie z art.11 u.z.z.z**.** kierownicy podmiotów leczniczych oraz inne osoby udzielające świadczeń zdrowotnych(w szczególności lekarze) są zobowiązani do podejmowania działań zapobiegających szerzeniu się zakażeń i chorób zakaźnych. Działania powyższe obejmują w szczególności:

1. ocenę ryzyka wystąpienia zakażenia związanego z wykonywaniem świadczeń zdrowotnych;
2. monitorowanie czynników alarmowych i zakażeń związanych z udzielaniem świadczeń zdrowotnych w zakresie wykonywanych świadczeń;
3. opracowanie, wdrożenie i nadzór nad procedurami zapobiegającymi zakażeniom i chorobom zakaźnym związanym z udzielaniem świadczeń zdrowotnych, w tym dekontaminacji:
a. skóry i błon śluzowych lub innych tkanek,
b. wyrobów medycznych, wyrobów medycznych do diagnostyki *in vitro*, wyposażenia wyrobów medycznych, oraz powierzchni pomieszczeń i urządzeń;
4. stosowanie środków ochrony indywidualnej i zbiorowej w celu zapobieżenia przeniesieniu na inne osoby biologicznych czynników chorobotwórczych;
5. wykonywanie badań laboratoryjnych oraz analizę lokalnej sytuacji epidemiologicznej w celu optymalizacji profilaktyki i terapii antybiotykowej;
6. prowadzenie kontroli wewnętrznej w zakresie realizacji przedmiotowych działań.

Kierownicy podmiotów leczniczych oraz inne osoby udzielające świadczeń zdrowotnych muszą prowadzić dokumentację realizacji powyższych działań. Realizacja przedmiotowych działań oraz prowadzenie dokumentacji tych działań, w tym wyniki kontroli wewnętrznej, podlegają, zgodnie z właściwością, kontroli organów Państwowej Inspekcji Sanitarnej.

W przypadku podejrzenia lub rozpoznania choroby zakaźnej na każdym lekarzu (niezależnie od posiadanej

specjalizacji i formy wykonywania zawodu) spoczywają dwa podstawowe obowiązki tj. obowiązek pouczenia i zgłoszenia. Bowiem zgodnie z art.26 u.z.z.z. lekarz, który podejrzewa lub rozpozna zakażenie lub chorobę zakaźną jest zobowiązany pouczyć zakażonego lub chorego na chorobę zakaźną bądź osobę sprawującą prawną pieczę nad zakażoną lub chorą na chorobę zakaźną osobą małoletnią, lub bezradną albo jej opiekuna faktycznego o:

1. środkach służących zapobieganiu przeniesienia zakażenia na inne osoby;
2. obowiązkach:

a. stosowania się do nakazów i zakazów organów Państwowej Inspekcji Sanitarnej służących zapobieganiu oraz zwalczaniu zakażeń i chorób zakaźnych,
b. udzielania danych i informacji: organom Państwowej Inspekcji Sanitarnej, Wojskowej Inspekcji Sanitarnej, Państwowej Inspekcji Sanitarnej Ministerstwa Spraw Wewnętrznych i Administracji, Inspekcji Weterynaryjnej, Wojskowej Inspekcji Weterynaryjnej, Inspekcji Ochrony Środowiska, oraz ośrodkom referencyjnym i instytutom badawczym – niezbędnych do prowadzenia nadzoru epidemiologicznego nad zakażeniami i chorobami zakaźnymi i zapobiegania oraz zwalczania zakażeń i chorób zakaźnych,
c. podleganiu obowiązkowym badaniom sanitarno-epidemiologicznym.

Badanie sanitarno-epidemiologiczne to badanie, w którego skład wchodzą badanie lekarskie, badania laboratoryjne oraz dodatkowe badania i konsultacje specjalistyczne, wykonywane w ramach nadzoru epidemiologicznego w celu wykrycia biologicznych czynników chorobotwórczych lub potwierdzenia rozpoznania choroby zakaźnej.

Kogo lekarz powinien pouczyć o powyższych obowiązkach? Lekarz powinien pouczyć przede wszystkim pacjenta, jeżeli jest on pełnoletni i nieubezwłasnowolniony. Natomiast w przypadku pacjentów małoletnich oraz ubezwłasnowolnionych powinien pouczyć ich przedstawiciela ustawowego (czyli rodzica posiadającego władzę rodzicielską lub opiekuna prawnego wyznaczonego przez sąd) ewentualnie opiekuna faktycznego. Opiekunem faktycznym w rozumieniu prawa jest osoba sprawującą, bez obowiązku ustawowego, stałą opiekę nad pacjentem, który ze względu na wiek, stan zdrowia albo stan psychiczny opieki takiej wymaga [11].

Co istotne, w przypadku rozpoznania zakażenia, które może przenosić się drogą kontaktów seksualnych (np. HIV), lekarz ma obowiązek poinformować zakażonego o konieczności zgłoszenia się do lekarza partnera lub partnerów seksualnych (np. współmałżonka, konkubenta) zakażonego. Takie postępowanie będzie miało miejsce m.in. w przypadku rozpoznania kiły i ma ono charakter obligatoryjny. Informację o powiadomieniu zakażonego o powyższym obowiązku należy wpisać do dokumentacji medycznej i potwierdzić podpisem zakażonego. Obowiązek poinformowania nie dotyczy innych osób czy instytucji (także pracodawcy). Norma ta, jakże istotna dla bezpieczeństwa zdrowotnego, niestety nie wyposaża lekarza w środki umożliwiające weryfikację wykonania przedmiotowego obowiązku przez pacjenta (w tym zgłoszenia się partnera zarażonego).

Lekarz, który podejrzewa lub rozpoznaje zakażenie, chorobę zakaźną lub zgon z powodu zakażenia lub choroby zakaźnej, określone w adekwatnym rozporządzeniu Ministra Zdrowia, jest zobowiązany do zgłoszenia tego faktu właściwemu państwowemu inspektorowi sanitarnemu . Zgłoszenia dokonuje się niezwłocznie, nie później jednak niż w ciągu 24 godzin od chwili powzięcia podejrzenia lub rozpoznania zakażenia, choroby zakaźnej lub zgonu z powodu zakażenia lub choroby zakaźnej. Kierownicy podmiotów wykonujących działalność leczniczą muszą zapewnić warunki organizacyjne i techniczne niezbędne do realizacji powyższego obowiązku oraz sprawują nadzór nad jego wykonywaniem.

Zgłoszenie powinno zawierać następujące dane osoby, u której podejrzano lub rozpoznano zakażenie, chorobę zakaźną lub stwierdzono zgon z tego powodu:

1. imię i nazwisko,
2. datę urodzenia,
3. numer PESEL (a w przypadku gdy osobie nie nadano tego numeru - serię i numer paszportu) oraz obywatelstwo,
4. płeć,
5. adres miejsca zamieszkania;
6. rozpoznanie kliniczne zakażenia lub choroby zakaźnej, charakterystykę podstawowych objawów klinicznych, okoliczności wystąpienia zakażenia, zachorowania lub zgonu z powodu zakażenia lub choroby zakaźnej, ze szczególnym uwzględnieniem czynników ryzyka, charakterystyki biologicznego czynnika zakaźnego, oraz inne informacje niezbędne do sprawowania nadzoru epidemiologicznego, zgodnie z zasadami współczesnej wiedzy medycznej.

Jednym z wyjątków od reguły uzyskiwania zgody na przekazanie informacji o stanie zdrowia pacjenta innym osobom jest prawny obowiązek informowania organów sanitarnych o przypadkach podejrzenia lub rozpoznania zakażenia, choroby zakaźnej lub zgonu z powodu zakażenia bądź choroby zakaźnej przewidziany w art.27 u.z.z.z.

Minister Zdrowia określa w drodze rozporządzenia zakażenia i choroby zakaźne, w przypadku których podejrzenia lub rozpoznania zakażenia, choroby zakaźnej lub zgonu z ich powodu dokonywane są powyższe obowiązkowe zgłoszenia. Przez wiele lat w przedmiotowym zakresie obowiązywało rozporządzenie Ministra Zdrowia z dnia 10 lipca 2013 r. w sprawie zgłoszeń podejrzenia lub rozpoznania zakażenia, choroby zakaźnej lub zgonu z powodu zakażenia lub choroby zakaźnej(Dz. U. 2013; poz. 848). Jednakże zostało ono uchylone z dniem 1 stycznia 2019 roku. Obecnie trwają pracę legislacyjne nad projektem nowego rozporządzenia Ministra Zdrowia w przedmiotowej sprawie(legislacja.rcl.gov.pl/projekt/12319358).

Dotychczasowe, jak i projektowane rozporządzenie nie przewidują obowiązku załączania przez lekarza do zgłoszenia wyników badań. Do chorób zakaźnych, których zgłoszenia mają być dokonywane w postaci papierowej lub elektronicznej w świetle projektowanego rozporządzenia należy m.in. kiła (poz.16 załącznika nr 1). Załącznik nr 4 do nowego rozporządzenia zawiera wzór formularza

zgłoszenia podejrzenia lub rozpoznania zachorowania na chorobę przenoszą drogą płciową (dotyczy on m.in. kiły). Projektowane zmiany dotyczą przed wszystkim wzorów formularzy zgłoszeniowych, zwanych formularzami ZLK. Główną zmianą, która została wprowadzona do wszystkich formularzy ZLK jest poszerzenie zawartych w zgłoszeniu danych osobowych osoby zakażonej, chorej lub zmarłej z powodu zakażenia lub choroby zakaźnej.

Państwowi powiatowi inspektorzy sanitarni, państwowi wojewódzcy inspektorzy sanitarni lub wskazane przez nich specjalistyczne jednostki oraz Główny Inspektor Sanitarny lub wskazane przez niego krajowe specjalistyczne jednostki prowadzą rejestr zakażeń i zachorowań na chorobę zakaźną oraz zgonów z powodu zakażenia lub choroby zakaźnej. Główny Inspektor Sanitarny sporządza i publikuje krajowe raporty liczbowe o zarejestrowanych zakażeniach, zachorowaniach i zgonach na zakażenia i choroby zakaźne podlegających zgłoszeniu.

## PRZYMUSOWE POSTĘPOWANIA W PRZYPADKU CHOROBY ZAKAŹNEJ – KIŁY

Podstawą legalnego udzielania każdemu pacjentowi świadczeń zdrowotnych jest wyrażenie przez niego (lub jego przedstawiciela ustawowego) zgody na konkretne świadczenie zdrowotne. Jednakże, prawo przewiduje w wyjątkowych sytuacjach możliwość udzielania świadczeń zdrowotnych bez zgody pacjenta, a nawet wbrew jego woli (tzw. przymus medyczny). Choroby zakaźne z uwagi na swą specyfikę, a w szczególności szybkie rozprzestrzenianie i poważne skutki dla zdrowia, są jedną z nielicznych sytuacji w ochronie zdrowia, gdzie możliwe jest zastosowanie przymusu medycznego zarówno dla dobra pacjenta, jak i zbiorowości [12].

Przymus w ochronie zdrowia stosowany jest wobec osób, które nie potrafią sobie poradzić same ze sobą, a także w stosunku do ludzi, którzy zagrażają swojemu życiu i zdrowiu lub zdrowiu albo życiu innych osób. Cecha wspólna wszystkich form przymusu medycznego (w ochronie zdrowia) jest interwencja medyczna niezależnie od, a niekiedy także wbrew woli pacjenta. Przymusowe udzielenie świadczeń zdrowotnych ma charakter wyjątkowy, bowiem zasadą jest ich udzielanie na podstawie świadomej i dobrowolnej zgody pacjenta. Przez postępowanie przymusowe w medycynie rozumie się leczenie lub inne postępowanie także hospitalizację lub inne formy faktycznego pozbawienia wolności, które może być legalnie podjęte, nawet mimo sprzeciwu pacjenta. Postępowanie przymusowe może być prowadzone tylko w sytuacjach i przy spełnieniu warunków określonych w odpowiednich ustawach. Rodzaje przymusu występujące w medycynie:

a. przymusowe badanie,
b. przymusowa hospitalizacja (izolacja, kwarantanna),
c. przymusowe leczenie,
d. przymus bezpośredni [13].

Przymusowe udzielanie świadczeń zdrowotnych występuje przede w psychiatrii(w stosunku do osób z zaburzeniami psychicznymi) oraz w sferze chorób zakaźnych (m.in. przymusowe leczenie niektórych chorób zakaźnych), a także w związku z prowadzonym postępowaniem karnym(wobec osób podejrzanych, oskarżonych i osadzonych).

Za najbardziej ingerującą w autonomię woli pacjenta procedurę przymusową w aspekcie chorób zakaźnych należy uznać przymusową hospitalizację (leczenie w szpitalu). Zgodnie z definicją zawartą w ustawie z dnia 15 kwietnia 2011 r. o działalności leczniczej (t. jedn. Dz. U. 2018; poz.2190) szpital to zakład leczniczy, w którym podmiot leczniczy wykonuje działalność leczniczą w rodzaju świadczenia szpitalne. Świadczenie szpitalne to wykonywane całą dobę kompleksowe świadczenia zdrowotne polegające na diagnozowaniu, leczeniu, pielęgnacji i rehabilitacji, które nie mogą być realizowane w ramach innych stacjonarnych i całodobowych świadczeń zdrowotnych lub ambulatoryjnych świadczeń zdrowotnych. Przez hospitalizację należy rozumieć umieszczenia pacjenta w szpitalu będącym podmiotem leczniczym o charakterze stacjonarnym w celu leczenia. Zasadą jest, że przyjęcie do szpitala wymaga świadomej i dobrowolnej zgody pacjenta (lub jego przedstawiciela ustawowego). Przymusowa hospitalizacją, czyli przyjęcie i pozostawienie pacjenta w szpitalu celem leczenia wbrew jego woli, stanowi wyjątek i jest związana jest z dwiema grupami jednostek chorobowych, tj. chorobami psychicznymi i chorobami zakaźnymi.

Zgodnie z art. 34 u.z.z.z. obowiązkowej hospitalizacji podlegają:

1. osoby chore na gruźlicę w okresie prątkowania oraz osoby z uzasadnionym podejrzeniem o prątkowanie;
2. osoby chore i podejrzane o zachorowanie na:

a. błonicę,
b. cholerę,
c. dur brzuszny,
d. dury rzekome A, B, C,
e. dur wysypkowy (w tym choroba Brill-Zinssera),
f. dżumę,
g. grypę H7 i H5,
h. ostre nagminne porażenie dziecięce (*poliomyelitis*) oraz inne ostre porażenia wiotkie, w tym zespół Guillaina-Barrégo,
i. ospę prawdziwą,
j. zespół ostrej niewydolności oddechowej (SARS),
k. tularemię,
l. wąglik,
m. wściekliznę,
n. zapalenie opon mózgowo-rdzeniowych i mózgu,
o. wirusowe gorączki krwotoczne, w tym żółtą gorączkę.

W przypadku podejrzenia lub rozpoznania zakażenia lub choroby zakaźnej wyżej wskazanych lekarz jest zobowiązany pouczyć pacjenta o obowiązku hospitalizacji oraz skierować go do szpitala. Fakt udzielenia pouczenia jest potwierdzany wpisem lekarza w dokumentacji medycznej oraz podpisem pacjenta. Informacja o skierowaniu do szpitala jest przekazywana państwowemu powiatowemu inspektorowi sanitarnemu właściwemu dla miejsca rozpoznania zakażenia lub choroby zakaźnej. Osoby podejrzane o zachorowanie lub chore na chorobę zakaźną są przyjmowane do szpitala zapewniającego skuteczną izolację.

Obowiązkowa hospitalizacja dotyczy tylko bezpośrednio określonych w ustawie chorób i zakażeń. Jako że kiła nie została wskazana wprost przez ustawodawcę, to nie podlega ona obowiązkowej hospitalizacji. Natomiast dotyczy jej przymus leczenia. Należy przyjąć, że wypadku chorych na kiłę będzie to tylko leczenie ambulatoryjne. Zgodnie z art. 40 u.z.z.z. obowiązkowemu leczeniu podlegają osoby chore na: gruźlicę płuc, kiłę oraz rzeżączkę. W przypadku podejrzenia lub rozpoznania zakażenia lub choroby zakaźnej wyżej wskazanych w tym, kiły lekarz zobowiązany jest pouczyć pacjenta o obowiązku leczenia. Fakt udzielenia pouczenia jest potwierdzany wpisem lekarza w dokumentacji medycznej oraz podpisem pacjenta. W przypadku zmiany podmiotu udzielającego choremu świadczeń zdrowotnych związanych z gruźlicą płuc, kiłą lub rzeżączką lekarz jest zobowiązany wystawić choremu skierowanie wskazujące podmiot, który będzie kontynuował leczenie oraz powiadomić o tym fakcie państwowego powiatowego inspektora sanitarnego właściwego dla dotychczasowego miejsca udzielania świadczenia zdrowotnego. Co istotne, w praktyce w przypadku uchylania się przez pacjenta od obowiązku leczenia lekarz prowadzący leczenie musi niezwłocznie zawiadomić o tym fakcie państwowego powiatowego inspektora sanitarnego właściwego dla miejsca udzielania świadczenia zdrowotnego.

Ponadto osoby, które miały styczność z chorymi na gruźlicę płuc w okresie prątkowania, chorymi na kiłę, rzeżączkę, dur brzuszny, chorymi na inwazyjne zakażenia *Neisseria meningitidis* lub *Haemophilus influenzae* typ b, podlegają nadzorowi epidemiologicznemu, badaniu klinicznemu, badaniom diagnostycznym, a także, w razie potrzeby, profilaktycznemu stosowaniu leków. Styczność należy rozumieć jako bezpośredni lub pośredni kontakt osoby ze źródłem zakażenia, jeżeli charakter tego kontaktu zagrażał lub zagraża przeniesieniem na tę osobę biologicznych czynników chorobotwórczych. Powyższe osoby podlegają przede wszystkim nadzorowi epidemiologicznemu. Zgodnie z definicją ustawową nadzór epidemiologiczny oznacza obserwację osoby zakażonej lub podejrzanej o zakażenie, bez ograniczenia jej swobody przemieszczania się, wykonywanie badań sanitarno-epidemiologicznych u tej osoby w celu wykrycia biologicznych czynników chorobotwórczych lub potwierdzenia rozpoznania choroby zakaźnej oraz zebranie, analizę i interpretację informacji o okolicznościach i skutkach zakażenia-nadzór indywidualny, jak i stałe, systematyczne gromadzenie, analizę oraz interpretację informacji o zachorowaniach lub innych procesach zachodzących w sferze zdrowia publicznego, wykorzystywane w celu zapobiegania i zwalczania zakażeń lub chorób zakaźnych-nadzór ogólny (art. 2 pkt 14 u.z.z.z.).

Świadczenia zdrowotne wyżej wskazane mogą obejmować również wydawanie leków przez podmiot, który udzielił świadczenia zdrowotnego. Koszty powyższych świadczeń zdrowotnych, oraz świadczeń zdrowotnych związanych przyczynowo z tymi zakażeniami i chorobami, udzielonych ubezpieczonym, a także koszty leków są finansowane na zasadach określonych w przepisach o świadczeniach opieki zdrowotnej finansowanych ze środków publicznych. Natomiast koszty powyższych świadczeń zdrowotnych oraz świadczeń zdrowotnych związanych przyczynowo z tymi zakażeniami i chorobami zakaźnymi, udzielonych osobom nieposiadającym uprawnień z tytułu ubezpieczenia zdrowotnego, a także koszty leków, są finansowane z budżetu państwa z części, której dysponentem jest Minister Zdrowia.

Przedstawiając procedury przymusowe związane z chorobami zakaźnymi, należy też wspomnieć o tzw. przymusie bezpośrednim. Bowiem na podstawie art. 36 u.z.z.z. wobec osoby, która nie poddaje się obowiązkowi szczepienia, badaniom sanitarno-epidemiologicznym, zabiegom sanitarnym, kwarantannie lub izolacji, a u której podejrzewa się lub rozpoznano chorobę szczególnie niebezpieczną i wysoce zakaźną, stanowiącą bezpośrednie zagrożenie dla zdrowia lub życia innych osób, może być zastosowany środek przymusu bezpośredniego polegający na przytrzymywaniu, unieruchomieniu lub przymusowym podaniu leków. O zastosowaniu środka przymusu bezpośredniego decyduje lekarz, który określa rodzaj zastosowanego środka przymusu bezpośredniego oraz osobiście nadzoruje jego wykonanie przez osoby wykonujące zawody medyczne.

## PODSUMOWANIE

Prawidłowe wykonywanie zawodu lekarza związane jest z realizacją prawnych standardów wykonywania tego zawodu. Jedną ze sfer medycyny, w którą ingeruje prawo są choroby zakaźne. Każdy lekarz powinien znać i realizować w praktyce normy dotyczące zapobiegania i zwalczania chorób zakaźnych. Choroby przenoszą drogą płciową, w tym kiła, należą do jednych z najczęściej występujących chorób zakaźnych. Kiła jest jedną z chorób zakaźnych, których dotyczą bezpośrednie regulacje ustawowe. W związku ze znacznym wzrostem zachorowań na kiłę w ostatnich latach procedury prawne z nią związane mają coraz większe znaczenie praktyczne dla lekarzy. W przypadku podejrzenia lub rozpoznania kiły na każdym lekarzu zarówno podstawowej opieki zdrowotnej, jak i dermatologu (innym specjaliście) ciążą konkretne obowiązki ustawowe opisane w niniejszym artykule. Należy pamiętać, że kiła należy do nielicznych chorób zakaźnych objętych przymusem leczenia. W przypadku chorób zakaźnych prawo ingeruje w autonomię woli pacjenta i w jego prawa.

Kiła przez lata wydawała się zapomnianą chorobą, stąd problemem bywa znikoma wiedza także wśród personelu medycznego (poza zasadniczo dermatologami) oraz młodzieży na temat tej choroby. Dlatego też konieczna jest edukacja lekarzy, szczególnie podstawowej opieki zdrowotnej, dotycząca rozpoznawania tej choroby, a także społeczeństwa dotycząca jej zapobiegania. Choroba może przebiegać w sposób utajony, ulegać samowyleczeniu lub postępować, wywołując poważne zmiany narządowe. W praktyce kiła diagnozowana bywa coraz częściej u polskich studentów szczególnie mających kontakty ze studentami z Ukrainy i Białorusi. Dlatego też zasadne byłoby wprowadzenie zajęć edukacyjnych (nie tylko dotyczących kiły, ale też innych chorób przenoszonych drogą płciową) dla młodzieży w szkole średniej.

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**Konflikt interesów**

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## AUTOR KORESPONDUJĄCY

**Małgorzata Paszkowska**
Wyższa Szkoła Informatyki i Zarządzania w Rzeszowie
Katedra Zarządzania
ul. Sucharskiego 2, 35-225 Rzeszów
e-mail: mpaszkowska@wsiz.rzeszow.pl



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CASE REPORT
OPIS PRZYPADKU

# STROKE IN THE ARTERY OF PERCHERON TERRITORY: THE TWO EDGES OF ONE DIAGNOSIS

**Angelika V. Payenok, Volodymyr M. Shevaha, Andrii R. Kulyk, Andrii M. Netliukh, Andrii V. Kulmatytskyi**
DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

**ABSTRACT**

Occlusion of artery of Percheron is a rare condition caused by a peculiar anatomic variation in cerebral blood supply, leading to a bilateral thalamic infarction. Strokes in artery of Percheron account for 0.1% to 2% of all cerebral infarctions. Thalamic area is supplied by the arteries arising directly from the P1 segment of the posterior cerebral artery. However, in 1/3 of cases the supply is provided by a single trunk referred to as artery of Percheron (AOP). Early diagnosis of stroke in AOP can be very challenging due to an ambiguous clinical presentation and the absence of neurovisualization findings.

This article presents two clinical cases of stroke in artery of Percheron observed at Lviv Emergency Hospital. Different clinical progression of a cerebrovascular accident contrasted with a similar neurovisualization pattern was a distinctive feature in these patients. Taking into consideration the rarity of this condition and a characteristic clinical presentation, these clinical cases were retrospectively analyzed and compared.

A stroke in AOP should be suspected in all patients with symptoms of interrupted blood supply in the vertebrobasilar territory. The diagnosis primarily depends on clinical features; patients with paramedian bilateral thalamic lesions may develop sudden problems with consciousness, vertical gaze palsy and memory disorders.

Early diagnosis of this condition allows for more effective therapeutic interventions and improves patient prognosis.

**KEY WORDS:** Stroke in artery of Percheron; Bilateral thalamic infarction; Artery of Percheron

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## INTRODUCTION

Occlusion of the artery of Percheron is a rare condition, which develops due to a peculiar anatomic variation in cerebral blood supply, leading to a bilateral thalamic infarction. Strokes in the artery of Percheron territory account for 0.1% to 2% of all cerebral infarctions.

The thalamic area is supplied by the arteries arising directly from the P1 segment of the posterior cerebral artery. However, in 1/3 of cases the supply is provided by a single blood vessel referred to as artery of Percheron (AOP).

Early diagnosis of stroke in the AOP territory can be very challenging due to an ambiguous clinical presentation and the absence of distinctive neurovisualization findings.

This article reports two cases of stroke in the artery of Percheron territory observed at Municipal Non-profit Enterprise 'Lviv Clinical Emergency Care Hospital'. As a distinctive feature in these patients, we noted different clinical progression of cerebrovascular accidents contrasted with similar neurovisualization patterns.

Taking into consideration the rarity of this condition and the variety of clinical presentations, a retrospective analysis was performed with a comparison of the two cases.

The thalamus and the midbrain have a complex blood supply with multiple nourishing arteries. The arterial blood supply of the thalamus and the midbrain consists of an integrated system embracing the territories of the carotid artery and the basilar artery. The ventral and the caudal part of the midbrain and the thalamus are nourished primarily from the internal carotid artery territory, while the medial, lateral and caudal parts of the thalamus are nourished from the vertebrobasilar territory [1].

Four principal vascular territories are distinguished in the thalamus: the anterior, the paramedian, the inferolateral and the posterior. The paramedian territory receives its blood supply from the paramedian (thalamoperforating) arteries that arise from the proximal segment of the posterior cerebral artery [2]. In 1973, Gerard Percheron described four anatomic variations of blood supply of medial thalamus, including artery of Percheron, a rare variation where one common thalamoperforating artery comes off the posterior cerebral artery and divides to provide blood supply to both paramedian thalami and also (in some cases) to a part of midbrain [3]. The occlusion of this artery leads to a characteristic bilateral infarction of both thalami with or without mesencephalic ischemia.

Bilateral paramedian thalamic infarctions are characterized by a classic triad of symptoms: acute impairment of consciousness, neuropsychiatric symptoms and impairment of vertical gaze.

Various degrees of impaired consciousness are seen in all patients. Impaired function of vertical gaze manifests as a palsy of upward gaze or a combination of upward/downward gaze impairments. Horizontal dysfunction is less typical. Neuropsychiatric disorders escalate with the level of loss of consciousness and manifest as amnesia, abulia and/or thalamic dementia [4].

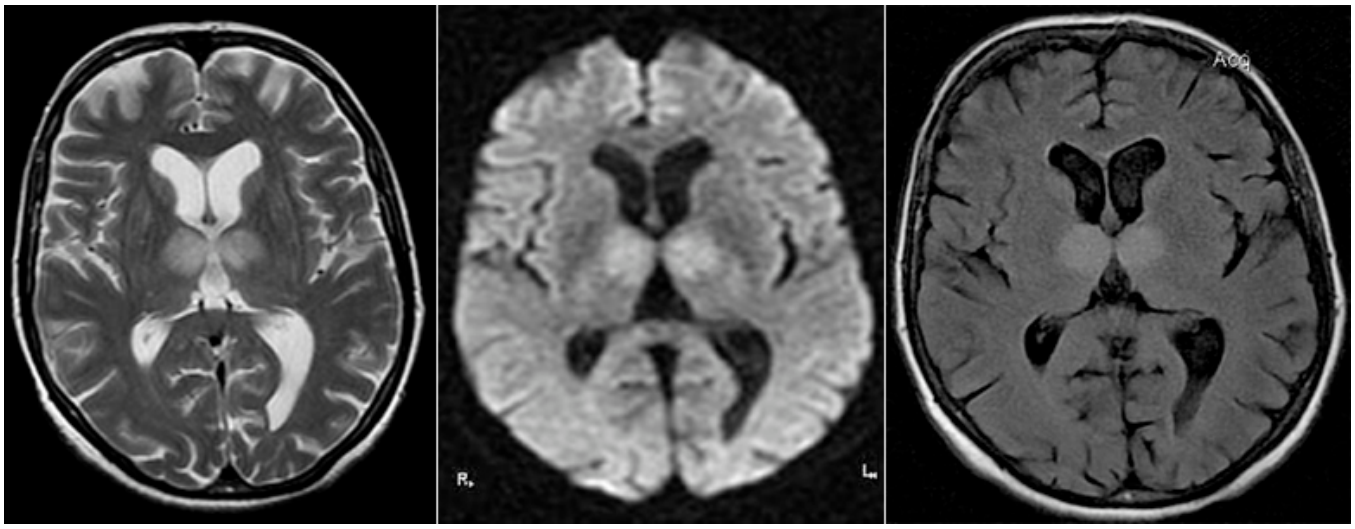

**Fig. 1.** A stroke in the artery of Percheron territory (MRI imaging)

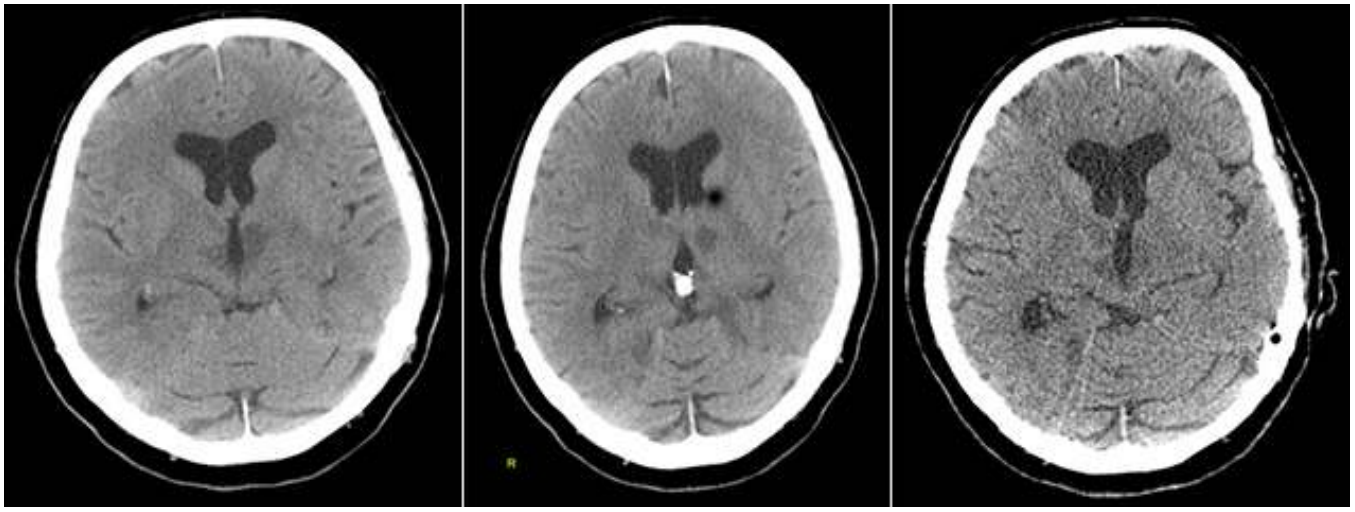

**Fig. 2.** A stroke in the artery of Percheron territory (CT imaging)

Patients with bilateral thalamic infarction with lesions in mesencephalic area may have hemiplegia, cerebellar ataxia, movement disorders or oculomotor disorders [5].

The available literature sources report that thalamic strokes account for 11% of the strokes in the vertebrobasilar territory. Paramedian strokes account for 22–35% of all thalamic strokes; these are predominantly cardioembolic strokes [6].

The pattern of infarctions in the artery of Percheron territory includes the following: bilateral paramedian infarction with a mesencephalic stroke (43%), isolated bilateral paramedian thalamic infarction (38%) and bilateral paramedian infarction with involvement of the anterior thalamus and the midbrain (14%) [7].

In our clinic, we observed two clinical cases of cerebral infarction in the artery of Percheron territory with different neurological symptoms and different disease outcomes. These cases are given below.

## CASE REPORT 1

A 71 y.o. woman was brought to the Admissions Department of the Emergency Care Hospital with sudden deterioration of health manifest as confusion and impaired speech. According to her relatives, these symptoms appeared suddenly in a setting of feeling well during recent months.

The patient did not verbalize any complaints due to her inability to talk. Medical history included coronary artery disease and stage II hypertension. The patient had 11 points on Glasgow coma scale; the NIHSS score was 9 points.

On examination, the patient's general condition was moderately severe. Visible mucous membranes were pale pink in color. Heart tones were rhythmic; BP 140/80 mm Hg. Neurological status: the patient was conscious, poorly oriented to space and time; retrograde amnesia. The patient was not answering any questions but performed the physician's instructions adequately. Cranial nerves assessment: the pupils were S=D, eye movements were unrestricted, photoreactions were inhibited; the face appeared symmetrical and the tongue was on the midline. Tendon reflexes were S=D. The subcortical reflexes of oral automatism were positive. No abnormal foot signs, impaired sensation or meningeal signs were documented. The patient performed the finger-to-nose test satisfactorily. The patient was not able to perform Romberg's maneuver.

On admission, an urgent computed tomography of the head was performed, with findings including bilaterally reduced density of brain tissue in basal ganglia, a tentative diagnosis of CVA and vascular encephalopathy. ECG findings included sinus rhythm, pronounced diffuse myocardial changes and left ventricular hypertrophy. Hematology test: hemoglobin 13.7 g/dL, WBCs 8,800 cells/μL and blood glucose 6.5 mmol/L. The patient's condition stabilized with treatment; her consciousness was restored and the patient was able to perform the physician's instructions. However, retrograde amnesia and speech impairment (manifest as motor aphasia) were retained. When hospitalized, the patient had a brain MRI with the following findings: bilateral thalamic infarctions and a typical presentation of artery of Percheron occlusion (Fig. 1).

The patient stayed in the hospital for 12 days. With neurological treatment, her status improved; there was a partial recovery of speech and improvements of coordination and gait. On discharge, the patient had pronounced cognitive problems, including retrograde amnesia and disorientation to time, space and person.

The patient's status was retrospectively reviewed one year after discharge from the hospital. The patient continued to have a cognitive deficit; her memory had partially recovered and disorientation to time, space and person had disappeared.

## CASE REPORT 2

A 79 y.o. female patient was hospitalized in a severe condition. Conscience status: coma II (5 to 10 points on Glasgow coma scale), 29 points on the NIHSS scale. No contact could be established; no instructions were performed by the patient. The eye fissures were closed, the eyeballs were fixed; a divergent strabismus to the left has been documented. The pupils were S=D, mydriasis, photoreactions are absent. The face was asymmetric; the tongue was in oral cavity. Tendon reflexes were D>S in the upper extremities and hyposthenic in the lower extremities. The muscles of the upper extremities were hypotonic; hypertonus in leg extensors. Babinski sign was bilaterally positive. Rigidity of neck muscles (1 finger wide range of neck mobility). No coordination and/or sensation tests were performed.

The medical history was positive for atrial fibrillation, hypertension and uncontrolled use of hypertensive medications.

The patient had brain CT scan on her admission and on Day 12 of hospital stay. The findings of brain CAT scan included the following: ischemic-type CVA in the territories of left and right PCAs. The first two CT sections contain evidence of an acute stage; the third section contains evidence of CVA in the territory of both PCAs, the stage of resorption (Fig. 2).

In course of treatment, there was only a modest improvement of patient's condition; the level of consciousness stabilized at the level of deep sopor; the movements in the extremities have not restored. The patient was discharged from the hospital under the care of a neurologist.

## CONCLUSIONS

In spite of literature reports of stroke in the artery of Percheron territory, this condition remains quite rare. As can be seen from the above, the course of the disease was different in our patients despite similar neurovisualization findings.

Taking into consideration a large number of variations in blood supply of posterior cranial fossa, it may be concluded that the presence of artery of Percheron is not that rare and that strokes in this artery remain largely undiagnosed.

A stroke in AOP should be suspected in any patient with a sudden onset of symptoms of impaired circulation in the vertebrobasilar territory. The diagnosis of stroke in the artery of Percheron territory primarily depends on clinical features: patients with paramedian bilateral thalamic lesions may develop sudden problems with consciousness, vertical gaze palsy and memory disorders.

Therefore, in a bilateral cerebral infarction in the distal portion of the basilar artery but provided that no occlusion of the basilar artery proper was found, a possibility of a stroke in the artery of Percheron territory must be considered.

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**Authors' contributions:**
*According to the order of the Authorship.*


**ORCID numbers:**
*Angelika V. Payenok - 0000-0003-0531-751X*
*Volodymyr M. Shevaha - 0000-0003-2402-1829*
*Andrii R. Kulyk - 0000-0002-0421-1628*
*Andrii M. Netliukh - 0000-0002-6499-1718*
*Andrii V. Kulmatytskyi - 0000-0003-3486-1143*


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## CORRESPONDING AUTHOR

**Andrii Netliukh**
Buchmy str., 22/32, 79035. Lviv, Ukraine
tel: +380679346393
e-mail: netliukh_andrii@ukr.net



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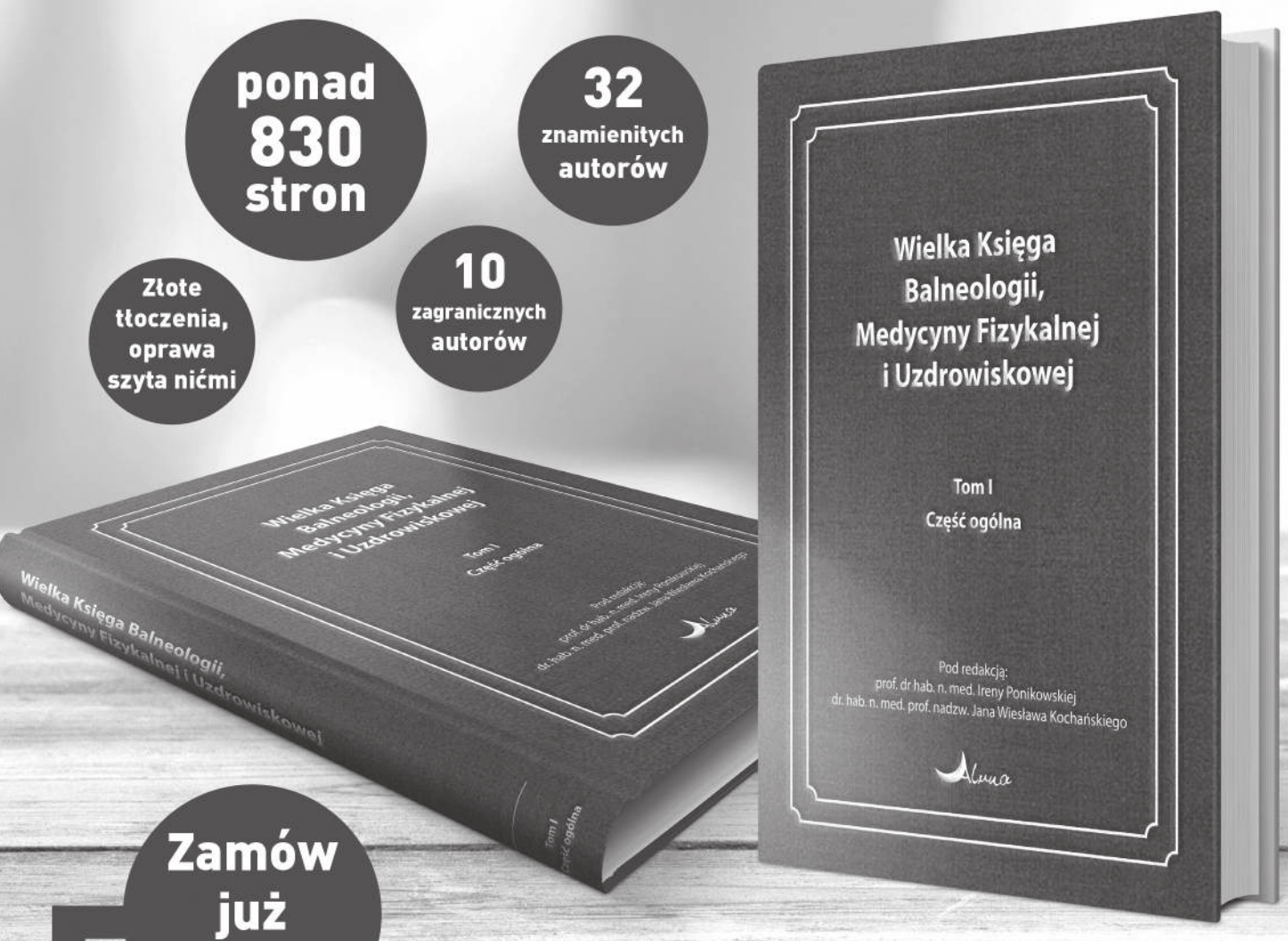


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