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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией и Международной академией наук, образования, искусств и естествознания (IASEIA) США с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения.

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GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

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7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

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ავტორთა საყურადღებოდ!

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2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

ქალებში კონტროლირებული გაურთულებელი არტერიული ჰიპერტენზიით.

კვლევაში მონაწილეობა მიიღო 44 ქალმა (ძირითადი ჯგუფი) არტერიული ჰიპერტენზიის II ხარისხით, საშუალო ასაკი - 69,04±0,72 წ., მენოპაუზის ხანგრძლივობა - 18,4±0,85 წ. შედარების ჯგუფი შეადგინა 30 ჯანმრთელმა ქალმა, საშუალო ასაკი – 69±1,21 წ., მენოპაუზის ხანგრძლივობა - 19,4±1,18 წ. (p>0,05). პაციენტებს ჩაუტარდა ზოგადი კლინიკური და ლაბორატორიული კვლევა ლიპიდების დონის განსაზღვრით სისხლში. შეფასებულია პულსური ტალღის პარამეტრები (SphygmoCor), ძვლოვანი ქსოვილის მინერალური სიმკვრივე, 25 (OH) D-ის, პარა-თიროიდული ჰორმონის, ტიპი 1 ამინოტერმინალური პროკოლაგენის პროპეპტიდის, ხ-ი ზომერიზებული C–ტელოპეპტიდების, იონიზებული კალციუმის და ფოსფორის დონე სისხლის შრატში.

პარამეტრების შესწავლით მიღებული მონაცემები მიუთითებს ათეროკალცინოზის, არტერიული კედლის სიმტკიცის მომატების და ოსტეოპოროზის ერთობლივი პათოგენეზური მექანიზმების არსებობის შესაძლებლობის შესახებ.

CHARACTERISTICS OF DRUG RESISTANT TUBERCULOSIS IN GEORGIA (2015-2020)

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In 2019, an estimated 10 million people fell ill with tuberculosis (TB) worldwide (5.6 million men, 3.2 million women and 1.2 million children). A total of 1.4 million people died from TB in 2019 (including 208 000 people with HIV). Worldwide, TB is one of the top 10 causes of death and the leading cause from a single infectious agent (above HIV/AIDS). Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat. A global total of 206 030 people with multidrug- or rifampicin-resistant TB (MDR/RR-TB) were detected and notified in 2019, a 10% increase from 186 883 in 2018. Worldwide, only 57% of MDR-TB patients are currently successfully treated [1,2].

According to the World Health Organization (WHO), in 2018, the total number of notified TB Cases in Georgia was 2 590 (incidence – 65 cases per 100 000 population).

MDR-TB was diagnosed in 12% of new, and in 31% of previously treated cases. The treatment outcome was defined as successful in 65% of MDR/RR-TB and in 56% of XDR-TB cases started on second-line treatment in 2016 (cohorts – 339 and 55, respectively) [3].

For three decades, drug-resistant tuberculosis (TB) has posed grave challenges to patients, communities and global TB control efforts. Treatment of multidrug-resistant (MDR)-TB and extensively drug-resistant (XDR)-TB was relied on medications that are less potent and more toxic than first-line TB therapy, which is used for treatment of drug susceptible TB. Consequently, prolonged drug-resistant TB treatment was associated with frequent and severe side-effects. This led to the high rate of unfavorable treatment outcomes. Fortunately, in recent years TB world globally has several key innovations that, together, have brought us to a tipping point in revolutionizing the care of patients with MDR- and XDR-TB. In 2012, bedaquiline, the first new TB medication in more than 40 years, was approved by the US Food and Drug Administration (FDA). Approximately 6 months later, delamanid, in yet another new drug class, was approved by the European Medicines Agency [4]. Since 2019, based on WHO's recommendations toxic injectable agents (Kanamycin and Capreomycin) are removed from the DR-TB regimens and patients has the access to the shorter fully oral regimens [5-6]. From 2020, the new treatment regimen with next new drug - Pretomanid is recommended for treatment of XDR-TB patients [6].

Georgia as the part of TB world has always had access to the all previously and newly recommended treatment regimens and today, at the stage of transition from old to new DR-TB treatment, it's important to compare general characteristics of different DR-TB cohorts and to assess possibility to raise the effectiveness of DR-TB treatment in the future.

Material and methods. A retrospective cohort study was conducted with individual data of >18 years old DR-TB patients from 2015 -2020 cohorts, whose treatment outcome was defined until August 2020.

Considering the inclusion criteria, 1581 DR-TB patients (n=503[2015 cohort] + n=387[2016 cohort] + n=345[2017 cohort] + n=229[2018 cohort] + n=113[2019 cohort] + n=4[2020 cohort]), with known treatment outcomes were selected as study participants.

The study was conducted at the National Center for Tuberculosis and Lung Disease as a part of the Georgian National TB Programme. During the study period the treatment of DR-TB patients was provided based on latest WHO's recommendations and in different cohorts the different combinations of old, repurposed or new II line drugs with different duration was used.

Data variables were collected in relation to study objectives and included socio-demographic characteristics, laboratory data, data about susceptibility to the anti-TB drugs, treatment regimens and treatment outcomes.

Treatment was defined as successful in case of "Cured" and "Completed" treatment. "Failure", "Default", "Not Evaluated" and "Death" was defined as unsuccessful outcomes.

The data collected were analyzed by using of EasyStat (https://easystat.app). A descriptive analysis was performed for socio-demographic, behavioral and clinical characteristics. Bivariate and multivariate logistic regression analysis was used to measure the link between these characteristics and treatment outcomes. Odds ratios and their 95% confidence intervals were calculated. All the variables significant at $p<0.05$ in the bivariate analysis were included in the adjusted model.

Permission to carry out the study was obtained from the National Center for Tuberculosis and Lung Diseases (NCTLD) in Georgia. Local ethics approval was obtained from the Ethics Review Board of the NCTLD.

Results and discussion. The data of 2031 DR-TB patients from 2015 and 2020 cohorts were extracted from the National Tuberculosis Electronic Register. According to the inclusion criteria, 1581 DR-TB patients with known treatment outcomes were selected as the study participants (Fig. 1).

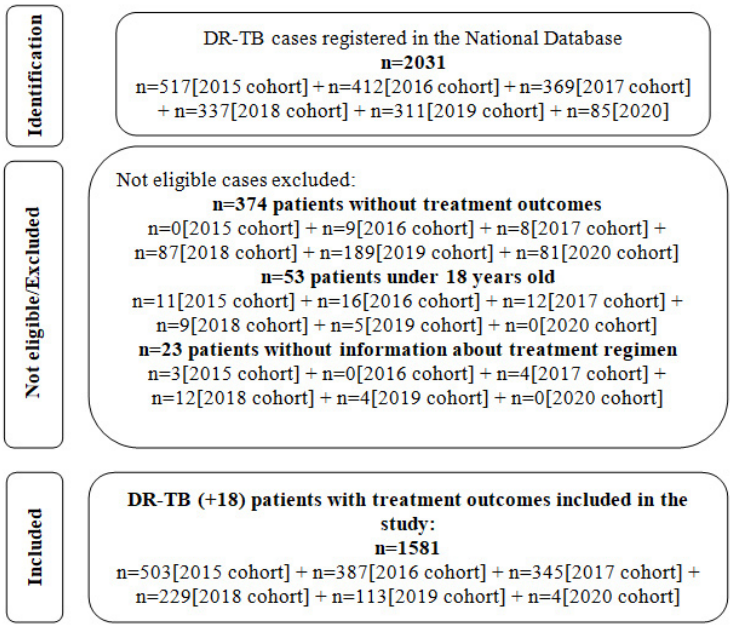


Fig. 1. Study flow chart

Table 1. Socio-demographic and clinical characteristics of the study participants, N=1581 (DR-TB patients with known treatment outcomes, Georgia, 2015–2020 cohorts)

Categories	Subcategories	Total N=1581
Gender (n,%)	Female	322 (20.4%)
	Male	1259 (79.6%)
Age (n,%)	>55	290 (18.3%)
	18-34	566 (35.8%)
	35-54	725 (45.9%)
Region (n,%)	High	675 (42.7%)
	Low	215 (13.6%)
	Middle	691 (43.7%)
Region_1 (n,%)	Adjara	130 (8.2%)
	Guria	22 (1.4%)
	Imereti	138 (8.7%)
	Kakheti	51 (3.2%)
	Kvemo Kartli	134 (8.5%)
	Mtskheta-mtianeti	23 (1.5%)
	Prison	89 (5.6%)
	Racha-Lechkhumi	3 (0.2%)
	Samegrelo	200 (12.7%)
	Samtskhe-Javakheti	45 (2.8%)
	Shida Kartli	71 (4.5%)
	Tbilisi	675 (42.7%)

Categories	Subcategories	Total N=1581
Employment (n,%)	Employed	186 (11.8%)
	Military	2 (0.1%)
	Unemployed	1393 (88.1%)
Alcohol abuse (n,%)	Excessive	127 (8%)
	Moderate	538 (34%)
	None	916 (57.9%)
Illicit Drug abuse (n,%)	No	1245 (78.7%)
	Unknown	256 (16.2%)
	Yes	80 (5.1%)
HIV (+) (n,%)	No	1479 (93.5%)
	Yes	102 (6.5%)
AFB (+) (n,%)	No	690 (43.6%)
	Not done	7 (0.4%)
	Yes	884 (55.9%)
Culture (+) (n,%)	No	26 (1.6%)
	Not Done	176 (11.1%)
	Yes	1379 (87.2%)
TB form (n,%)	EPTB	83 (5.2%)
	PTB	1498 (94.8%)
TB Case (n,%)	New Case	782 (49.5%)
	Previously Treated Case	799 (50.5%)
Hr (n,%)	_	305 (19.3%)
	No	58 (3.7%)
	Yes	1218 (77%)
RR (n,%)	_	96 (6.1%)
	No	109 (6.9%)
	Yes	1376 (87%)
Er (n,%)	_	344 (21.8%)
	No	279 (17.6%)
	Yes	958 (60.6%)
Zr (n,%)	_	797 (50.4%)
	No	245 (15.5%)
	Yes	539 (34.1%)
Sr (n,%)	_	398 (25.2%)
	No	80 (5.1%)
	Yes	1103 (69.8%)
Kmr (n,%)	_	312 (19.7%)
	No	778 (49.2%)
	Yes	491 (31.1%)
Cmr (n,%)	_	321 (20.3%)
	No	1076 (68.1%)

Categories	Subcategories	Total N=1581
	Yes	184 (11.6%)
Ofxr (n,%)	_	320 (20.2%)
	No	829 (52.4%)
	Yes	432 (27.3%)
Ptor (n,%)	_	1489 (94.2%)
	No	66 (4.2%)
	Yes	26 (1.6%)
Etor (n,%)	_	1536 (97.2%)
	No	38 (2.4%)
	Yes	7 (0.4%)
PASr (n,%)	_	497 (31.4%)
	No	985 (62.3%)
	Yes	99 (6.3%)
Csr (n,%)	_	1496 (94.6%)
	No	76 (4.8%)
	Yes	9 (0.6%)
Amx/clvr (n,%)	_	1574 (99.6%)
	No	7 (0.4%)
Cfzr (n,%)	_	1572 (99.4%)
	No	9 (0.6%)
Bdq and/or Dlm in the regimen (n,%)	Bdq	336 (21.3%)
	Bdq+Dlm	102 (6.5%)
	Dlm	140 (8.9%)
	No	1003 (63.4%)
New drug in the regimen	No	1003 (63.4%)
(Bdq or Dlm or Bdq+Dlm) (n,%)	Yes	578 (36.6%)
Fq in the regimen (n,%)	LFX	511 (32.3%)
	MFX	810 (51.2%)
	No	260 (16.4%)
Fq in the regimen (n,%)	No	260 (16.4%)
	Yes	1321 (83.6%)
Treatment outcome (n,%)	Successful	987 (62.4%)
	Unsuccessful	594 (37.6%)
Treatment outcome_1 (n,%)	Completed	141 (8.9%)
	Cured	846 (53.5%)
	Default	318 (20.1%)
	Died	88 (5.6%)
	Failure	133 (8.4%)
	Not Evaluated	55 (3.5%)

Legend:

HIV – human immunodeficiency virus	Sr- Streptomycin resistance	Csr- Ciclosiren resistance

PTB- Pulmonary Tuberculosis	Kmr – Kanamycin resistance	Amx/clvr – Amoxicillin/clavulanate resistance
EPTB – Extrapulmonary Tuberculosis	Cmr – Capreomycin resistance	Cfz- Clofazimine resistance
Hr – Isoniazid resistance	Ofxr – Ofloxacin resistance	Bdq - Bedaquiline
RR-Rifampicin resistance	Ptor – Prothionamide resistance	Dlm – Delamanid
Er – Ethambutol resistance	Etor- Ethionamide resistance	LFX – Levofloxacin
Zr- Pyrazinamide resistance	PASr- para-aminosalicylic acid resistance	MFX - Moxifloxacin

As the first stage the socio-demographic and clinical characteristics of selected 1581 (100%) DR-TB patients were summarized (Table 1). The majority of the DR-TB patients were Males (79.6%), from 35-54 age group (45.9%), from the regions with the middle (100-500 cases) TB prevalence (43.7%), unemployed persons (88.1%), without alcohol (57.9%) or illicit drug (78.7%) abuse.

Based on the study data 1498 (94.8%) patients were diagnosed as the pulmonary and 83 (5.2%) patients as the extrapulmonary TB cases. 782 (49.5%) patients were defined as the "New" and 799 (50.5%) as the "Previously treated" cases. HIV status of 102 (6.5%) DR-TB patients were positive.

Laboratory tests conducted at initial stage of diagnosis was AFB positive in 884 (55.9%) cases and Culture positive in 1379 (87.2%) cases. The data of the resistance to the key anti-TB drugs was following: Rifampicin resistance was detected in 1376 (87%), Isoniazid resistance in 1218 (77%) and Ofloxacin resistance in 432 (27.3%) cases.

Fluoroquinolones (Levofloxacin or Moxifloxacin) as the key anti-DR-TB drugs was used in the 1321 (83.6%) regimens. Bedaquiline (Bdq), or Delamanid (Dlm), or Bedaquiline and Delamanid together was used in the treatment regimen of 578 (36.6%) patients. Bdq as alone new drug was used in the majority of cases (336 (21.3%)), Dlm alone was used in 140 (8.9%) and Bdq and Dlm together in 102 (6.5%) cases.

Data of the new drugs (Bdq and/or Dlm) in the DR-TB regimens by cohort shows a picture of their implementation over the years (Table 2 and Fig. 2). If in 2015 the new drugs was prescribed in 18% cases, in 2019 this number was raised to the 84%. In 2016-2018, Bdq was prescribed in half of cases (52.7%-44.9%-46.6%) and in 2019 this number was raised to the 80%. Number of regimens with Dlm alone, or with Bdq and Dlm together was low comparing to the regimens with Bdq alone and this number in case of Dlm was decreased from maximum 36% (2017) to 3.2% (2019) and in case of Bdq+Dlm from maximum 29.6% (2018) to 16.8% (2019) of cases. These data is in line with WHOs recommendations based on which in period from 2015 to 2018 using of Bdq and Dlm separately or in combination was equally recommended. Since 2019, Bdq is recommended as the first choice "A" group drug, while Dlm, due the low safety, is recommended as the last choice "C" group drug [5-7].

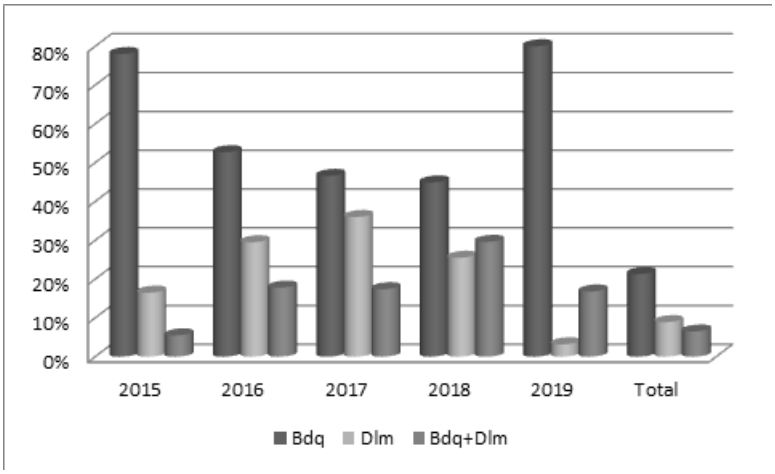
From the study population the successful treatment outcome was defined in 987 (62.4%) ("Cured" in 846 (53.5%) and "Completed" in 141 (8.9%) cases) and unsuccessful outcome in 594 (37.6%) cases ("Lost to follow-up" in 318 (20.1%), "Failure" in 133 (8.4%), "Death" in 88 (5.6%) and "Not evaluated" in 55 (3.5%) cases).

All key factors were analyzed for association with the treatment outcomes. The adjusted analysis was used for factors defined as significantly associated with the treatment outcomes (Table 3).

Table 2. Data of the new drugs in the DR-TB regimens and treatment outcomes by cohorts (2015-2020)

	New drug in the regimen			**Successful outcome**	**Unsuccessful outcome**
	Bdq	**Dlm**	**Bdq+Dlm**		
	n=91 (18%)				
2015 (n=503 100%))	71 (78%)	15 (16.5%)	5 (5.5%)	287 (57%)	216 (43%)
	n=129 (33.3%)				
2016 (n=387 (100%))	68 (52.7%)	38 (29.5%)	23 (17.8%)	260 (67%)	127 (33%)
	n=161 (47%)				
2017 (n=345 (100%))	75 (46.6%)	58 (36%)	28 (17.4%)	223 (64.6%)	122 (35.4%)
	n=98 (43%)				
2018 (n=229 (100%))	44 (44.9%)	25 (25.5%)	29 (29.6%)	150 (65.5%)	79 (34.5%)
	n=95 (84%)				
2019 (n=113 100%))	76 (80%)	3 (3.2%)	16 (16.8%)	67 (59.3%)	46 (40.7%)
	n=4 (100%)				
2020 (n=4 (100%))*	2 (50%)	1 (25%)	1 (25%)	0 (0%)	4 (100%)
	n=578 (36.6%)				
Total (n=1581 (100%))	336 (21.3%)	140 (8.9%)	102 (6.5%)	987 (62.4%)	594 (37.6%)

**Study population was selected from the patients with known treatment outcomes. By August 2020, in the National Tuberculosis Electronic Register the treatment outcomes of 4 patients were entered only*



Legend: Bdq- Bedaquiline; Dlm - Delamanid
Fig. 2. New drugs in the DR-TB regimens by years (2015-2019)

Table 3. Factors associated with TB treatment outcomes (DR-TB cases, Georgia, 2015–2020 cohorts)

Categories	Subcategories	Total N=8468	Successful N=6833	Unsuccessful N=1635	Bivariate			Multivariate		
					OR	95% CI	p	OR	95% CI	p
Gender (n,%)	Female	322 (20.4%)	247 (25%)	75 (12.6%)	2.31	[1.74, 3.06]	<0.001	1.78	[1.33, 2.39]	<0.001
	Male	1259 (79.6%)	740 (75%)	519 (87.4%)	1			ref.	ref.	ref.
Age (n,%)	>55	290 (18.3%)	179 (18.1%)	111 (18.7%)	1	-	-			
	18-34	566 (35.8%)	357 (36.2%)	209 (35.2%)	1.06	[0.79, 1.42]	0.699			
	35-54	725 (45.9%)	451 (45.7%)	274 (46.1%)	1.02	[0.77, 1.35]	0.886			
Region (n,%)	High	675 (42.7%)	414 (41.9%)	261 (43.9%)	1	-	-			
	Low	215 (13.6%)	130 (13.2%)	85 (14.3%)	0.96	[0.7, 1.32]	0.82			
	Middle	691 (43.7%)	443 (44.9%)	248 (41.8%)	1.13	[0.9, 1.4]	0.289			
Employment (n,%)	Employed	186 (11.8%)	143 (14.5%)	43 (7.2%)	1	-	-			
	Military	2 (0.1%)	2 (0.2%)	0 (0%)	Inf	[0.06, Inf]	1			
	Unemployed	1393 (88.1%)	842 (85.3%)	551 (92.8%)	0.46	[0.32, 0.66]	<0.001			
Alcohol abuse (n,%)	Excessive	127 (8%)	71 (7.2%)	56 (9.4%)	1	-	-			
	Moderate	538 (34%)	314 (31.8%)	224 (37.7%)	1.11	[0.75, 1.63]	0.614			
	None	916 (57.9%)	602 (61%)	314 (52.9%)	1.51	[1.04, 2.2]	0.0303			
Illicit Drug abuse (n,%)	No	1245 (78.7%)	819 (83%)	426 (71.7%)	1	-	-			
	Unknown	256 (16.2%)	131 (13.3%)	125 (21%)	0.55	[0.42, 0.72]	<0.001			
	Yes	80 (5.1%)	37 (3.7%)	43 (7.2%)	0.45	[0.28, 0.71]	<0.001			
HIV (+) (n,%)	No	1479 (93.5%)	946 (95.8%)	533 (89.7%)	2.64	[1.75, 3.98]	<0.001	2.33	[1.53, 3.55]	<0.001
	Yes	102 (6.5%)	41 (4.2%)	61 (10.3%)	1			ref.	ref.	ref.
AFB (+) (n,%)	No	690 (43.6%)	435 (44.1%)	255 (42.9%)	1	-	-			
	Not done	7 (0.4%)	4 (0.4%)	3 (0.5%)	0.78	[0.13, 5.38]	0.714			
	Yes	884 (55.9%)	548 (55.5%)	336 (56.6%)	0.96	[0.78, 1.17]	0.669			
Culture (+) (n,%)	No	26 (1.6%)	16 (1.6%)	10 (1.7%)	1	-	-			
	Not Done	176 (11.1%)	106 (10.7%)	70 (11.8%)	0.95	[0.41, 2.2]	0.898			
	Yes	1379 (87.2%)	865 (87.6%)	514 (86.5%)	1.05	[0.47, 2.34]	0.901			
TB Form (n,%)	EPTB	83 (5.2%)	49 (5%)	34 (5.7%)	0.86	[0.55, 1.35]	0.512			
	PTB	1498 (94.8%)	938 (95%)	560 (94.3%)	1					

Categories	Subcategories	Total N=8468	Successful N=6833	Unsuccessful N=1635	Bivariate			Multivariate		
					OR	95% CI	p	OR	95% CI	p
TB Case (n,%)	New Case	782 (49.5%)	575 (58.3%)	207 (34.8%)	2.61	[2.11, 3.22]	<0.001	2.34	[1.88, 2.91]	<0.001
	Previously Treated Case	799 (50.5%)	412 (41.7%)	387 (65.2%)	1			ref.	ref.	ref.
Hr (n,%)	_	305 (19.3%)	197 (20%)	108 (18.2%)	1	-	-			
	No	58 (3.7%)	38 (3.9%)	20 (3.4%)	1.04	[0.58, 1.88]	0.892			
	Yes	1218 (77%)	752 (76.2%)	466 (78.5%)	0.88	[0.68, 1.15]	0.358			
RR (n,%)	_	96 (6.1%)	59 (6%)	37 (6.2%)	1	-	-			
	No	109 (6.9%)	77 (7.8%)	32 (5.4%)	1.51	[0.84, 2.7]	0.165			
	Yes	1376 (87%)	851 (86.2%)	525 (88.4%)	1.02	[0.66, 1.56]	0.94			
Ofxr (n,%)	_	320 (20.2%)	209 (21.2%)	111 (18.7%)	1	-	-			
	No	829 (52.4%)	544 (55.1%)	285 (48%)	1.01	[0.77, 1.33]	0.921			
	Yes	432 (27.3%)	234 (23.7%)	198 (33.3%)	0.63	[0.47, 0.85]	0.00213			
New drug in the regimen (n,%)	No	1003 (63.4%)	595 (60.3%)	408 (68.7%)	0.69	[0.56, 0.86]	<0.001			
	Yes	578 (36.6%)	392 (39.7%)	186 (31.3%)	1					
Fq in the regimen (n,%)	No	260 (16.4%)	147 (14.9%)	113 (19%)	0.74	[0.57, 0.98]	0.0319			
	Yes	1321 (83.6%)	840 (85.1%)	481 (81%)	1					

Legend: ref. – reference category

In bivariate analysis, TB treatment success was positively associated with the female gender (OR 2.31; 95% CI [1.74–3.06]; p<0.001); new case (OR 2.61; 95% CI [2.11-3.22]; p<0.001); and with HIV negative status (OR 2.64; 95% CI [1.75–3.98]; p<0.001).

Adjusted analysis confirms significant association of a successful TB treatment outcome with the female gender (adjusted OR 1.78, 95% CI: 1.33 – 2.39, p<0.001), new TB case (adjusted OR 2.34, 95% CI: 1.88–2.91, p<0.001) and with HIV negative status (OR 2.33; 95% CI 1.53–3.55; p<0.001). Association of a treatment outcome with other key factors, including "New drugs in the regimen" was not found.

Data of the new drugs (Bdq and/or Dlm) in the DR-TB regimens in total and by cohort was assessed to evaluate association between regimens with the new drugs and successful treatment outcomes. Based on bivariate and multivariate analysis association between these factors ("New drugs in the regimen" and "Treatment outcomes") was not found. This may be explained by the fact that until 2019, Bdq and/or Dlm mostly were prescribed in combination with less effective and safe drugs, which based on the latest WHO's recommendations are defined as the last choice "C" group drugs. Since 2019, Bdq is mostly prescribed in combination with other "A" and "B" group drugs, but the number of DR-TB patients on such regimens with known treatment outcomes was low in the study population and does not allow reliable assessment. Further studies are necessary to assess complete data of the patients on new DR-TB regimens and its association with the treatment outcomes.

Statistical analysis also excluded association between treatment outcome and factors such as Alcohol or Illicit drug abuse and etc. This suggests that the factors that are proven to be associated with the increased risks for development of TB disease, does not have the statistically significant impact on the overall rate of the unfavorable treatment outcomes. But to what extent the other factors, such as effectiveness of the DR-TB regimens may affect on the treatment outcome, should be evaluated through the complete assessment and comparison of past, current and potentially applicable DR-TB regimens in the future.

Study data show, that despite of many efforts the rate of "Lost to follow-up" is still high in DR-TB cases (318 (20.1%)) and filling this gap still requires additional activities.

Study also shows that rate of "New" and "Previously treated" DR-TB cases are almost equal (782 (49.5%) "New" and 799 (50.5%) "Previously treated" cases). This indicates the high risk of DR-TB transmission and necessity to improve the quality of infection control measures at country level.

Adjusted analysis show, that "Female gender", "New case" and HIV negative status are significantly associated with successful TB treatment outcomes, which is in line with the results of previously conducted similar studies [8,9].

Limitations of the study. As mentioned, the study population was selected from the patients whose treatment outcomes were known by August 2020. 189 patients from 2019 cohort and 81 patients from 2020 cohorts with unknown treatment outcomes were excluded from the study (the treatment outcomes of only 4 patients from 2020 cohort were entered in the National Tuberculosis Electronic Register). As a result the study contains limited information about DR-TB patients from the last two cohorts, where the new DR-TB regimens most widely were used. This is the main reason why the new DR-TB regimens and its association with treatment outcomes were not fully assessed and this is the main limitation of the study.

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SUMMARY

CHARACTERISTICS OF DRUG RESISTANT TUBERCULOSIS IN GEORGIA (2015-2020)

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The aim of the study was to assess general characteristics of drug resistant tuberculosis and its association with treatment outcomes in Georgia. A retrospective cohort study was conducted among 1581 DR-TB adult (18+) patients, from 2015 - 2020 cohorts, whose anti-tuberculosis treatment outcomes was known. Adjusted analysis of the study participants data [1581 (100%)] shows significant association of a successful TB treatment outcome with the "Female gender" (adjusted OR 1.78, 95% CI: 1.33 – 2.39, p<0.001), "New TB case" (adjusted OR 2.34, 95% CI: 1.88–2.91, p<0.001) and with "HIV negative status" (OR 2.33; 95% CI 1.53–3.55; p<0.001).

Based on bivariate and multivariate analysis of the study data, the significant association of a treatment outcome with other key factors, including "New drugs in the regimen" was not found.

Since the programmatic using of the new effective DR-TB regimens are widely recommended only from 2019, the treatment outcomes of all patients on these regimens are still not defined. Further studies are necessary to assess complete data of the patients on new DR-TB regimens and its association with the treatment outcomes.

Keywords: Tuberculosis, Drug Resistant Tuberculosis (DR-TB), New anti-DR-TB drugs/regimens, TB treatment outcomes.

РЕЗЮМЕ

ХАРАКТЕРИСТИКА ЛЕКАРСТВЕННО-УСТОЙЧИВОГО ТУБЕРКУЛЕЗА В ГРУЗИИ (2015-2020)

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Целью исследования явилась оценка общих характеристик лекарственно-устойчивого туберкулеза и результатов его лечения в Грузии.

Проведено ретроспективное (2015-2020 гг.) когортное исследование 1581 пациента старше 18 лет с лекарственно-устойчивым туберкулезом (ЛУ-ТБ), чьи исходы противотуберкулезного лечения были известны. Уточненный анализ данных участников исследования показал статистический достоверную связь успешного исхода лечения туберкулеза у женщин (уточненное ОШ 1.78, 95% ДИ: 1.33 – 2.39, p<0,001), с "новым случаем туберкулеза" (уточненное ОШ 2.34, 95% ДИ: 1.88-2.91, p<0,001) и с "ВИЧ отрицательным статусом" (уточненное ОШ 2.33, 95% ДИ: 1.53-3.55, p<0,001). Двухмерный и многомерный анализы результатов исследования достоверной связи исхода лечения с другими ключевыми факторами, включая «новые препараты в схеме», не выявили. Поскольку программное использование новых эффективных схем лечения ЛУ-ТБ широко рекомендуется только с 2019 года, результаты лечения по этим схемам по сей день не определены. Авторы считают целесообразным проведение дальнейших исследований с целью оценки эффективности новых схем лечения ЛУ-ТБ.

რეზიუმე

რეზისტენტული ტუბერკულოზის მახასიათებლები საქართველოში (2015-2020)

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კვლევის მიზანს წარმოადგენს რეზისტენტული ტუბერკულოზის ძირითადი მახასიათებლების და მათი

მკურნალობის გამოსავალთან ასოცირების შეფასება.

2015-2020 წწ. ჩატარდა რეტროსპექტული კოჰორტული კვლევა 1581 მოზრდილი (18+) პაციენტთის, რომელთა მკურნალობის გამოსავალი ცნობილი იყო.

კვლევის მონაწილეთა მონაცემების დაზუსტებულმა ანალიზმა აჩვენა, რომ რეზისტენტული ტუბერკულოზის საწინააღმდეგო მკურნალობის წარმატებული გამოსავალი სარწმუნოდ ასოცირდება „მდედრობით სქესთან“ (adjusted OR 1.78, 95% CI: 1.33 – 2.39, p<0.001), „ახალ შემთხვევასთან“ (adjusted OR 2.34, 95% CI: 1.88–2.91, p<0.001) და „ახალ აივ ნეგატიურ სტატუსთან” (OR 2.33; 95% CI 1.53–3.55; p<0.001).

კვლევის მონაცემთა ბი- და მულტივარიაციულ ანალიზზე დაყრდნობით, მკურნალობის გამოსავლის სარწმუნო ასოცირება რეზისტენტული ტუბერკულოზის სხვა საკვანძო მახასიათებლებთან, მათ შორის „ახალი ტუბსაწინააღმდეგო მედიკამანტების შემცველი რეჟიმებით მკურნალობასთან“, არ გამოვლინდა.

რეზისტენტული ტუბერკულოზის ახალი, ეფექტური რეჟიმებით პროგრამული მკურნალობა ფართოდ რეკომენდებულია 2019 წლიდან, აქედან გამომდინარე, სადღეისოდ ამ რეჟიმებზე მყოფი ყველა პაციენტის მკურნალობის გამოსავალი არ არის შეფასებული. ავტორებს მიზანშეწონილად მიაჩნია რეზისტენტული ტუბერკულოზის სამკურნალო ახალ რეჟიმებზე მყოფი პაციენტების სრული მონაცემების და მათი მკურნალობის გამოსავალთან ასოცირების სრულყოფილად შესასწავლად დამატებითი კვლევების ჩატარება.

CYPRESS POLLEN SESITIZATION IN GEORGIA: CLINICAL AND MOLECULAR CHARACTERISTICS

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Cypress pollen allergy is a widely distributed, highly prevalent and severe winter pollinosis [3] that may be caused by several Cupresaceae species around the Mediterranean basin, in North America and Asia. Exposure to cypress pollen has increased steadily over the last few decades and the prevalence of allergy to cypress pollen has also dramatically increased from 0.6% to 9.8% in the general population and from 9% to 35% in allergic patients, probably because of the allergen load has become more intense [2]. The first cases of cypress pollinosis were described in South Africa in 1945 and in France in 1962. During the following decades, cypress species have been extensively planted for ornamental purpose, since they have low water needs, fast growth and have a low-cost maintenance [3]. These plants are anemophilous, shedding large amounts of pollen, being an important cause of allergic diseases, especially during the winter [5]. This increased exposure has been responsible for the increase in prevalence of sensitization and clinical manifestations of cypress pollen allergy [7].

Concerning the clinical expression, the main clinical symptom associated with allergy to cypress tree pollen is rhinitis, often associated with disabling conjunctivitis, whereas the incidence of asthma is generally lower than in patients sensitized to other allergenic sources [6]. The allergic reactions to *Cupressaceae* pollen, which usually occur in winter, could have overlapping symptoms with common cold or influenza [5]. Cypress pollinosis symptoms are often hard to control. Caimmi reported a 57.9% of cypress pollen allergic patients needing immunotherapy to control their symptoms [2].

In Mediterranean areas, C. sempervirens (Italian cypress or Mediterranean cypress) is by far the most common pollinating species. It accounts for half of the total pollination level [3]. According to Georgian pollen count data, cypress pollen is the major aeroallergen component in winter and early spring [1], but there have been no studies regarding the influence of cypress pollen high exposure in patients with pollen allergy. Thus, the objective of the study was to evaluate cypress pollen allergy in Georgia and describe clinical characteristics and the molecular profile of sensitization.

Material and methods. Patients attended to allergy clinic with suspected cypress pollen allergy (n=492) were included. Diagnostic workup was performed according to local guidelines, specific IgE antibody against cypress allergen was performed using ImmunoCAP and ISAC assay platform. Primary cypress pollen reactivity was confirmed by measuring IgE specific to *Cupressus arizonica* component Cup a 1 (t226) and *Cupressus Sempervirens* extract (t23) by ImmunoCAP (ThermoFisher, Uppsala, Sweden). IgE levels exceeding 0.35 kU/L were considered positive. The allergen microarray assay (ImmunoCAP ISAC; ThermoFisher) was used to analyse the specific IgE repertoire of cypress positive patient's serum. ISAC is a test for semi-quantitative determination of IgE in serum samples. The solid phase in this test is provided by the surface of a plate on which 112 components (43 native and 69 recombinant) have been adsorbed and arranged in triplets. Antibody levels were expressed in standardised units, ISU-E (ISAC Standardised Unit for specific IgE). The measured values ranged from 0.3 to 100 ISU-E, and values ≥ 0.30 ISU-E were considered to be positive results.

Symptoms Diary. Cypress positive patients were interviewed with the seasonal symptom's questionnaire. The severity of eye (itching and/or tear flow and/or conjunctival redness), nose (sneezing and/or runny nose and/or blocked nose), and bronchial (cough and/or wheezing and/or asthma) symptoms were recorded on a 4-point scale (0, no symptoms; 1, mild symptoms; 2, moderate symptoms; 3, severe symptoms). They were asked regarding medication use (antihistamines, local treatment for conjunctivitis and/or rhinitis and asthma) during the cypress season.

Plant Aeroallergens/Pollen Monitoring. The airborne pollen