ОРГАНІЗАЦІЯ ТА ЕКОНОМІКА ФАРМАЦІЇ

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The DDD-monitoring of consumption of fluoroquinolones when treating community-acquired pneumonia in a multi-specialty hospital in the Republic of Tajikistan

Community-acquired pneumonia is one of the most common diseases and is still the leading cause of death among infectious diseases. Such drugs as β-lactam antibiotics, new macrolides (azithromycin, clarithromycin) and respiratory fluoroquinolones are of the greatest importance in the treatment of community-acquired pneumonia in adult patients worldwide.

Aim. To analyze and assess the dynamics of consumption of fluoroquinolones for the treatment of community-acquired pneumonia in a multi-specialty hospital in the Republic of Tajikistan using the DDD-methodology.

Materials and methods. A retrospective descriptive analysis of medical prescriptions for pharmacotherapy of patients treated in the Pulmonology department of the Sogdigh Regional Clinical Hospital (Khujand, Republic of Tajikistan) was performed. The consumption of fluoroquinolones was estimated according to the ATC/DDD index of the WHO. The unit of measurement used was the number of grams of the active substance with further calculation of the DDD/100 bed-days and % of the total DDD.

Results and discussion. The DDD analysis of consumption of fluoroquinolones in the Pulmonology department of the multi-specialty hospital showed a significant change in the structure of consumption of this group of drugs for the initial antibiotic therapy of community-acquired pneumonia in the last five years. A clear tendency was observed to reduce the consumption of this class of drugs in 2011-2015. There is a significant reduction in the consumption of ofloxacin and levofloxacin against the background of a slight tendency to increase the demand for ciprofloxacin in the treatment of pneumonia in the inpatient drug treatment.

Conclusions. Monitoring of the consumption of antimicrobial drugs from the fluoroquinolone group for the treatment of community-acquired pneumonia in the Pulmonology department of the multi-specialty hospital using the ATS/DDD-methodology makes it possible to assess the tactics of community-acquired pneumonia treatment in this region, its compliance with the international standards and the risks of developing the drug-resistant microflora, in particular to fluoroquinolones.

Key words: *pharmacoepidemiology; fluoroquinolones; community-acquired pneumonia*

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DDD-моніторинг споживання фторохінолонів при позалікарняній пневмонії в багатопрофільному стаціонарі Республіки Таджикистан

Позалікарняна пневмонія відноситься до числа найбільш поширених захворювань і до теперішнього часу залишається провідною причиною смерті через інфекційні хвороби. Найбільше значення в лікуванні пневмонії у дорослих пацієнтів у світі мають β-лактамні антибіотики, «нові» макроліди (азитроміцин, кларитроміцин) та «респіраторні» фторохінолони.

Мета: аналіз та оцінка динаміки споживання фторохінолонів для лікування пневмонії в багатопрофільному стаціонарі Республіки Таджикистан з використанням DDD-методології.

Матеріали та методи. Здійснено ретроспективний описовий аналіз лікарських призначень при фармакотерапії пацієнтів, які перебувають на лікуванні в пульмонологічному відділенні Согдізької обласної клінічної лікарні (м. Худжанд, республіка Таджикистан). Оцінювали споживання фторохінолонів згідно з індексом АТС/DDD ВООЗ. В якості одиниці вимірювання використовували кількість грамів активної речовини з подальшим розрахунком показника DDD/100 ліжко-днів та % від загальної DDD.

Результати та їх обговорення. DDD-аналіз споживання фторохінолонів у пульмонологічному відділенні багатопрофільного стаціонару показав істотну зміну структури споживання цієї групи лікарських засобів для стартової антибактеріальної терапії пневмонії за останні п'ять років. Виявлено явну тенденцію до скорочення обсягів споживання препаратів даного класу за 2011-2015 рр. Відзначається значне зменшення споживання офлоксацину та левофлоксацину на тлі незначної тенденції до збільшення попиту на ципрофлоксацин у схемах лікування пневмонії на стаціонарному етапі фармакотерапії.

Висновки. Моніторинг споживання антимікробних препаратів з групи фторохінолонів для лікування пневмонії в пульмонологічному відділенні багатопрофільного стаціонару з використанням АТС/DDD-методології дозволяє оцінити тактику лікування пневмонії в даному регіоні, її відповідність міжнародним стандартам і оцінити ризики розвитку лікарсько-стійкої мікрофлори, зокрема до фторохінолонів.

Ключові слова: *фармакоепідеміологія; фторохінолони; позалікарняна пневмонія*

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DDD-мониторинг потребления фторхинолонов при внебольничной пневмонии в многопрофильном стационаре Республики Таджикистан

Внебольничная пневмония относится к числу наиболее распространенных заболеваний и до настоящего времени остается ведущей причиной смерти среди инфекционных болезней. Наибольшее значение в лечении внебольничной пневмонии у взрослых пациентов в мире имеют β-лактамные антибиотики, «новые» макролиды (азитромицин, кларитромицин) и «респираторные» фторхинолоны.

Цель: анализ и оценка динамики потребления фторхинолонов для лечения внебольничной пневмонии в многопрофильном стационаре Республики Таджикистан с использованием DDD-методологии.

Материалы и методы. Осуществлен ретроспективный описательный анализ врачебных назначений при фармакотерапии пациентов, находящихся на лечении в пульмонологическом отделении Согдигской областной клинической больницы (г. Худжанд, республика Таджикистан). Оценивали потребление фторхинолонов для лечения согласно индекса ATC/DDD ВООЗ. В качестве единицы измерения использовалось количество граммов активного вещества с дальнейшим расчетом показателя DDD/100 койко-дней и % от общей DDD.

Результаты и их обсуждение. DDD-анализ потребления фторхинолонов в пульмонологическом отделении многопрофильного стационара показал существенное изменение структуры потребления данной группы лекарственных средств для стартовой антибактериальной терапии внебольничной пневмонии за последние пять лет. Выявлена явная тенденция к сокращению объемов потребления препаратов данного класса за 2011-2015 гг. Отмечается существенное сокращение потребления офлоксацина и левофлоксацина на фоне незначительной тенденции к увеличению спроса на ципрофлоксацин в схемах лечения пневмонии на стационарном этапе фармакотерапии.

Выводы. Мониторинг потребления антимикробных препаратов из группы фторхинолонов для лечения внебольничной пневмонии в пульмонологическом отделении многопрофильного стационара с использованием ATC/DDD-методологии позволяет оценить тактику лечения внебольничной пневмонии в данном регионе, ее соответствие международным стандартам и оценить риски развития лекарственно-устойчивой микрофлоры, в частности к фторхинолонам.

Ключевые слова: *фармакоэпидемиология; фторхинолоны; внебольничная пневмония*

Community-acquired pneumonia (CAP) is one of the most common diseases and is still the leading cause of death among infectious diseases. According to the WHO pneumonia occurs in 10-14 people out of 1000, in the age group over 50 years it is in 17 persons out of 1000 people. As evidenced by modern pharmacoeconomic studies, only direct costs of the US healthcare related to the management of patients with CAP are $ 10-12 billions per year. The urgency of the issue of CAP incidence persists despite introduction of new antimicrobial drugs (AD), as well as a high percentage of complications and mortality (up to 9 %) of pneumonia. According to the data of the WHO experts mortality in pneumonia is only inferior to that of cardiovascular and cerebrovascular diseases [1].

Statistical data of the Statistic Agency under the President of the Republic of Tajikistan (RT) make it possible to state that since 2000 the prevalence of respiratory diseases in the country has consistently ranked among the classes of diseases, exceeding the similar indicators of other diseases by 3 times [2]. Information on Tajikistan has a collective nature from various domestic, foreign and official sources, but these figures do not reflect the true incidence of CAP in Tajikistan, the actual incidence of pneumonia is many times higher due to unaccounted cases and diagnostic errors. Obviously, this is due to inaccurate registration of the incidence of CAP in certain areas, the difficulty of access to qualified medical care and self-treatment of the population, as well as errors in diagnosis [2, 3, 4].

As is known, at the present stage *S. pneumoniae* is the most essential pathogen of CAP, which accounts for 30-50 % of cases, there are also "atypical" microorganisms such as *C. pneumoniae*, *M. pneumoniae*, *Legionella pneumophila* (8-30 % of cases of CAP). *H. influenza*, *S. aureus*, *Kl. pneumoniae* are rare (3-5 %) pathogens, even more rare are cases associated with other enterobacteria and non-fermenting gram-negative bacteria [5, 6].

Antibacterial therapy of CAP is vital and should start, if possible, in the first hours after the diagnosis/hospitalization of the patient. According to experts, postponement with prescription of antibiotics for 4-8 hours or more significantly worsens the prognosis of the disease: duration of the hospital treatment period and lethality increase. In the vast majority of cases, AD are empirically prescribed, and it requires the physician's knowledge of the spectrum of the most probable pathogens and epidemiology of local antibiotic resistance. When choosing a specific AD it is necessary to take into account the antimicrobial activity of the drug against potential pathogens of CAP; its bioavailability considering the age characteristics of a patient; the safety profile; the dosage regimen and the acceptable level of drug interactions.

Currently, β-lactam antibiotics, new macrolides (azithromycin, clarithromycin) and respiratory fluoroquinolones are of the greatest importance in the treatment of CAP in adults in the world. The indisputable advantages of β-lactams are their bactericidal activity against the typical pathogens of CAP and a favorable safety profile. However, AD of this class are inactive with respect to "atypical" pathogens (*M.pneumoniae, C.pneumoniae* and *Legionella spp*.), there is resistance of a number of strains of *H. influenza* producing β-lactamases to "unprotected" aminopenicillins (ampicillin, amoxicillin), and insufficient activity of

most oral cephalosporins against *S. pneumoniae*. At present the problem of spreading pneumococcus strains with reduced sensitivity to penicillin becomes more and more urgent, many of them are resistant to several classes of antibiotics (multidrug resistant strains) [5, 7].

The main advantage of modern macrolides is their activity in relation to "atypical" pathogens of CAP. However, the prevalence of *S. pneumoniae* strains that are highly resistant to macrolides should be taken into account in a number of geographic regions [8].

In this context, the AD-fluoroquinolone (FQ) group deserves special attention. For more than 20 years nalidixic acid and its derivatives (pipemidic and oxolinic acids), which have the activity against gram-negative microorganisms, have been used to treat the urinary tract infections. The appearance of fluorinated derivatives with a fundamentally new level of the antimicrobial activity at the pharmaceutical market allowed expanding the range of indications for the use of drugs of this class. FQ were effective against gram-negative and some gram-positive microorganisms, extracellular pathogens and were characterized by attractive pharmacokinetic characteristics [9, 10, 11, 12, 13]. However, the low antipneumococcal activity of this generation of fluoroquinolones limited their use in community-acquired infections of the lower respiratory tract, including CAP. The appearance of di- and trifluorinated compounds with the enhanced activity against gram-positive bacteria (especially *S. pneumoniae*) and intracellular pathogens gave the name "respiratory" fluoroquinolones to these drugs (levofloxacin, moxifloxacin, hemifloxacin, etc.) with the increased activity against *S. pneumoniae* compared to the classical fluoroquinolones (ofloxacin, ciprofloxacin) [14, 15, 16, 17]. It is a wide spectrum of activity in relation to both gram-positive and gram-negative microorganisms, a long half-life, which allows them to be taken once a day, high bioavailability and rapid gastrointestinal absorption, have led to an increased interest in drugs of this series in the treatment of the respiratory tract infections, as well as CAP in the world.

Considering the relevance of CAP as one of the most common diseases with high mortality and the cost of the healthcare system for its treatment the primary goal of the healthcare system is the analysis of approaches to pharmacotherapy and the choice of the starting antibacterial therapy.

The aim of the study was to assess the dynamics of consumption of fluoroquinolones for the treatment of community-acquired pneumonia in a multi-specialty hospital in the Republic of Tajikistan using the DDD-methodology**.**

Materials and methods

The research was conducted at the premises of the Pulmonology department of the Sogdigh Regional Clinical Hospital (Khujand, Republic of Tajikistan). A retrospective descriptive analysis of medical prescriptions for pharmacotherapy of patients with CAP treated in this department was carried out. The study was conducted in dynamics within 2011-2015. The intake of FQ for the treatment of CAP according to the WHO ATC/DDD index was estimated [18]. The unit of measurement used was the number of grams of the active substance with further calculation of the total DDDs, DDDs/100 bed-days and % of the total DDDs. To calculate the research results, data of descriptive statistics, and construct diagrams the software resources of the Microsoft Office Excel 2007 package were used.

Results and discussion

The DDD analysis of AD consumption in the Pulmonology department of the multi-specialty hospital for the treatment of CAP has shown that AD with various pharmacodynamic and pharmacokinetic characteristics are used for the antimicrobial therapy of this disease. At the same time, the intensity of AD consumption in the dynamics has a clear tendency to decrease; it can be regarded as a positive fact in the fight against unjustified use of AD and as a factor in combating antibiotic resistance (Fig. 1).

Taking into account the generally accepted approaches to the starting antibacterial therapy of CAP in the world, the place and role of FQ in the system of drug support for this treatment it was interesting to analyze further the consumption of AD from the group of FQ for the treatment of CAP in the Republic of Tajikistan. As a retrospective analysis of the consumption of this group of drugs for the treatment of pneumonia has shown, FQ are widely used for the starting antibacterial therapy of CAP. It should be noted that in 2011-2013 the share of drug consumption in this class was 41.38-38.17 % of the total DDDs of all AD used to treat CAP. From Fig. 2 it can be seen that in subsequent years (2014-2015) the

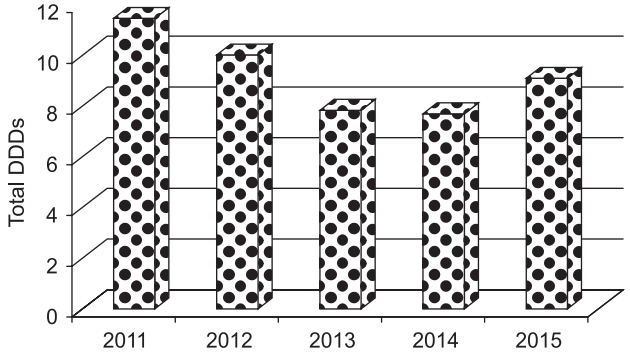

Fig. 1. The dynamics of AD consumption in the Pulmonology department of the multi-speciality hospital for the treatment of community-acquired pneumonia (the total DDDs)

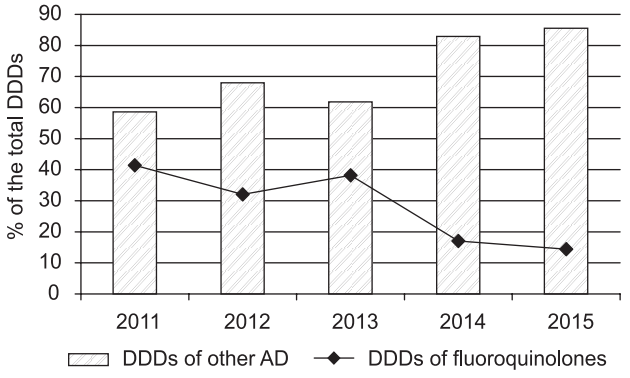

Fig. 2. The dynamics of the consumption of fluoroquinolones for the treatment of community-acquired pneumonia in the Pulmonology department of a multi-specialty hospital (% of the total DDDs)

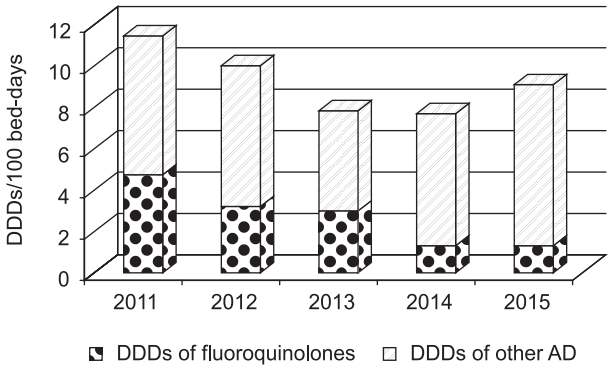

Fig. 3. Consumption of fluoroquinolones for the treatment of community-acquired pneumonia in the Pulmonology department of a multi-specialty hospital (DDDs/100 bed-days)

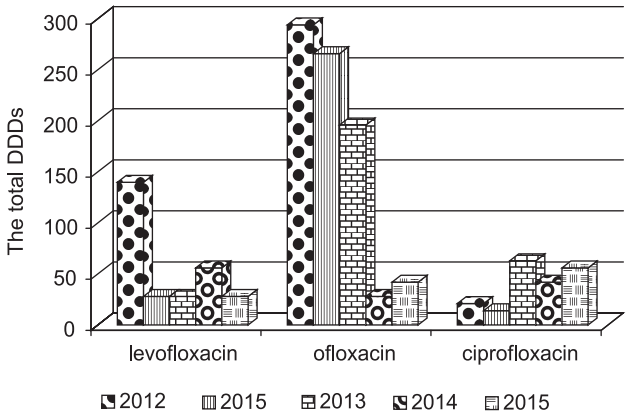

Fig. 4. The dynamics of consumption of individual drugs from the group of fluoroquinolones for the treatment of community-acquired pneumonia (the total DDDs)

consumption of drugs of this class is significantly reduced to only 14.44-17.07 % of the total DDDs. For the last 5 years the share of consumed FQ and their role in the treatment of CAP decreased almost 3 times.

The data obtained were confirmed in the analysis of the main indicator of drug consumption in the hospital – DDDs/100 bed-days. As shown by the frequency analysis of the use of FQ for the treatment of CAP, the DDDs consumed for the initial antibacterial therapy of pneumonia in 2011 were 4.74 DDDs, while in 2015 this indicator for FQ decreased almost 3.6 times and was 1.31 DDDs (Fig. 3).

Taking into account the spectrum of the antimicrobial activity of FQ, the low antipneumococcal activity of early FQ this fact should be regarded as positive with the transition to universally recognized standards of medical care, including antibacterial care in the treatment of pneumonia.

Further frequency analysis of the use of antibacterial drugs from the FQ group for the treatment of CAP in a multi-specialty hospital in the Republic of Tajikistan in dynamics showed that the most popular drugs from this group were the so-called early FQ – ciprofloxacin and ofloxacin, as well as levofloxacin – one of the "respiratory" FQ (Fig. 4).

Fig. 4 shows that the most consumed FQ for the period of 2011-2013 was ofloxacin, which total DDDs in 2011 exceeded that of ciprofloxacin by 2 times and for levofloxacin by 14 times. Further (2014-2015), the use of ofloxacin for the treatment of CAP almost 10 times decreased. At the same time, % of the total DDDs ofloxacin in the early analysis period was 26.06-27.66 %, and in 2014-2015 it was only 3.79-4.72 % of the total DDDs.

A similar dynamics is also observed for the representative of "respiratory" FQ – levofloxacin, which consumption for the period from 2011 to 2015 decreased by 5 times. Thus, the total DDDs of this drug in 2011 were 140 DDDs, and in 2015 only 28 DDDs (Fig. 4).

The representative of FQ – ciprofloxacin widely used in clinical practice occupies a small segment in the structure of AD used to treat CAP. Thus, the total DDDs of this drug in different years varies from 14 to 63 DDDs (Fig. 4). At the same time, there is an insignificant but obvious tendency to increase its consumption during the period analyzed: the total DDDs of ciprofloxacin in 2015 exceeded this indicator in 2012 by 4 times (Fig. 4).

A similar pattern is observed in the analysis of AD consumption of this class for 100 bed-days. It can be seen in Fig. 5 that FQ as a whole lost their positions in the treatment of CAP in the dynamics (reduction of DDDs/100 bed-days from 4.74 in 2011 to 1.31 in 2015), and the spectrum of FQ used changed.

It was found that DDDs/100 bed-days for ofloxacin decreased 6.95 times in the period analyzed, this indicator decreased by 5 times for levofloxacin, and the increase in drug consumption by 2.6 times was noted for ciprofloxacin.

It should be noted that such "respiratory" FQs as moxifloxacin, hemifloxacin, etc., were not used in the Pulmonology department for the treatment of CAP within the period studied.

Thus, the analysis of FQ consumption in the Pulmonology department of the multi-specialty hospital of the Republic of Tajikistan as a whole showed a significant reduction in consumption of this class of drugs for the treatment of CAP. There is a significant reduction in the consumption of ofloxacin and levofloxacin against the background of a slight tendency to increase the demand for ciprofloxacin in the treatment of pneumonia in the inpatient drug treatment.

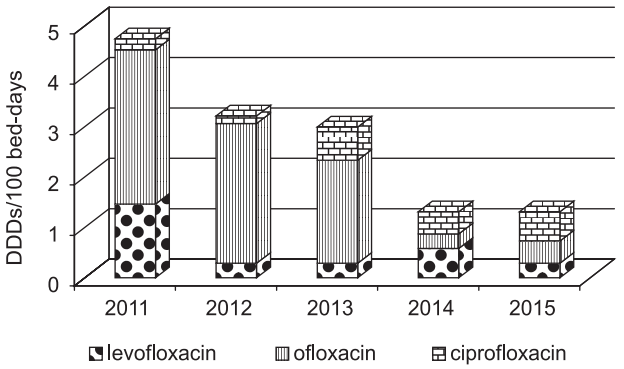

Fig. 5. The dynamics of consumption of fluoroquinolones for the treatment of community-acquired pneumonia in the Pulmonology department of the multi-specialty hospital (DDDs/100 bed-days)

Taking into account the existing approaches of the Republic of Tajikistan to the treatment of CAP and the WHO international recommendations the reduction of demand for drugs from the FQ group should be regarded as a positive moment in optimizing approaches to the pharmacotherapy of CAP. On the one hand, the use of early FQ should be regarded as erroneous taking into account the low natural antipneumococcal activity of both ciprofloxacin and ofloxacin. In this case, the widespread, sometimes unjustified use of "respiratory" FQ bears the risk of selection of drug-resistant microorganisms. Thus, monitoring of the dynamics of *S. pneumoniae* resistance to levo-, moxi- and gatifloxacin indicates that it is the highest in levofloxacin, and the lowest in moxifloxacin. Currently, in several countries (South Korea, Hong Kong), due to the uncontrolled use, an increase in the resistance of *S. pneumoniae* to levofloxacin has already been observed [19]. However, in Europe more than 97 % of strains of *S. pneumoniae* remain sensitive to "respiratory" fluoroquinolones [20], and in Russia only isolated strains with a moderate resistance to levofloxacin and moxifloxacin have been isolated [21].

Currently, a weighted approach to the clinical use of "respiratory" fluoroquinolones in the treatment of community-acquired respiratory tract infections, including CAP, dominates. Unjustifiably, the wide use of "respiratory" fluoroquinolones in a number of countries, which is fraught with the risk of losing this very promising class of antibiotics, should be countered by a weighted approach, actualizing their use primarily in patients at risk. In this context, the position of the Russian experts looks as if "respiratory" fluoroquinolones are considered as alternatives to β-lactams and macrolides or their combined use. The use of "respiratory" FQ in the treatment of CAP is preferable in the presence of the known risk factors in patients.

CONCLUSIONS

1. There is a significant in consumption of fluoroquinolones for the treatment of community-acquired pneumonia in a multi-specialty hospital of the Republic of Tajikistan for the period of 2011-2015. There is a significant reduction in consumption of ofloxacin and levofloxacin against the background of a slight tendency to increase the demand for ciprofloxacin in the treatment of pneumonia in the inpatient drug treatment.

2. The data obtained can be used in educational programs for physicians on the rational antimicrobial therapy of community-acquired pneumonia in a hospital.

Conflict of Interests: authors have no conflict of interests to declare.

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