THE TROUBLE WITH ANTIBIOTICS

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During the long history of antibiotics, resistance of causative agents of main infectious diseases was estimated as a very serious threat to effective treatment of patients and as a social and economic problem faced by the entire mankind. The activities performed by the medical society provided no significant effect resulting in growing antibiotic resistance. The pandemic of novel coronavirus infection only made things worse. It became a new challenge for the medical community regarding searching solutions which are clinical, organizational and methodological by nature in the global struggle with resistance to antibiotics. The reviews of several studies of coronaviral infections have shown that treatment with antibiotics failed to correlate with the decreased all-cause mortality. In this work, we have reviewed some aspects of therapy with antibiotics, including ethical ones. Ethical aspects of antibiotic therapy concern decisions of physicians about administration of commonly unnecessary antimicrobial agents.

Keywords: antibiotics, antibiotic resistance, antibiotic therapy, COVID-19, ethics

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ПРОБЛЕМЫ АНТИБИОТИКОТЕРАПИИ

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На протяжении всей истории применения антибиотиков риск развития устойчивости возбудителей основных инфекционных заболеваний оценивался как очень серьезная угроза для эффективного лечения пациентов и, в целом, как социально-экономическая проблема для всего человечества. Принимаемые медицинским сообществом меры не давали значимого эффекта, рост антибиотикорезистентности продолжался. Пришедшая пандемия новой коронавирусной инфекции лишь усугубила ситуацию и стала новым вызовом для медицинского сообщества в плане поиска решений как клинического, так и организационно-методического характера в борьбе с устойчивостью к антибиотикам, получившей глобальное распространение. В обзорах, включавших несколько исследований по коронавирусной инфекции, было продемонстрировано, что лечение антибиотиками не коррелировало со снижением смертности от всех причин. В данной работе рассмотрены некоторые аспекты проведения антибиотикотерапии, в том числе этического характера. Этические аспекты назначений антибиотикотерапии касаются решений врача о назначении конкретному пациенту антимикробных препаратов, в которых очень часто нет никакой необходимости.

Ключевые слова: антибиотики, антибиотикорезистентность, антибиотикотерапия, COVID-19, этика

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I. USE OF ANTIBIOTICS IN THE COVID-19 ERA.

Years of the COVID-19 (*COronaVIrus Disease 2019)* pandemic exacerbated the problem of antibiotic resistance and rational use of antibiotics in clinical practice even more. Until the pandemic, the level of antibiotic resistance of some infectious agents, especially nosocomial infections, raised very serious concerns of the world medical community. Let's remember a famous report of a group of English economists headed by J. O'Neill [1, 2], made for the government of the Great Britain. In that report, an increase of lethal outcomes due to resistance of challenging causative agents from 700 thousand to 10 million a year was predicted by 2050. Negative trends of increased resistance of basic clinically significant causative agents were noted even within community-acquired flora.

Some people believed that these figures were slightly exaggerated [3].

However, another data analysis was performed in 2019 to examine antibiotic resistance and its effect on healthcare in 204 countries [4]. The figures predicted by a team of English economists in 2014 will be presented much earlier.

4.95 million lethal outcomes associated with bacterial resistance in 2019, including 1.27 million attribute-based outcomes, were determined in a novel study. In 2019, lower respiratory tract infections included over 1.5 million resistance-associated lethal outcomes, which turns them into the most severe infectious syndrome. In 2019, six leading lethal antibiotic-resistant pathogens (*Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*) were

attributively responsible for 929,000 deaths and associated with 3.57 million lethal outcomes. A pathogen/medicinal agent (MRSA) combination resulted in over 100,000 lethal outcomes associated with antibiotic resistance in 2019. Six more similar combinations were the reasons for 50,000–100,000 deaths each: multidrug resistant tuberculosis, excluding extensively drug-resistant tuberculosis, third generation cephalosporin-resistant collibacillus, carbapenem-resistant *A. baumannii*, fluoroquinolone-resistant collibacillus, carbapenem-resistant *K pneumoniae* and third generation cephalosporin-resistant *K pneumoniae*.

The SARS-CoV-2 (severe acute respiratory syndrome-related coronavirus 2) pandemic, high incidence of COVID-19 and an associated round of excessive and unjustifiable administration of antibiotics brought medicine even closer to the postantibiotics era, according to many experts.

The analyses devoted to the strategy of using antibiotics in case of novel coronavirus were published in 2020–2022. It has been confirmed that bacterial involvement is not that large. Thus, a wide use of antibiotics in this pathology is not justified. For instance, in a significantly characteristic review that included 19 studies [5] it has been demonstrated that the secondary or concurrent infection (coinfection) was confirmed in 17.6% of patients only with the level of antibiotics administration being 74%. Meanwhile, a half of those who used antibiotics were not related to the group of severe and critical patients. It has been noted that the signs that confirm accession of the secondary bacterial infection developed on days 14 and 17 after the diagnosis was made for those who survived/failed to survive respectively. An excessive strategy of early and unjust administration of antibiotics has been traced.

A work of famous Spanish investigators [6] has been released approximately at the same time. Its meta-analysis has shown that a bacterial or fungal infection was diagnosed only in 7–8% of hospitalized patients with COVID-19. The infections occurred more frequently among patients from the intensive care units (8–14%) as compared with patients from other departments (4–6%).

Coinfections were found in 3.5% patients only, with secondary infections occurring in 14.3%. Meanwhile, *Mycoplasma, Haemophilus influenzae и Pseudomonas aeruginosa* belonged to the most frequent bacterial concomitant microorganisms.

In spite of low registered levels of bacterial infections, the use of antibiotics among patients with COVID-19 was rather high: 71.9% of patients with COVID-19 were administered antibiotics. It should be noted that 74% of administered antibiotics belonged to third generation fluoroquinolones and cephalosporines.

In April 2021, researchers from Pakistan [7] analyzed data of 617 patients hospitalized with COVID-19. It has been established that 97.3% of patients were administered antibiotics on the examination day. The secondary bacterial infections or co-infection (concomitant infection in patients with COVID-19) developed in 1.4% of patients only. On the date of examination, one patient got 1.7 antibiotics and 85.4% of antibiotics were given for the purpose of prevention. Azithromycin (35.6%), ceftriaxone (32.9%) and meropenem (7.6%) were most commonly administered antibiotics.

Doubtful early use of antibiotics in patients with COVID was confirmed in LEOSS trial [8], when 3.627 cases that corresponded to all inclusion criteria (episodes from March 18, 2020 to February 16, 2021; age ≥ 18 years; data about antibiotic therapy; with a minimum observation period of 3 days (≥72 hours)) were registered. In addition to qualified cases, the ones with no documented treatment outcomes were excluded as well. Procalcitonin (PCT) was dichotomized with a threshold value commonly used for lower respiratory tract diseases. The value was equal to 0.5 ng/ml (≤0.5 ng/ml and >0.5 ng/ml). The clinical outcomes considered in this trial included all-cause mortality and progression to the next advanced phase of the disease as per the LEOSS regimen until the end of SARS-CoV-2 acute phase each (for instance, convalescence or death).

When the primary endpoint was estimated, the authors have decided that treatment with antibiotics failed to correlate with a decreased all-cause mortality or transition to the next, more advanced (critical) phase ($p > 0.05$ for both indicators). As far as the secondary endpoints go, patients who were administered antibiotics during a non-complicated phase showed a no less all-cause mortality irrespective of the PCT level and progressed at least to the next, more advanced (complicated) phase ($p > 0.05$). Patients with PCT > 0.5 ng/ml who were administered antibiotics during a complicated phase demonstrated a higher all-cause mortality ($p = 0.029$) with no significant difference in a possible progression to a critical phase ($p > 0.05$).

The authors conclude that the use of antibiotics in patients with SARS-CoV-2 wasn't associated with a positive effect on all-cause mortality or disease progression.

Physicians who actively prescribed and recommended antibiotic therapy during the first year of the pandemic were slightly trapped in terminology as the changes in the pulmonary tissue were estimated as 'pneumonia'. Incidence rate of pneumonia in Russia is reported, especially during the first year of the pandemic. In Russia, the Federal Service for Surveillance in Healthcare recorded 2.722,292 cases of community-acquired pneumonia in 2020 and only 760.074 cases in 2019. The growth accounted for 258%, making community-acquired pneumonia the leading cause of morbidity in Russia in 2020. In the future, a better comprehension of processes occurring in case of coronavirus infection was accompanied by a more responsible definition of pneumonia and administration of antibiotics.

The use of antibiotics is growing worldwide. However, the growth is associated with developing and actively developing countries (China, India, Russia) [9].

In this study, the tendencies and driving forces of using antibiotics from 2000 to 2015 were analyzed in 76 countries and the total global consumption of antibiotics until 2030 was predicted. From 2000 to 2015, consumption of antibiotics expressed as defined daily doses (DD) was increased by 65% and the level of antibiotic consumption was increased by 39%. In has been established in the report that the mean DDD per 1,000 citizens was about 20 per day in 2015.

The authors stated that a sharp increase of using of drugs of last resort such as glycylcyclines, oxazolidinones, carbapenems and polymyxins was of particular concern. As per the presented prognosis, the global consumption of antibiotics in 2030 will exceed the indicators of 2015 by 200%, in case of no changes in the policy.

A reasonable assumption can be made that years of the pandemic made antibiotic resistance worse and complicated the issue of selecting an adequate antibiotic by physicians.

The pandemic highlighted some interesting facts about how western and Russian physicians reacted to the situation. For instance, there was a 56% drop in administration of 10 most popular antibiotics in the outpatient setting during the first pandemic peak (1st half of 2020) [10]. In the USA, consumption of such medicinal preparations as azithromycin and amoxicillin [11] during the first months after the pandemic was reduced

by 64% and 63% respectively; April 2020 was compared with April 2019.

In Russia, the situation was slightly different. In October 2020, 9 professional medical communities released an appeal to Russian doctors [12]. It stated that a significant growth of sale of antibacterial medicinal preparations by pharmacies and their purchase by therapeutic institutions discovered against the background of novel coronavirus pandemic were of serious concern. According to some trials, over 90% of patients with COVID-19 were given antibiotics, including combined therapy and parenteral medicinal agents on the outpatient basis.

According to some authors, consumption of azithromycin and, to a lesser extent, of levofloxacin and amoxicillin/clavulanate in Russia was dramatically increased in 2020. Subsequently, organizational efforts of the Ministry of Health of Russia and expert community still resulted in an interrupted negative tendency. As pharmacy analysts state [13], the pharmacy market grew by 7% in January–November 2021 as compared with January–November 2020, and sales of antiviral and antibacterial medicinal preparations dropped. A decrease of sale of systemic antibacterial medicinal preparations by 10.2% was especially emphasized. This was associated with optimized medicinal expenses to treat coronaviral infection. It has also been noted that dispensation of the antibiotic most actively sold in 2020 (azithromycin) has been cut nearly in half in natural terms (by 42% in packs).

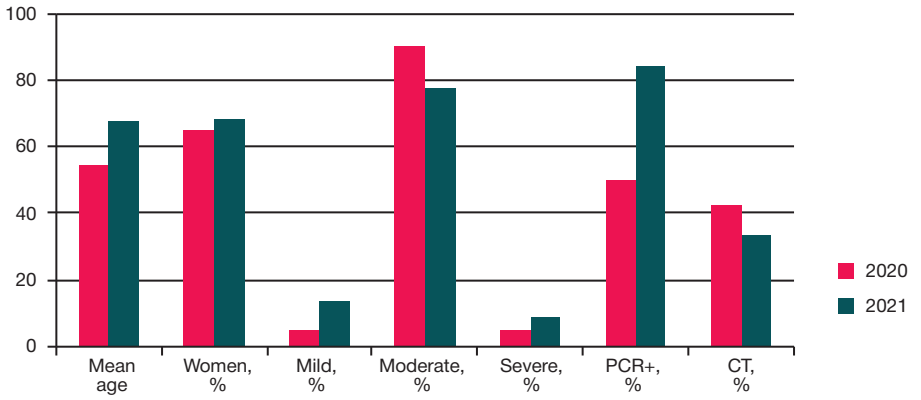
A positive decrease in excessive use of antibiotics in patients with coronavirus was noted only in some months after the pandemic when physicians came across the first analytical works devoted to management of patients with coronavirus pneumonia and the role of separate groups of medicinal preparations in the course of the disease, its complications, and decreased lethality.

Organizational aspects and extensive work of the Ministry of Health of Russia served its purpose as well. Activization of distance learning to some extent even simplified access to the latest data obtained by researchers from different countries.

The data are confirmed in our region as well. Case histories of hospitalized patients were analyzed in repurposed COVID hospitals.

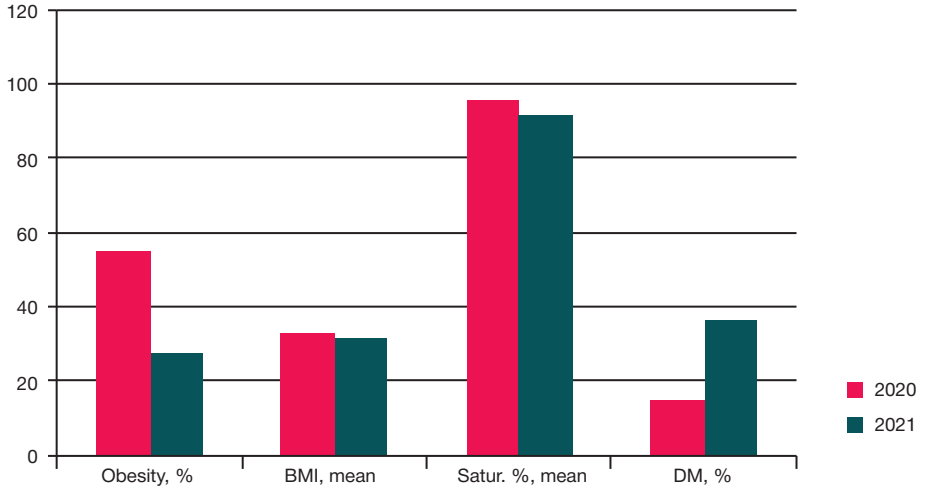
The repurposed department for patients with COVID-19 had two observational stages (February 2020 and February 2021). The object of observation included hospitalized patients (2020, n = 20; 2021, n = 22).

It should be noted that in 2021 the age of hospitalized patients was slightly increased and percentage of verified diagnosis of novel coronavirus was significantly increased (fig. 1). The patients had rather similar profiles in 2020 and 2021 (fig. 1, 2): women predominated among those who were admitted to the department. No significant difference was found in distribution of patients by the rate of severity. Percentage of patients with concomitant diabetes mellitus was increased (fig. 2).



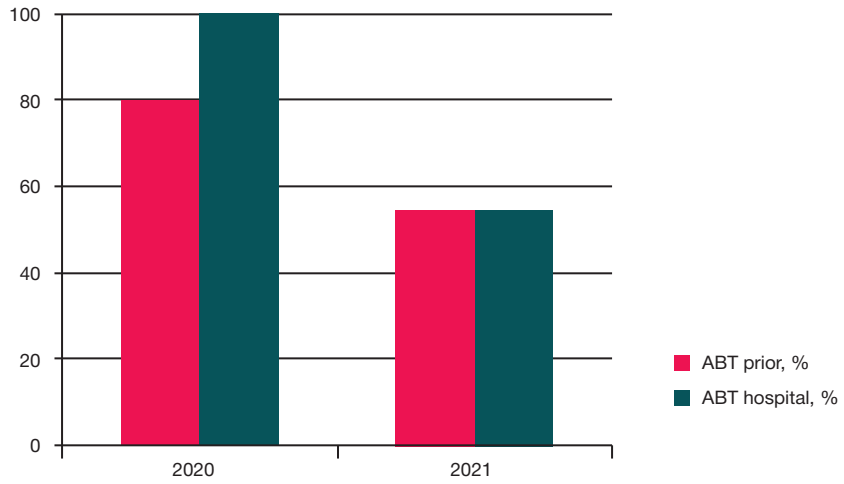
Notes: mild — mild course; mod. — moderate course, sev. — severe course; PCR+ — polymerase chain reaction, positive test for SARS-CoV-2; CT% — computed tomography, percentage of involved pulmonary tissue.

Fig. 1. Characteristics of patients included into analysis (I)



Notes: obesity — obesity was diagnosed based on the case history, BMI — body mass index; satur% — percentage of oxygen saturation (pulse oximetry); DM — diabetes mellitus.

Fig. 2. Characteristics of patients included into the analysis (II)



Note: — ABT prior,% — a share of patients who were given antibiotics on the outpatient basis prior to admission to the hospital; ABT hospital,% — a share of patients who were given antibiotics on the hospital basis.

Fig. 3. Use of antibiotics at the outpatient and inpatient stages (2020–2021)

In February 2020, 80% of patients included into the analysis were given antibiotics at the prehospital stage, whereas 100% of hospital-based patients were administered antibiotics starting from the first day (fig. 3). And this is the most important aspect of the topic discussed.

In February 2021, only 55% of patients with a history of outpatient antibiotic therapy were admitted to the department, and antibiotics were given to approximately 55% of hospital-based patients as well (fig. 3).

The global medical society has placed and is still placing great expectations in the program of control (or management) of antibiotic therapy still hoping for its effectiveness. In English literature, the program was called '*Antimicrobial stewardship*' (AMS). However, in the recent past, active implementation of these principles came across serious difficulties in real clinical practice. There existed objective and subjective reasons for that. According to authors of a work [14] devoted to this problem, the World Health Organization adopted a global plan of actions to combat resistance to antimicrobial medicinal agents including five basic objectives such as improved awareness of the society and suppliers of medical services, investment in diagnostics and therapy, update of epidemiological surveillance, prevention of infections and optimization of use of antimicrobial agents [15]. However, during the COVID-19 pandemic, more attention was given to the principles of management of antimicrobial medicinal substances (AMS), and their effect on the total resistance of pathogens was decreased [16]. Though the strategies were announced by the WHO in 2015, the emphasis of an increased attention of medical society on antibiotic resistance was not taken seriously even prior to the pandemic [17]. The fact is no less important.

II. ETHICAL ASPECTS OF ANTIBIOTIC THERAPY

Let's concentrate on several ethical aspects of antibiotic therapy including the issues of pharmacovigilance and actions of regulatory bodies and taking fluoroquinolones as an example. In the early days of the pandemic, levofloxacin was included into the risk group due to unreasonable use of antibacterial agents in COVID-19. Levofloxacin belongs to the so-called respiratory fluoroquinolones.

Grepafloxacin was the first respiratory fluoroquinolone in the Russian market. The medicinal agent was registered in the Russian Federation in 1997. In a year, the medicine was withdrawn from the market due to significant problems with cardiotoxicity (increase in QT interval) when even lethal arrhythmias were developed. In other words, the medical community realized the risks of therapy with fluoroquinolones. Cardiotoxicity was essentially a class effect typical of this group of preparations. In this regard, organizational solution of the manufacturing company seemed ethically logical. The company produced a novel and potentially effective medicinal agent. The agent was simultaneously registered in many countries. However, as soon as grepafloxacin-associated adverse drug reaction reports occurred, the company, having weighted the pros and cons, decided to withdraw the agent from all the markets approximately at the same time.

In the beginning of 2000, the leading experts were waiting for novel agents belonging to this group (gatifloxacin, in particular).

The history of gatifloxacin is unique in some way.

In the USA, gatifloxacin was registered by BMS in 1999.

In 2006, data about serious safety issues of gatifloxacin were published [18, 19].

In the Russian Federation, gatifloxacin was registered in 2009.

In 2019, the registration was cancelled. In letter of the Federal Service for Surveillance in Healthcare No. 02и-360/19 as of Febr. 08, 2019 [20], a history of gatifloxacin is described in detail: 'Having analyzed the international regulatory solutions, Bristol-Myers Squibb that developed Tequin (gatifloxacin) withdrew the medicinal agent from the market of the USA in 2006 due to the risk of dysglycemia.

Subsequently, FDA withdrew reproduced preparations of gatifloxacin from the market [21]. No data about registration of gatifloxacin systemic preparations in the EU, Canada and Australia were found during analysis of information obtained from the foreign regulatory agencies. In India, circulation of gatifloxacin preparations was terminated in 2011 [22].

Then a just question arises. Why gatifloxacin was still registered in the Russian Federation in spite of all 'shortcomings' that prevented its manufacture due to safety-related serious issues?

Of course, one can argue that the medicinal agent is still used in many countries, though in a limited way (only eye drops). Dysglycemic effects of gatifloxacin are not well explained yet (it causes both hypoglycemic and hyperglycemic episodes) and different adverse effects can be rarely found with the same preparation.

Ethical aspects refer to antibiotic therapy in general and solutions of a certain doctor about unnecessary use of antimicrobial drugs.

In conclusion, one can quote Jan Carlzon, a famous Swedish businessman: 'An individual without information can't take responsibility. An individual with information can't help but take responsibility'. Doctors all together and every doctor as an individual should take the responsibility for their solutions and risks associated with antibiotic therapy and antibiotic resistance.

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