The 5-year Impact of the Ukrainian National Drug Hypersensitivity and Anaphylaxis Guideline on the Management of Hypersensitivity Induced by Local Anesthetics

5-letni wpływ ukraińskich krajowych wytycznych dotyczących nadwrażliwości na leki i anafilaksji na postępowanie w przypadku nadwrażliwości wywołanej miejscowymi środkami znieczulającymi

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Summary

Background: In Ukraine, drug hypersensitivity and anaphylaxis were traditionally practiced combining aspects of American and European schools. In 2015, the up-to-date Ukrainian National Drug Hypersensitivity and Anaphylaxis Guideline (UNDHAG) which covered diagnostic issues, indications, dosage, mechanisms, adverse effects, and future expectations, was implemented in clinical practice. We investigated the 5-year impact of UNDHAG on the management of drug hypersensitivity and anaphylaxis caused by local anesthetics.

Methods: With a nationwide group of allergists, including mentors from postgraduate training programs in Allergy/Clinical Immunology, a questionnaire was developed. The questionnaire consisted of several sections: clinical facilities, physician specialty and experience, number of anesthesia done per week, first aid ability and staffing, anesthesia type and anesthetics used, clinical characteristics of hypersensitivity reactions, epinephrine use, drug diagnostic tests, management of patients with hypersensitivity to local anesthetics, continuous medical education. In total 272 physicians were interviewed in 2016, and 271 – in 2020. Data was expressed as numbers and percentages. Statistical comparison between 2 groups was analyzed using the chi-square test. The probability of $P<0.05$ was considered statistically significant.

Results: The majority of interviewed medical specialists were dentists and traumatologists with sufficient work experience. We observed an increase in the use of lidocaine 11.05% (21.86% $P<0.0001$), bupivacaine 7.99% (13.48%, $P<0.0001$), and a decrease in the use of chloroprocaine, trimecaine, etidocaine, pyromecaine, oxybuprocaine, bimecaine, prilocaine ($P<0.05$). The most frequent drug reactions were hypotension, hypertension, loss of consciousness, abdominal syndrome, skin reactions, dyspnea, anaphylaxis (66.95% and 59.97%), and anaphylactic shock (65.53% and 65.77%). Epinephrine administration during anaphylaxis and anaphylactic shock was decreased from 2016 to 2020. There was a dramatic increase in the number of physicians who never used epinephrine from 1.1% to 39.85% ($P<0.0001$). There was an increase in drug tests provided by allergists up to 21.32% and 36.53% ($P=0.0003$). We observed a decrease in the conjunctival and subcutaneous drug tests. Unfortunately, the growth of scarifica-

Streszczenie

Wstęp: Na Ukrainie nadwrażliwość na leki i anafilaksja były tradycyjnie praktykowane, łącząc aspekty szkół amerykańskich i europejskich. W 2015 roku do praktyki klinicznej wdrożono aktualne Ukraińskie Narodowe Wytyczne dotyczące nadwrażliwości na leki i anafilaksji (UNDHAG), które obejmowały zagadnienia diagnostyczne, wskazania, dawkowanie, mechanizmy, działania niepożądane oraz przyszłe perspektywy. Zbadaliśmy 5-letni wpływ UNHAG na leczenie nadwrażliwości na leki i anafilaksji wywołanej miejscowymi środkami znieczulającymi.

Metody: Wraz z ogólnokrajową grupą alergologów, w tym mentorami ze szkoleń podyplomowych z zakresu alergologii/immunologii klinicznej, opracowano kwestionariusz. Kwestionariusz składał się z kilku sekcji: placówka kliniczna, specjalizacja i doświadczenie lekarza, liczba znieczuleń wykonywanych w tygodniu, umiejętność udzielania pierwszej pomocy i personel, rodzaj znieczulenia i stosowane środki znieczulające, charakterystyka kliniczna reakcji nadwrażliwości, stosowanie epinefryny, testy diagnostyczne leków, postępowanie z pacjentami z nadwrażliwością na środki miejscowo znieczulające, ustawiczna edukacja medyczna. Łącznie w 2016 roku przeprowadzono wywiady z 272 lekarzami, a w 2020 roku z 271. Dane wyrażono liczbowo i procentowo. Porównanie statystyczne między 2 grupami analizowano za pomocą testu chi-kwadrat. Prawdopodobieństwo $P<0,05$ uznano za istotne statystycznie.

Wyniki: Większość ankietowanych lekarzy specjalistów stanowili lekarze dentyści i traumatolodzy z wystarczającym stażem pracy. Zaobserwowaliśmy wzrost zużycia lidokainy o 11,05% (21,86% $P<0,0001$), bupiwakainy o 7,99% (13,48%, $p<0,0001$) oraz spadek zużycia chloroprokainy, trimekainy, etidokainy, piromekainy, oksybuprokainy, bimekainy, prylokaina ($P<0,05$). Najczęstszymi reakcjami na lek były niedociśnienie, nadciśnienie, utrata przytomności, zespół brzuszny, reakcje skórne, duszność, anafilaksja (66,95% i 59,97%) oraz wstrząs anafilaktyczny (65,53% i 65,77%). Podawanie epinefryny podczas anafilaksji i wstrząsu anafilaktycznego zmniejszyło się w latach 2016-2020. Nastąpił dramatyczny wzrost liczby lekarzy, którzy nigdy nie stosowali epinefryny, z 1,1% do 39,85% ($P<0,0001$). Nastąpił wzrost testów na obecność narkotyków wykonanych przez alergologów do 21,32% i 36,53% ($P=0,0003$). Zaobserwowaliśmy spadek testów spojówkowych i podskórnych. Niestety

tion and intradermal tests was detected. Positive and negative controls for *in vivo* testing were ever used only 8.45% and 8.12%. In case of hypersensitivity to local anesthetics, physicians referred patients to allergists 55.14% and 46.86%, but physicians changed anesthesia type more frequently – 6.98% and 18.45% (P=0.0002). Physicians referred patients to laboratory investigation only in 9.55% and 8.12%. 47.42% and 50.18% of respondents did not use any *in vitro* tests. At the same time, the Ukrainian Ministry of Health Public Service changed the policy for National Guidelines to liberate it. After that clinics might choose the preferable guidelines from international sources.

Conclusion: The Ukrainian National Drug Hypersensitivity and Anaphylaxis Guideline significantly influenced the management of hypersensitivity induced by local anesthetics from 2016 to 2020. On the other hand, the number of anaphylaxis cases was underestimated. There were issues with epinephrine use and drug testing. In our opinion, national regulators should pay more attention to such national guidelines.

Keywords: *Drug Hypersensitivity, Anaphylaxis, Local anesthetics, Anaphylactic shocks, Drug allergy.*

stwierdzono wzrost skaryfikacji i badania śródskórne. Kontrole pozytywne i negatywne do testów in vivo były kiedykolwiek używane tylko w 8,45% i 8,12%. W przypadku nadwrażliwości na środki miejscowo znieczulające lekarze kierowali pacjentów do alergologa 55,14% i 46,86%, ale częściej zmieniali rodzaj znieczulenia – 6,98% i 18,45% (P=0,0002). Lekarze skierowali pacjentów na badania laboratoryjne tylko w 9,55% i 8,12%. 47,42% i 50,18% ankietowanych nie stosowało żadnych badań in vitro. W tym samym czasie ukraińskie Ministerstwo Zdrowia Służby Publicznej zmieniło politykę Krajowych Wytycznych, aby ją uwolnić. Następnie kliniki mogą wybrać preferowane wytyczne ze źródeł międzynarodowych.

W**niosek:** Krajowe wytyczne Ukrainy dotyczące nadwrażliwości na leki i anafilaksji znacząco wpłynęły na postępowanie w przypadku nadwrażliwości wywołanej miejscowymi środkami znieczulającymi w latach 2016-2020. Z drugiej strony liczba przypadków anafilaksji była niedoszacowana. Wystąpiły problemy z używaniem epinefryny i testowaniem narkotyków. Naszym zdaniem krajowe organy regulacyjne powinny zwracać większą uwagę na takie krajowe wytyczne.

Słowa kluczowe: *Nadwrażliwość na lek, Anafilaksja, Leki miejscowo znieczulające, Wstrząs anafilaktyczny, Alergia na lek.*

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1. Introductions

Drug hypersensitivity reactions (DHRs) are one of the major causes of morbidity among adults [1] and children [2] in the inpatient and outpatient settings. The modern approach to drug allergy and anaphylaxis management is based on the development of international and national guidelines, and on the estimation of their impact on health care [3-5]. In 2015, the Ukrainian National Drug Hypersensitivity and Anaphylaxis Guideline (UNDHAG) was developed according to the ADAPTE methodology [6]. This guideline was targeted at all physicians. UNDHAG clearly structured the levels of drug allergy and anaphylaxis care. For example, drug skin and provocation tests should be performed by allergists. Drug Hypersensitivity and Anaphylaxis guidelines from the European Academy of Allergy and Clinical Immunology, the American Academy of Allergy, Asthma and Immunology, the World Allergy Organization, the British Society for Allergy and Clinical Immunology, and the French Society of Anesthesia and Intensive Care were selected as source guidelines, as they received the highest AGREE-II score, and their evidence conforms with the scientific basis for this document.

Modern guidelines should initiate changes in clinical practice, induce physicians' and patients' adherence to following the conventional management and evidence-based medicine, and motivate researchers to provide new recommendations [7]. Hypersensitivity to local anesthetic agents might be used as a marker of guidelines' impact on clinical practice [8]. Hypersensitivity to local anesthetic agents is a rare condition in both adults and children [9, 10], but this hypersensitivity has a significant effect on society.

The aim of our study was to investigate the 5-year impact of UNDHAG on the management of drug hypersensitivity and anaphylaxis caused by local anesthetic agents.

2. Methods

After the release of the EAACI, WAO, and AAAAI guidelines on drug allergy and anaphylaxis, the Executive Committee of the Ukrainian Society of Specialists for Immunology, Allergology and Immunorehabilitation met with the leading clinical immunologists and allergists to adapt them for usage locally.

Guidelines were selected as source guidelines, as they received the highest AGREE-II score. The Ukrainian National Drug Hypersensitivity and Anaphylaxis Guideline (UNDHAG) was developed according to the ADAPTE methodology. UNDHAG was approved by the Ukrainian Ministry of Health Public Service on the 30th of December 2015. The first symposium for the UNDHAG implementation took place in March 2016, in Kyiv.

Prior to the implementation of this guideline in 2016 and after their 5-year use by 2020, physicians were interviewed with a special questionnaire. All respondents declared an awareness of the guideline. Respondents were selected randomly among physicians performing local anesthesia regularly. The questionnaire consisted of several sections: clinical facilities; physician specialty and experience; the number of local anesthesia per week; first aid availability and staffing; anesthesia type and anesthetics used; clinical characteristics of hypersensitivity reactions; epinephrine using; drug diagnostic tests; management of patients with hypersensitivity to local anesthetics; continuous medical education (Supplement 1). Questionnaire consists of several types of question, such as questions for collecting demography, occupational information; estimating of knowledge and understanding (with complete, incomplete answers, distractors and wrong answers). The same team of trained allergists interviewed physicians in 2016 and 2020. Information about anaphylaxis numbers

and anesthetics` adverse events was obtained from «The State Expert Center of the Ukrainian Ministry of Health Public Service».

Statistical analysis

We used Pearson's χ^2 test to compare 2 groups. The probability of $P<0.05$ was considered statistically significant.

3. Results

A total of 272 physicians were interviewed in 2016, and 269 – in 2020. The physician cohort comprised dentists 51.47% (37.64%), traumatologists/orthopedists 20.58% (6.27%) surgeons (otolaryngologists, ophthalmologists, gynecologists included) 16.17% (26.94%), anesthesiologists 11.02% (29.89%) and other specialists 0.73% (0.37%).

The work experience of physicians interviewed in 2016/2020 was as follows: up to 5 years – 10.29% (27.31%); 5-10 years – 15.44% (14.2%); 11-15 years – 11.39% (11.07%); 16-20 years – 15.80% (14.39%); 21-25 years – 17.64% (10.33%); 26-30 years – 14.33%, and more than 31 years – 15.07%. Thus, dentists and traumatologists with sufficient work experience were the majority within the total number of interviewees. The interviewed physicians worked in academic clinics 23.16% (23.99%), regional hospitals 38.97% (32.47%), municipal hospitals 28.30% (35.06%), and private clinics 8.08% (12.18%). Additionally, 48.89% (62.36%) of physicians worked at inpatient departments, 42.64% (26.57%) – at outpatient departments, and 9.55% (13.65%) in private settings. The physicians interviewed worked at clinical settings comprised by: up to 5 physicians – 45.95% (39.48%); 6-10 physicians – 11.39% (29.15%); 11-15 physicians – 23.16% (12.55%), more than 15 – 19.48% (18.82%).

The usual number of local anesthesia per week did not have a significant difference in 2016 and 2020. There were differences between types of local anesthesia – conduction anesthesia 15.12% (19.98%) (P=0.0012); epidural anesthesia 11.51% (15.64%) (P=0.0023); regional anesthesia 20.02% (12.77%) (P<0.001).

We observed an increase in the use of lidocaine up to 11.05% (21.86%) (P<0.0001); bupivacaine 7.99% (13.48%) (P<0.0001), and a decrease in the use of chloroprocaine, trimecaine, etidocaine, pyromecaine, oxybuprocaine, bimecaine, prilocaine (P<0.05) (Table 1).

We investigated the clinical characteristics of hypersensitivity reactions to local anesthetic agents reported by physicians in 2016/2020. Hypotension (80.63%), hypertension (75.34%), loss of consciousness (72.84%), abdominal syndrome (71.27%), skin reactions (70.2%), dyspnea (68.83%), anaphylaxis (66.95%) and anaphylactic shock (65.53%) were the most frequent reactions in 2016. There were significant differences in clinical characteristics in 2020, such as hypotension (95.68%; P=0.0133) and hypertension (53.65%; P=0.0036) (Table 2).

Epinephrine administration during anaphylaxis and anaphylactic shock decreased from 2016 to 2020. Proportions of physicians who administrated epinephrine in 2020 were lower than in 2016: ever used 38.97% and 29.89% (P<0.0001); in 70% of cases – 8.82% and 4.43% (P=0.0007). There was a dramatic increase in the number of physicians who never used epinephrine 1.1% and 39.85% (P<0.0001) (Table 3).

We observed a decrease in drug test frequency in 2016/2020: the number of physicians who never provided drug tests was 8.82% and 28.41%, respectively (P<0.0001); rarely – 30.88% and 28.62% (P=0.0747); usually – 24.26% and 16.98% (P=0.0484); ever – 34.92% and 29.52% (P=0.2189).

There was an increase in drug tests provided by allergists in 2016 and 2020 – 21.32% and 36.53% (P=0.0003), respectively. Also, a decrease in drug tests provided by other physicians was observed at 16.54% and 5.90% (P=0.0001).

During the observation period, we observed a decrease in conjunctival drug tests 25.73% and 2.58% (P<0.0001), and subcutaneous 27.94% and 18.45% (P=0.0183). Unfortunately, an increase in scarification at 37.50% and 46.49% (P=0.0032), and intradermal tests at 14.33% and 35.42% (P<0.0001) was detected.

Usually, physicians applied ready for use (undiluted) anesthetics for *in vivo* drug tests (50.36% and 50.92%). A smaller proportion of physicians used 1:10-1:100 dilution. We observed a significant increase in the frequency of individual dilutions for drug testing – 4.41% and 19.19% (P<0.0001).

Positive (histamine) and negative (saline) controls for *in vivo* drug tests were used as well: never – 69.85% and 76.38% (P=0.6978); rarely 13.97% and 14.02% (P=0.867); ever 8.45% and 8.12% (P=0.8283) (Table 4).

In the next step, the management of patients with suspected hypersensitivity to LA was investigated (Table 5). In most cases, physicians referred patients with suspected LA hypersensitivity to an allergist. However, we observed a decrease in these referrals from 2016 to 2020 – 55.14% and 46.86% (P=0.0247). At the same time, physicians changed the anesthesia type more frequently 6.98% and 18.45% (P=0.0002). Often physicians provided drug tests with LA from the other group and if the test was negative they administered alternative preparation (40.80% and 38.75%; P=0.4301).

In the case of confirmed hypersensitivity to LA, physicians referred patients to allergists to determine causative LA (75.36% and 69.37%; P=0.7018) and completed medical documentation with sufficient reaction description (70.22% and 70.11%; P=0.5663). Physicians referred patients to laboratory investigation only in 9.55% and 8.12% of cases (P=0.7985). 47.42% and 50.18% (P=0.1675) of respondents did not use any *in vitro* tests. We observed an increase in basophil degranulation/activation tests from 2.94% to 14.39% (P<0.0001) and a decrease in lymphocyte proliferation tests from 10.29% to 2.21% (P<0.0001).

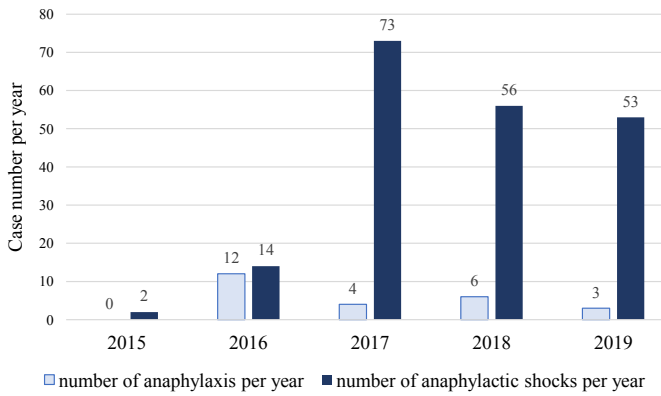

Figure 1. Prevalence of anaphylactic reactions in Ukraine (2015-2019).

Table 1. Number, type of local anesthesia and anesthetic agents used in 2016 and 2020.

		2016		2020		χ^2 test	
		(n)	(%)	(n)	(%)	χ^2	P value
Usual number of local anesthetics per week	up to 5	104	38.23	74	27.30	1.792	0.1807
	5-10	28	10.23	38	14.02	3.475	0.0623
	11-15	45	16.54	30	11.07	0.9968	0.3181
	16-20	40	14.70	39	14.39	0.2669	0.6054
	21-25	48	17.64	28	10.33	2.557	0.1098
	26-30	29	10.66	28	10.33	0.05108	0.8212
	over 30	26	9.55	36	13.28	3.509	0.061
Type of local anesthesia (in of order to frequencies decreased)	mucosal irrigation	186	15.98	261	15.94	0.0007292	0.9785
	conduction anesthesia	176	15.12	327	19.98	10.56	**0.0012**
	epidural/ peridural	134	11.51	256	15.64	9.323	**0.0023**
	infiltration	232	19.93	344	21.01	0.09408	0.7591
	regional	233	20.02	209	12.77	26.36	**< 0.0001**
	spinal	203	17.44	240	14.66	3.740	0.0531
Anesthetic agents used (in order to frequencies decreased)	novocaine (procaine)	146	8.27	188	13.48	0.0531	**< 0.0001**
	dicain (tetracaine)	91	5.16	77	5.52	0.1391	0.7092
	chloroprocain	54	3.06	21	1.51	7.465	**0.0063**
	trimecaine	68	3.85	31	2.22	6.299	**0.0121**
	articaine (ultracaine)	229	12.97	189	13.55	0.1764	0.6745
	anesthesin (benzocaine)	78	4.42	61	4.37	0.0005783	0.9808
	lidocaine (xicain)	195	11.05	305	21.86	67.62	**< 0.0001**
	mepivacaine	132	7.48	83	5.95	2.636	0.1044
	bupivacaine	141	7.99	188	13.48	24.57	**< 0.0001**
	ethidocaine	72	4.08	5	0.36	43.83	**< 0.0001**
	pyromecain	68	3.85	24	1.72	11.79	**0.0006**
	oxybuprocaine	95	5.38	23	1.65	29.19	**< 0.0001**
	proparacaine	112	6.35	36	2.58	23.90	**< 0.0001**
	bimecaine	101	5.72	34	2.44	19.77	**< 0.0001**
	prilocaine	82	4.65	37	2.65	8.004	**0.0047**
	other	101	5.72	93	6.67	1.047	0.3061

Table 2. Clinical characteristics of hypersensitivity reactions to local anesthetics.

Symptom	2016		2020		χ^2 test	
	(n)	(%)	(n)	(%)	χ^2	P value
hypotension	219	80.63	259	95.68	6.133	0.0133
hypertension	205	75.34	145	75.65	8.459	0.0036
loss of consciousness	198	72.84	192	70.83	0.008744	0.9255
abdominal syndrome	194	71.27	194	71.64	0.1743	0.6763
skin reactions	191	70.2	179	66.13	0.1097	0.7405
dyspnea	187	68.83	176	64.99	0.01107	0.9162
anaphylaxis	182	66.95	163	59.97	0.3459	0.5564
anaphylactic shock	178	65.53	178	65.77	0.1543	0.6944

Table 3. Epinephrine administration during anaphylaxis and anaphylactic shock, induced by local anesthetics.

(n)		2016		2020	χ^2 test		
		(%)	(n)	(%)	χ^2	P value	
Epinephrine injection by anaphylaxis and anaphylactic shock	ever	106	38.97	81	29.89	41.39	**< 0.0001**
	in 10% of cases	23	8.45	37	13.65	0.0007890	0.9776
	in 50% of cases	16	5.88	31	11.44	0.3356	0.5624
	in 70% of cases	24	8.82	12	4.43	11.38	**0.0007**
	never	3	1.1	108	39.85	80.13	**< 0.0001**

Table 4. Prevalence of drug tests and their characteristics.

(n)		2016		2020	χ^2 test		
		(%)	(n)	(%)	χ^2	P value	
Frequency of drug tests provided	never	24	8.82	77	24.41	33.47	**< 0.0001**
	rarely	84	30.88	64	23.62	3.177	0.0747
	usually	66	24.26	46	16.97	3.897	**0.0484**
	ever	95	34.92	80	29.52	1.511	0.2189
Staff provided tests	physician personally	101	37.13	99	36.53	0.03954	0.8424
	another physician	45	16.54	16	5.90	14.69	**0.0001**
	allergist	58	21.32	99	36.53	13.01	**0.0003**
	nurse	100	36.76	94	34.69	0.2965	0.5861
Types of drug tests	sublingual	34	12.50	34	12.55	0.004863	0.9444
	conjunctival	70	25.73	7	2.58	54.70	< 0.0001
	skin scarification	102	37.50	126	46.49	8.710	0.0032
	skin prick test	31	11.39	38	14.02	0.6655	0.4146
	intradermal	39	14.33	96	35.42	29.22	< 0.0001
	subcutaneous	76	27.94	50	18.45	5.565	0.0183
	unknown	27	9.92	23	8.49	0.1525	0.6962
Solutions for drug	ready for use (undiluted)	137	50.36	138	50.92	3.149	0.076
	dilution 1:10	30	11.02	28	10.33	0.6213	0.4306
	dilution 1:100	40	14.70	37	13.65	1.023	0.3119
	dilution 1:1000	17	6.25	22	8.12	0.02178	0.8827
	individual dilution for specific preparation	12	4.41	52	19.19	20.63	**< 0.0001**
Positive (histamine) and negative control use	never	190	69.85	207	76.38	0.1508	0.6978
	rarely	38	13.97	38	14.02	0.02803	0.867
	ever	23	8.45	22	8.12	0.04706	0.8283

Table 5. Management of patients with suspected hypersensitivity to local anesthetics.

Event	Action	2016		2020		Chi-square test	
		(n)	(%)	(n)	(%)	Chi-square	P value
Suspected hypersensitivity to local anesthetics by medical history	drug test with LA of other group, if the test is negative - administration of alternative preparation	111	40.80	105	38.75	0.6224	0.4301
	drug test with suspected LA, if the test is negative - administration of this LA	16	5.88	26	9.59	1.707	0.1914
	the change of anesthesia type	19	6.98	50	18.45	13.42	**0.0002**
	patient referred to an allergist	150	55.14	127	46.86	5.046	**0.0247**
Objectively confirmed hypersensitivity to local anesthetics	completion of medical documentation with a reaction description	191	70.22	190	70.11	0.3290	0.5663
	patient's referral to an allergist to determine the causative LA	205	75.36	188	69.37	0.1466	0.7018
	patient's referral to laboratory investigation	26	9.55	22	8.12	0.06515	0.7985
Application of *in vitro* test	tryptase concentration	6	2.20	17	6.27	2.836	0.0922
	specific immunoglobulin E management	69	25.36	85	31.37	0.0058	0.9393
	basophil degranulation / activation test	8	2.94	39	14.39	15.40	**< 0.0001**
	leukocyte lysis	21	7.72	31	11.44	0.6786	0.4101
	lymphocyte proliferation test	28	10.29	6	2.21	18.36	**< 0.0001**
	nothing of above	129	47.42	136	50.18	1.905	0.1675

We asked the national authority to provide official information about the prevalence of anaphylaxis and anaphylactic shock cases. As provided in Fig.1, there was an increase in anaphylaxis and anaphylactic shock cases in 2016 after the implementation of UNDHAG. A further increase in anaphylactic shock cases in 2017-2019 without an increase in anaphylaxis was observed.

4. Discussion

In 2015, the Ukrainian National Drug Hypersensitivity and Anaphylaxis Guideline (UNDHAG) was developed according to the ADAPTE methodology. Cardinally, UNDHAG was harmonized with the International consensus on drug allergy and the International consensus on (ICON) anaphylaxis (2014). At the same time, the Ukrainian Ministry of Health Public Service changed the policy for National Guidelines to make them more flexible. After that clinics were allowed to choose their preferred guidelines from international sources. Unfortunately, many clinics did not choose high-quality recommendations and guidelines.

To estimate the 5-year impact of UNDHAG on the management of drug hypersensitivity and anaphylaxis, we interviewed 272 physicians in 2016, and 269 – in 2020. The majority of physicians were dentists, surgeons, traumatologists/orthopedists. As the target drug group, the local anesthetics have been chosen due to their clinical importance [11].

A total of 272 physicians were interviewed in 2016, and 269 – in 2020. The physician cohort comprised mainly dentists, traumatologists/orthopedists, surgeons (otolaryngologists, ophthalmologists, gynecologists included), anesthesiologists with sufficient work experience (5-30 years). The interviewed physicians worked in academic clinics, regional hospitals, municipal hospitals, and private clinics (8-12%). Thus, the respondents' groups did not have significant differences.

We observed an increase in conduction, epidural anesthesia and a decrease in the frequency of regional anesthesia. A significant increase in the use of lidocaine, bupivacaine, and a statistically significant decrease in the use of chloroprocaine, trimecaine, etidocaine, pyromecaine, oxybuprocaine, bimecaine, prilocaine were found.

After the implementation of UNDHAG in 2020, there were significant differences in clinical characteristics of drug reactions – an increase in hypotension frequency and a decrease in hypertension. These data went in parallel with other observations of the high frequency of hypoten-

sion after local anesthetics administration [12].

Epinephrine administration during anaphylaxis and anaphylactic shock decreased from 2016 to 2020. The proportion of physicians who administrated epinephrine in 2020 were lower than in 2016. About 30% of physicians never used epinephrine. Paradoxically, today many investigators report the underuse of epinephrine in the prehospital and hospital settings [13-15].

There was an increase in drug tests provided by allergists. Furthermore, a decrease in drug tests provided by other physicians was observed. We observed a decrease in unvalidated tests using such as conjunctival and subcutaneous tests. Unfortunately, an increase in potentially harmful tests – scarification and intradermal tests – was detected. This observation conflicted with the state-of-art position that the evaluation of drug allergy included patch tests, skin prick tests and intradermal tests. Intradermal tests seem sensitive for immediate hypersensitive reactions to anesthetics [16].

Usually, physicians applied ready for use (undiluted) anesthetics for *in vivo* drug tests. Only a small proportion of physicians used 1:10-1:100 dilutions as well as positive (histamine) and negative (saline) controls. These observations displayed an inappropriate testing procedures of hypersensitivity to local anesthetics [17]. In contrast, allergists and other physicians were still using invalidated tests such as basophile degranulation as an alternative to mast cell activation tests [18].

In most cases (about 50%) of LA hypersensitivity, physicians referred patients to an allergist but a decrease in these referrals was observed. At the same time, physicians changed the anesthesia type more frequently. Often physicians provided drug tests with LA from the other group and if the test was negative they administered an alternative prescription. In 70% of cases of confirmed hypersensitivity to LA, physicians referred patients to allergists to determine causative LA and completed medical documentation with sufficient reaction description. Generally, these actions were in accordance with international guidelines [4,19-21].

We asked the national authority to provide official information about the prevalence of anaphylaxis and anaphylactic shock cases. There was an increase in anaphylaxis and anaphylactic shock cases in 2016 after the implementation of UNDHAG. Further growth of anaphylactic shock cases in 2017-2019 without an increase in anaphylaxis numbers was observed. This data supports the view that the number of anaphylaxis cases is still underestimated. The number of anaphylaxis cases should be significantly higher than that of anaphylactic shocks [22].

5. Conclusions

The Ukrainian National Drug Hypersensitivity and Anaphylaxis Guideline significantly influenced the management of hypersensitivity induced by local anesthetics from 2016 to 2020. On the other hand, the number of anaphylaxis cases was underestimated. There were issues with epinephrine use and drug testing. In our opinion, national regulators should pay more attention to such national guidelines.

Statements

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Not applicable

Statement of Ethics:

Written informed consent was obtained from all study participants. Ethics approval and consent to participate the study was approved by the Committee on Bioethics and Ethical Issues of Poltava State Medical University.

Conflict of Interest Statement

The authors declare that there are no competing interests regarding the publication of this paper.

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Author Contributions

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Data Availability Statement

All data generated or analyzed during this study are included in this published article.

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