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B-LACTAM ANTIBIOTICS IN UKRAINE: MARKET AND CONSUMPTION ANALYSIS IN 2013–2018

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Стратегія боротьби проти розвитку антибіотикорезистентності – глобальний виклик для наукової спільноти задля життя і здоров'я населення. Аналіз взаємозв'язку між рівнями споживання антимікробних препаратів та розвитком антибіотикорезистентності – один з інструментів стримування останньої. Збільшення споживання антимікробних препаратів знижує можливості лікування інфекційних захворювань.

Антимікробні препарати групи β-лактамів, за даними звітів Європейської мережі нагляду за споживанням антимікробних засобів, є одними з найбільш споживаних серед інших груп антибіотиків у Європі. В Україні рівень споживання β-лактамів значно нижчий середньоєвропейського. Такі дані вимагають детальної оцінки рівня споживання β-лактамних антимікробних препаратів, за окремими МНН, аналізу балансу їх застосування.

***Метою роботи є** аналіз ринку та споживання АМП групи β-лактамів в Україні за 2013-2018 роки за допомогою ATC/DDD-методології, а також порівняння отриманих об'ємів споживання з аналогічними результатами в Європейському Союзі.*

***Результати.** Загальна кількість АМП групи β-лактамів представлених на ринку України у 2018 році становить 343 торгових найменування (ТН), з них – 92 пропозиції вітчизняних і 251 – іноземних фірм-виробників, що свідчить про високу насиченість українського фармацевтичного ринку імпортними препаратами*

В Україні у 2017 році пеніцилінів спожито у 4,48 разу менше ніж у середньому по ЄС, а цефалоспоринів та карбапенемів майже стільки ж.

Найбільше було спожито препаратів МНН з групи пеніцилінів – Амоксициліну та Амоксициліну з інгібіторами β-лактамаз, а лідерами за об'ємами споживання серед цефалоспоринів є лікарські засоби за МНН Цефтріаксону і Цефуроксиму.

***Висновки.** Антимікробні препарати групи β-лактамів добре вивчені та широко використовуються у медичній практиці, в асортименті представлені на ринку України (343 ТН), але тільки менше третини з них (92 ТН) – вітчизняного виробництва, що свідчить про високу насиченість українського фармацевтичного ринку імпортними препаратами. Об'єм споживання антимікробних препаратів групи β-лактамів в Україні майже в 4,5 рази менший, ніж у країнах ЄС.*

Найбільш споживаними є препарати Амоксициліну – групи пеніцилінів широкого спектру дії та серед цефалоспоринів – препарати Цефтріаксону та Цефуроксиму

***Ключові слова**: фармацевтичний ринок; β-лактамні антибіотики; споживання лікарських засобів; ATC/DDD-методологія*

1. Introduction

After the discovery of penicillin in 1928 by a Scottish scientist and Nobel laureate, Alexander Fleming, antibiotics have come a long way to development [1].

More than 100 different types of antimicrobials (AMIs) have been invented to date. It has also been established that AMIs are active against different types of pathogens of infectious diseases, but there are "supermicroorganisms" with resistance to drugs, which creates new challenges for researchers.

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

Strategy against antibiotic resistance (ABR) is a global challenge for the scientific community for life and health of the population. Over the past decades around the world there has been a sharp increase in infections caused by pathogens with multiple ABR [2, 3].

3. Analysis of recent studies and publications in which a solution of the problem are described and to which the author refers

The authors of the ABR study note the importance of a systematic view of current knowledge about the use of AMI and the prevention of infectious diseases [2–5]. Among publications, an important place is meta-analysis that allows us to rely on a number of relevant sources about the relationship between AMI consumption and the development of ABR [4].

A study of the consumption of β-lactam antibiotics in Ukraine was conducted by prof. Iakovlieva L. V. and assistant Matyashova N. O., but their work was published in 2010-2013, which requires updating data in order to identify new trends in the use of these drug groups.

4. The field of research considering the general problem, which is described in the article

Increased resistance to antibiotic drugs may be due to reasons such as inappropriate and uncontrolled use of

antibiotics (affordability through sale without prescription); the use of antibiotics with a wide spectrum of action in the case of the effectiveness of agents with a narrower spectrum; non-compliance by patients with certain conditions of admission and inappropriate prophylactic use; uncontrolled and unregulated use in veterinary and rural (agrarian) farming; the absence of new groups of antibacterial agents. An analysis of the relationship between AMI consumption levels and the development of ABR is one of the tools to curb the latter. Increasing AMI consumption can not only provide greater stability at the level of individual strains of pathogens to antibiotics, which creates problems for their further use [4, 5].

5. Formulation of goals (tasks) of article

The aim of this work is to analyze the market and consumption of AMI of the β-lactam group in Ukraine for 2013–2018, using the ATC / DDD methodology, identify trends in their use, and compare the obtained consumption volumes with similar results in the European Union.

6. Presentation of the main research material (methods and objects) with the justification of the results

Data on the consumption of the investigational drugs are determined using the ATC / DDD methodology recommended by the WHO. The DDDs per 1000 inhabitants per day (DID) were used to calculate the consumption of antibacterial agents of the study group. The value of DDD (Defined Daily Dose), each international nonproprietary name (INN), is presented on the WHO website. PDD (Prescribed Daily Dose) was used for those INN for which there is no calculated DDD on the WHO website [6].

The calculations were carried out according to the analytical system of the pharmaceutical market research "Pharmstandard" of "Morion" company.

Results and their discussion

Today, the group of β-lactam AMI includes a number of drugs, most of which are well-studied and have long existed on world markets.

β-lactam antibiotics are bactericidal agents that interrupt the formation of a bacterial cell wall as a result of covalent binding to etheric penicillin-binding proteins (PBPs), enzymes involved in the final stages of cross-linking peptidoglycan, a bacterial wall component in gram-negative and gram-positive bacteria. Each bacterial species has its own distinct set of PBPs, which can range from three to eight enzymes to one species. The death of microbial cells can occur as a result of inhibition of one or more of these PBPs [7].

Penicillin G (Benzylpenicillin) was the first β-lactam to be used in the clinic, most often for the treatment of streptococcal infections, to which it exhibited high activity. Another natural penicillin-Phenoxymethylpenicillin is used therapeutically and prophylactically for the mild and moderate severity of infections caused by susceptible *Streptococcus spp.*, including use in children [8]. Among the penicillinase-resistant penicillins, clinical significance has Methicillin, Oxacillin, Cloxacillin and Nafcillin, and the latter is proposed as β-lactate for skin infections caused by methicillin-susceptible *Staphylococcus aureus*.

All these drugs were used primarily for the treatment of patients with *Staphylococcus aureus* before the onset of methicillin resistant *S. aureus* (MRSA) strains in 1979–1980 [9].

Penicillins with improved activity relative to gram-negative pathogens included bioavailable Ampicillin and Amoxicillin, both of which were marketed in the 1970s. These AMIs were initially used to treat infections caused by *Enterobacteriaceae* and did not effectively suppress the growth of *Pseudomonas aeruginosa*. Carbenicillin was the first anti-pseudomonal penicillin, but did not have resistance to hydrolysis by β-lactamase and was less potent than Piperacillin or Ticarcillin. The latter preparations were considered as potent penicillins of a wide range of effects, which counteract penicillin-sensitive staphylococci, intestinal bacteria, anaerobes and *P. aeruginosa*. Since the late 1980s, they have been widely used to treat intra-infectious diseases, especially in combination with a β-lactamase inhibitor [11].

The increase in β-lactamase levels limited the therapeutic use of penicillins as monotherapy. Ampicillin, Amoxicillin, Piperacillin, and Tricacillin are continued in combination with a β-lactamase inhibitor [10]. However, Ampicillin, Amoxicillin, Benzylpenicillin, and Phenoxymethylpenicillin are still active as monotherapy for Group A streptococci and *Treponema pallidum*, which do not produce β-lactamase [12].

In the 1950's, the discovery of natural penicillin-resistant Cephalosporin C indicated the pathway for the development of new cephalosporins for the treatment of infections, mainly caused by pathogens producing penicillinase (*S. aureus*). At that time dozens of cephalosporins were introduced into clinical practice either as parenteral or as oral agents [13]. The molecules showed antibacterial activity not only against staphylococci, but also against *Streptococcus pneumoniae* and non-β-lactamase-producing bacteria.

Cefazolin is often used for the prevention of surgery and the treatment of abdominal infections [14] and is effective as empirical therapy in 80 % of Japanese children at the first infection of the upper urinary tract [15].

The total amount of AMI of the group β-lactams presented in the market of Ukraine in 2018 is 343 trade names (TNs), of which 92 are domestic and 251 foreign manufacturers, which indicates the high saturation of the Ukrainian pharmaceutical market with imported drugs (Table 1).

For comparison, in 2011 in the domestic market, 13 INN of penicillin group with 118 TNs were presented (26 Ukrainian and 92 imported) [16]. From 2011 to 2018, 4 INNs were taken from the market - Ampicillin + Oxacycline, Amoxicillin + Sulbactam, Ticarcillin + Clavulanic acid, Amoxicillin + Cloxacillin sodium.

Cefalosporins in 2010 in the Ukrainian market were represented by 13 INNs, which are based on 128 TNs (domestic – 84 TNs and 44 TNs of foreign manufacturers) [17]. From the market went 2 INN – Cefadroxil and Cefpirome. Between 2010 and 2018, there were 7 INNs on the market, but only 3 INNs – Cefditoren (1 TN) and the combination of Cefoperazone + Sulbactam and Ceftriaxone + Sulbactam remained at the end of the period.

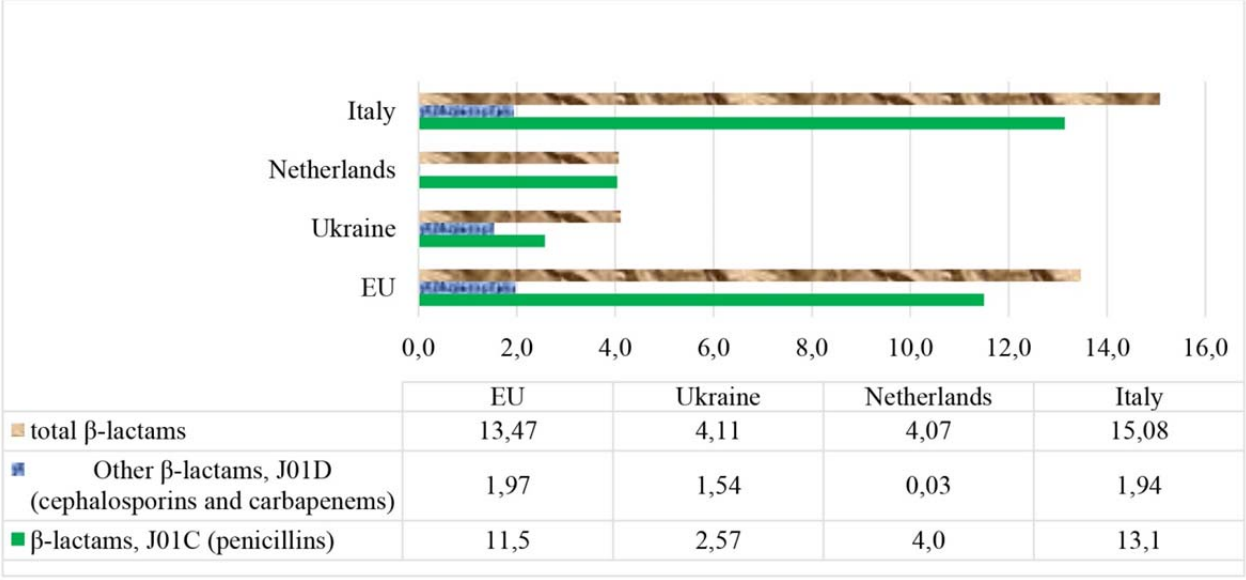
Table 1

Structure of the Ukrainian market of AMI of β-lactam group in 2018

ATC-code	International non-proprietary name	Number of items taking into account all dosage forms (pcs.)		
		domestic	foreign	total
β-lactamase sensitive penicillins				
J01CE01	Benzylpenicillin	3	1	4
J01CE08	Benzathine benzylpenicillin	-	1	1
J01CE30	Benzathine benzylpenicillin + Benzylpenicillin	2	–	2
Extended-spectrum penicillins				
J01CA01	Ampicillin	3	–	3
J01CA04	Amoxicillin	3	17	20
J01CA51	Ampicillin + Oxacycline	Absent from 2015		
Combinations of penicillins with β-lactamase inhibitors				
J01CR01	Ampicillin + Sulbactam	1	1	2
J01CR02	Amoxicillin + Clavulanic acid	3	35	38
J01CR02	Amoxicillin + Sulbactam	Absent from 2016		
J01CR03	Ticarcillin + Clavulanic acid	Absent from 2018		
J01CR05	Piperacillin + Tazobactam	–	6	6
J01CR50	Amoxicillin + Cloxacillin sodium	Absent from 2015		
Total penicillins		**15**	**61**	**76**
Other β-lactam antibiotics, cephalosporins of the first generation				
J01DB01	Cefalexin	2	5	7
J01DB04	Cefazolin	8	–	8
J01DB05	Cefadroxil	Absent from 2017		
Other β-lactam antibiotics, cephalosporins of the second generation				
J01DC02	Cefuroxime	10	29	39
Other β-lactam antibiotics, cephalosporins of the third generation				
J01DD01	Cefotaxime	10	4	14
J01DD02	Ceftazidime	4	16	20
J01DD04	Ceftriaxone	23	36	59
J01DD07	Ceftizoxime	Absent from 2017		
J01DD08	Cefixime	–	13	13
J01DD12	Cefoperazone	2	3	5
J01DD13	Cefpodoxime	–	17	17
J01DD14	Ceftibuten	–	2	2
J01DD16	Cefditoren	–	1	1
J01DD51	Cefotaxime + Sulbactam	Absent from 2015		
J01DD52	Ceftazidime + Sulbactam	Absent from 2018		
J01DD62	Cefoperazone + Sulbactam	7	9	16
J01DD63	Ceftriaxone + Sulbactam	1	3	4
J01DD63	Ceftriaxone + Tazobactam	Absent from 2016		
Other β-lactam antibiotics, cephalosporins of the fourth generation				
J01DE01	Cefepime	6	23	29
J01DE02	Cefpirome	Absent from 2015		
J01DE51**	Cefepime + Amikacin	Absent from 2015		
J01DE51**	Cefepime + Sulbactam	Absent from 2018		
Total cephalosporins		**73**	**161**	**234**
Other β-lactam antibiotics, carbapenems				
J01DH02	Meropenem	4	18	22
J01DH03	Ertapenem	–	1	1
J01DH04	Doripenem	–	1	1
J01DH51	Imipenem + Cilastatin	–	9	9
Total carbapenems		**4**	**29**	**33**
Total AMI of β-lactams group		**92**	**251**	**343**

Data on the consumption of AMI β-lactams by the European Union (EU) in 2017 were taken from the reports of the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [18].

In Ukraine, in 2017 penicillins consumed at 4.48 and 3.7 times less than the EU average and Italy (the country with the highest consumption), and cephalosporins and carbapenems are almost the same. Comparison with the Netherlands (the country with the lowest levels of consumption) suggests practically the same level of consumption of AMI of the β-lactam group and 51.3 times higher consumption of the subgroup of cephalosporins and carbapenems (Fig. 1).



	EU	Ukraine	Netherlands	Italy
total β-lactams	13,47	4,11	4,07	15,08
Other β-lactams, J01D (cephalosporins and carbapenems)	1,97	1,54	0,03	1,94
β-lactams, J01C (penicillins)	11,5	2,57	4,0	13,1

Fig. 1. Consumption of AMI β-lactams group in 2017 in DID

The consumption of AMI of β-lactam group in the period from 2013 to 2018 in Ukraine has increased (Tabl. 2); although in 2015 there was a decrease in consumption.

The most commonly used drugs were INNs from the penicillin group – Amoxicillin and Amoxicillin with inhibitors of β-lactamase. This choice of physicians is due to the wide range of amoxicillin used as a monotherapy for infectious diseases caused by streptococci and the activity of combinations of amoxicillin with β-lactamase inhibitors to all coccidian pathogens producing β-lactamase. In Ukraine, these combinations (see tab. 2) are used as first-line drugs that stimulate the development of ABR and should only be used as second-line drugs [19].

The leaders in terms of consumption among cephalosporins are INN Ceftriaxone (III generation) and Cefuroxime (II generation). The choice of these drugs is due to their pharmacological properties. Cefuroxime has a wider range of antimicrobial effects than I generation drugs and is widely used for monotherapy not only in Ukraine but also in Europe as a cheap generic drug. Ceftriaxone is widely used in connection with its pharmacokinetic properties, because it is sufficient to administer once a day, which characterizes its high compliance [19].

Table 2

Consumption of AMI of β-lactam group from 2013 to 2018 in Ukraine

ATC-code	INN	DID, 2013	DID, 2014	DID, 2015	DID, 2016	DID, 2017	DID, 2018
Penicillins							
J01CE01	Benzylpenicillin	0.02526807	0.020134595	0.01678717	0.0150048	0.015336723	0,01500076
J01CE08	Benzathine benzylpenicillin	0.001649271	0.001505727	0.000952328	0.000057648	0.001717412	0,00016052
J01CE30	Benzathine benzylpenicillin + Benzylpenicillin	0.277156233	0.225740965	0.201470371	0.126706359	0.161092185	0,186163267
J01CA01	Ampicillin	0.157458578	0.148354107	0.129336352	0.114465254	0.100101304	0,10019797
J01CA04	Amoxicillin	1.49576407	1.449766877	1.23464417	1.36392695	1.29446641	1,41922942
J01CA51	Ampicillin + Oxacycline	0.00862075	0.000353343	0	0	0	0
J01CR01	Ampicillin + Sulbactam	0.003139876	0.002284162	0.001999695	0.002462311	0.0019926	0,002261964
J01CR02	Amoxicillin + Clavulanic acid	0.900023924	0.850775222	0.770569519	0.917767737	0.991406093	1,213728191
J01CR02	Amoxicillin + Sulbactam						
J01CR03	Ticarcillin + Clavulanic acid	0.000042771	0.000024555	0.000020532	0.000008919	0.000000071	0
J01CR05	Piperacillin + Tazobactam	0.000030162	0.000054478	0.00008014	0.000221418	0.000297439	0,000396671
J01CR50	Amoxicillin + Cloxacillin sodium	0.000631398	0.000005995	0	0	0	0
Total penicillins		2.86978510	2.69900003	2.35586028	2.54062140	2.56641024	2.93713876

Continuation of the Table 2

Other β-lactam (cephalosporins, penems)							
J01DB01	Cefalexin	0.046096712	0.038442212	0.040549815	0.039318029	0.032934063	0,033812803
J01DB04	Cefazolin	0.028900426	0.024824942	0.019616375	0.016463447	0.014087073	0,012142283
J01DB05	Cefadroxil	0.001426198	0.000136987	0.000012522	0.000000577	0	0
J01DC02	Cefuroxime	0.237972182	0.232717685	0.253255106	0.300854272	0.323316637	0,377361485
J01DD01	Cefotaxime	0.042510725	0.038658907	0.021800941	0.029547082	0.025066557	0,022150384
J01DD02	Ceftazidime	0.015811968	0.014346836	0.012999263	0.016554000	0.019759001	0,022113270
J01DD04	Ceftriaxone	0.692756273	0.724138433	0.684487897	0.710039182	0.692891371	0,718067922
J01DD07	Ceftizoxime	0.001931611	0.002488001	0.001223237	0.000468221	0.000001576	0,000000000
J01DD08	Cefixime	0.144507512	0.133303584	0.10599875	0.148122416	0.189076064	0,252576834
J01DD12	Cefoperazone	0.015506133	0.014357411	0.012044526	0.017214064	0.017963413	0,018819143
J01DD13	Cefpodoxime	0.090328509	0.097109764	0.064720248	0.10089433	0.138228144	0,195922714
J01DD14	Ceftibuten	0.014783068	0.017650589	0.005002473	0.003827213	0.000273628	0,000002746
J01DD16	Cefditoren	0	0	0	0	0	0,000003141
J01DD51	Cefotaxime + Sulbactam	0.000398223	0.000042895	0	0	0	0
J01DD52	Ceftazidime + Sulbactam	0	0	0	0.000000128	0.000000764	0
J01DD62	Cefoperazone + Sulbactam	0.014842769	0.013445164	0.008152608	0.011631412	0.015861226	0,022207589
J01DD63	Ceftriaxone + Sulbactam	0.020304078	0.013771381	0.008104589	0.018000474	0.02013727	0,027389671
J01DD63	Ceftriaxone + Tazobactam						
J01DE01	Cefepime	0.018236363	0.010594809	0.010729312	0.017543085	0.022811842	0,028004787
J01DE02	Cefpirome	0.000000708	0.000000092	0	0	0	0
J01DE51**	Cefepime + Amikacin	0.018236363	0.010594809	0.010729312	0.017543085	0.022811842	0
J01DE51**	Cefepime + Sulbactam						
J01DH02	Meropenem	0.002534316	0.002564556	0.002683536	0.004486215	0.005776414	0,007686309
J01DH03	Ertapenem	0.000371074	0.000229582	0.000057528	0.000031028	0.000024825	0,000041419
J01DH04	Doripenem	0.000014305	0.000004307	0.000011288	0.000074997	0.000046026	0,0000149
J01DH51	Imipenem + Cilastatin	0.001379425	0.00085284	0.000905867	0.00098583	0.000947914	0,001382926
Total other β-lactames		1.40884894	1.39027579	1.26308519	1.45359909	1.54201565	1.73970033
Total		**4.27863404**	**4.08927582**	**3.61894547**	**3.99422049**	**4.10842589**	**4.67683909**

7. Conclusions from the conducted research and prospects for further development of this field

1. Antimicrobial preparations of the β-lactam group are well-studied and widely used in medical practice.

2. Preparations of the β-lactam group are widely represented in the Ukrainian market (343 TNs), but only less than a third of them (92 TNs) of domestic production, indicating a high saturation of the Ukrainian pharmaceutical market with imported drugs.

3. The volume of consumption of AMI of the β-lactam group (penicillins) in Ukraine is almost 4.5 times lower than in the EU, which may indicate unbalanced use of different groups of AMI in terms of DDDs per 1000 inhabitants per day (DID).

4. Consumption in general of all β-lactam groups from 2013 to 2018 has increased, although years of decline in consumption (2015) have been noted.

5. The most consumed during the study period are drugs Amoxicillin - a group of broad-spectrum penicillins and among cephalosporins preparations Ceftriaxone and Cefuroxime.

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