ETHICAL AND LEGAL ASPECTS OF ADMINISTRATION OF ANTIBACTERIAL RESERVE PREPARATIONS

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The article explains what an antibacterial reserve preparation means. It has been shown that the drug belonging to the group is determined by its pharmacological properties only such as a clinically significant (sufficient for empirical application) activity in relation to Pseudomonas aeruginosa or nosocomial (methicillin-resistant) strains of Staphylococcus aureus. It allows to differentiate between two categories of reserve antibiotics, which exert an anti-Gram-negative and anti-Gram-positive activity. There is an exhaustive list of preparations included into each group and available in the Russian market. Meanwhile, no drugs that correspond to inclusion requirements for both groups are available. Possible conflicts that occur during clinical application of antibacterial reserve drugs are comprehensively analyzed. It is based on divergence of interests of a patient and the patient's representatives, treating physician, management of the clinic, hospital epidemiologists and manufacturers of reserve generics. Economic and general biological (selection of drug-resistant strains in extensively wide application) arguments commonly contradict the legal (compliance with clinical recommendations), moral and ethical (independence of aid quality from the patient's prognosis) standards. The Legislator's position in relation to the issue has been reviewed. Imperfect regularity framework and insufficient legal safety of a doctor make it possible to resolve conflicts through concessions and agreements including reserve antibiotics prescribed as per conditionally social indications.

Keywords: antimicrobial therapy, reserve antibiotics, selection of polyresistant strains

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ЭТИЧЕСКИЕ И ЮРИДИЧЕСКИЕ АСПЕКТЫ НАЗНАЧЕНИЯ АНТИБАКТЕРИАЛЬНЫХ ПРЕПАРАТОВ РЕЗЕРВА

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В статье разъяснено понятие антибактериального препарата резерва. Показано, что принадлежность лекарственного средства к этой группе определяется исключительно его фармакологическими свойствами — клинически значимой (достаточной для эмпирического применения) активностью в отношении *Pseudomonas aeruginosa* или нозокомиальных (метициллинрезистентных) штаммов *Staphylococcus aureus*. Это позволяет выделить две категории резервных антибиотиков — соответственно «антиграмотрицательные» и «антиграмположительные». Приведен исчерпывающий перечень препаратов, входящих в каждую из групп и представленных на отечественном рынке. При этом лекарственные средства, отвечающие требованиям включения одновременно в обе группы, отсутствуют. Всесторонне проанализированы возможные конфликтные ситуации, возникающие при клиническом применении антибактериальных препаратов резерва. В их основе лежит расхождение интересов пациента и его представителей, лечащего врача, администрации клиники, больничного эпидемиолога и производителей дженериков препаратов резерва. Экономические и общебиологические (селекция лекарственноустойчивых штаммов при чрезмерно широком применении) аргументы нередко входят в противоречия с аспектами юридическими (следование клиническим рекомендациям) и нравственно-этическими (независимость качества помощи от прогноза пациента). Рассмотрена позиция Законодателя, касающаяся изучаемого вопроса. Несовершенство нормативной базы и недостаточная юридическая защищенность врача делает возможным разрешение конфликтов лишь путем уступок и договоренностей, в том числе и за счет назначения резервных антибиотиков по условно «социальным» показаниям.

Ключевые слова: противомикробная терапия, антибиотики резерва, селекция полирезистентных штаммов

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THE NOTION OF A RESERVE ANTIBIOTIC

In real clinical practice, the term 'reserve antibiotics' is occasionally defined in a broad and obscure way. Novel, highly effective and, thus, cheap antibacterial agents are considered as reserve ones by the hospital management. To restrict their widely application. Reserve drugs commonly include costly medicinal products.

However, logical inconsistencies appear immediately. If the medicinal product belongs to the group of reserves due to its cost, it is not clear which threshold limit, when exceeded, turns the basic drug into the reserve one. Nobody has ever named and will hardly name any specific numbers. It is because the modern pharmaceutical market offers numerous antimicrobial generics, including very cheap ones. It can occur that medicinal agents with the same active substance produced by various manufacturers who offered different prices for the product can be classified both as basic and reserve preparations. It is inaccurate to believe that the antibiotics status is somehow related to the price.

From the point of view of clinical pharmacology, reserve antibiotics include the means that stay in the reserve if the pathogen is resistant to basic drugs. Thus, we can say that the drug belongs to the reserve group due to its antimicrobial activity or ability to suppress strains of pathogens with acquired resistance to drugs. Neither wide specter, nor cost of the drug can play an essential role.

A wide number of costly antibacterial agents with a wide specter of antimicrobial activity is found in the market. They are not capable to inhibit nosocomial infections. Thus, they are basic but not reserve. This is not an indicator of poor

quality but specific properties of a particular drug are inherent in the development phase. IV generation (antianaerobic) fluoroquinolones represent a classic example. Initially, their significant specter of antimicrobial activity typical of the entire pharmacological group is additionally expanded towards S. pneumonia and B. fragilis [1]. The expansion is provided at a higher cost which is quite compatible with antipseudomonal cephalosporins and cheap carbapenems. However, even novel IV generation fluoroquinolones did not become reserve ones.

Let's note the key feature of antibacterial reserve preparations.

The reserve preparation is developed to suppress microorganisms with high resistance to antimicrobial agents such as hospital or nosocomial strains. There are only two categories of reserve preparations such as anti-Gram-negative and anti-Gram-positive ones. Actual belonging of a drug to the group of reserve medicines is determined by formal features.

The agents of the anti-Gram-positive reserve should suppress methicillin(oxacilline, cefoxitin)-resistant strains of Staphylococcus (MRSA and MRSE). They include vancomycin, ceftarolin, linezolid, tigecycline, and daptomycin.

The agents of the anti-Gram-positive reserve should be active in relation to Pseudomonas aeruginosa (P. aeruginosa). These include antipseudomonal cephalosporins (ceftazidime, cefepime, cefoperazone/sulbactam, cefepime/sulbactam, ceftazidime/avibactam), antipseudomonal penicillins (piperacillin/tazobactam, ticarcillin/clavulanate), amikacin, and antipseudomonal carbapenems (meropenem, imipenem/cilastatin, doripenem).

The activity mentioned above is clinically significant and rather high to be used in the empirical mode.

The same drug can have a different status in relation to various groups of pathogens. Moreover, it seldom happens that one drug property can't be applied in clinical practice. For instance, carbapenems are not used in therapy of gram-positive infectious processes though they have a clinically significant anti-Gram-positive activity against wild strains of Staphylococcus spp. and Streptococcus spp.

CONFLICT OF INTERESTS WHILE ADMINISTERING ANTIBACTERIAL RESERVE DRUGS

From the time of occurrence and until now, antibacterial reserve drugs are the subject of endless debates and conflicts. It is natural as interests of at least five parties interact here. But total coincidence of interests is possible under no circumstances.

1. A patient who acts as a client and consumer of a medical service from the legal point of view is interested in the best effectiveness of therapy 'here, now and using any affordable means'. He is indifferent about the economic part of the issue and risk of selection of hospital strains. He does not wish to comply with profile clinical recommendations until complications or adverse effects occur. Until any risks are implemented.

It means that the patient, the patient's relatives/representatives will insist on the rapid use of reserve drugs which seem more effective to him as compared to basic ones as they are capable to suppress both wild, and hospital strains of pathogens. In contrast to basic drugs which are active against wild strains only.

The situation is aggravated by decision of the Plenum of the Supreme Court No. 1 as of 26.01.2010, where the principle of presumption of innocence for a medical organization was actually withdrawn in relation to medical matters [2]. As a result, any competent individual can write nonsense like 'the result of treatment of my elderly relative does not seem satisfactory to me because he used to be physically fit and could take care of himself, whereas now, following a stroke, he fails to understand why he should take care of himself; I believe that treatment was not provided in time and that it does not totally comply with the Clinical recommendations; and this was the reason of failure; I ask to hold XXX liable and pay me XXX RUB to compensate for moral damage'. In accordance with the acting legislation, he does not have to prove anything.

Meanwhile, nobody asked the opinion of the elderly relative who developed an acute cerebrovascular accident but was not deprived of legal capacity de ure. To initiate the check by the supervisory authority it's enough to have a detached view and a fantastic complaint.

2.Provision of a **treating physician** directly depends on satisfaction of patients. His patients. Condition of other patients and epidemiological welfare of the hospital are secondary to him. In words, it is essential. But in real life, it does not mean anything at all. A hospital doctor won't be responsible if carbapenem-resistant Klebsiella spp. are found at the hospital. An unhappy patient or relatives will write a complaint consisting of non-use or untimely (as assessed by the patient) use of any available means. Controlling companies will hardly ignore the 'insufficiently active therapy'.

Among administrators and lawyers, there is a widely spread belief that properly selected therapy should totally correspond to the current regulatory framework. The position is precarious because no regulatory framework determines therapy in the form of an order. Only regulations and limitations but not commands are provided there. This is how medical regulatory framework differs from the military regulations.

All motivating instructions related to drug-induced therapy of patients are executed as 'Recommendations', which are literally non-binding. It is obviously done so to reduce the liability of their developers. Direct compliance with profile recommendations approved by the order of the Ministry of Health of the Russian Federation or Antimicrobial Stewardship program [3] does not warrant legal safety of a treating physician for claims in case of unsuccessful treatment. Unlike military personnel, a doctor is responsible for the results of actions but not for formal adherence to the law irrespective of consequences. And if you look deeper, responsibility lies not even with administration of a drug, which constitutes a doctor's meaningful action, but with the clinical effect of the drug, which can be tried to predict but not to make! Effect of the drug is the same as effect of nature.

So, a treating physician will practice early administration of reserve antibacterial drugs using the terms 'novel', 'highly effective', etc. especially if the patient or the patient's relatives are prone to barratry.

3. An epidemiologist is interested in control over nosocomial strains of pathogens and no deaths from hospital-acquired infection. Prognosis for a certain patient or the situation surrounding the epidemiologist is definitely important but secondary.

Control over nosocomial strains de facto means that its spread is minimized. This can be achieved only with wild strains without acquired drug resistance but capable to use the living space and nutrient medium faster and more effectively. Drug-induced suppression of a certain microorganism releases the niche that will be inhabited by microorganisms which are resistant to the agent. Wild strains or strains with low resistance can survive only within the environment lacking antimicrobial agents. It means that to achieve the goals, an epidemiologist should cut the administration of all antibiotics, especially reserve drugs, which make selection of superresistant hospital strain possible.

But the only voice of an epidemiologist is nothing against that of clinicians and scandalous relatives!

4. Management of the clinic is ambivalent. On the one hand, conflicts with patients, their relatives and inspecting authorities

should be settled exclusively by diplomatic means because other options (conditionally powerful) currently remind of a suicide attack due to total disability of the entire state machine.

The definition 'we did what we could; combined therapy with the best reserve drugs was administered since the time of admission to the clinic' sounds great, it sounds fine while dealing with a low-competent partner. None of those who make arrangements is bothered by the fact that the practice makes hospital welfare doubtful.

On the other part, reserve preparations are costly. Many of them are required. Sometimes there are too many of them. In some branches of clinical medicine, for instance, pulmonary medicine, expenses on the purchase of reserve antibiotics only can exceed 80% of the total amount of drug-induced therapy financing. So, **almost any solution associated with distribution of reserve antimicrobial agents has a high economical significance**.

There are two ways how consumption of any product (or preparation) can be reduced: economy or normalized consumption. From the ethical point of view, both options are doubtful.

What do we save for? And who? 'Irrational prescription' is a common answer. The answer is neutral and, thus, has external beauty. Nevertheless, it is fatally flawed. Are employees competent enough to allow the things happen in the presence of numerous irrational prescriptions and significant economy? Can management be considered adequate if no timely interference occurred? In the presence of a few irrational prescriptions, the saved means can not even compensate for expenses on time and labor associated with searching and correction. It is not about economy. It is about imitation of economy.

In fact, we'll have to save on comorbid decompensated patients with a poor diagnosis who sometimes determine up to ¾ of total expenditure of carbapenems, antipseudomonal cephalosporins, vancomycin and linezolid at intensive care units. This totally contradicts the principles of ethics in accordance with which qualitative and adequate aid should be provided to all patients irrespective of their prognosis.

It is the same with normalized consumption. These attempts are constant and unintentional. Erratic arrival of some agents results in the following definition: 'I can provide xxx of vials with meropenem but no more, so you can distribute the available vials as you like. The preparation has already been ordered and paid for but is not available today. Nobody knows for sure whether it can be available tomorrow, the day after tomorrow or in a week. It is supplied by private companies'.

Based on the real practice, economy allows to use the critical resource in a more efficient way as compared with the consumption rate.

An epidemiologist's opinion is essential for administration as well. The idea of economy is totally supported as well. Until the first serious complaint though.

5. Pharmaceutical companies producing generics represent private companies that want profit by any legal means. The cost of an original drug used to be a very serious constraining factor. Relatively cheap generics imipenem/cilastatin, meropenem linezolide and other reserve antibitoics that can be seen in the market only increase the temptation. It is still disputable whether using cheap reserve preparations is good or bad. It seems good, and the aid becomes more affordable. However, it is bad in reality because after certain (not significant enough as carbapenem-related proper data have been obtained but are still being published) rate of administration, the reserve agent can't be classified as reserve any more, and no aid will be provided any longer. There will be what the aid can be provided with, but the aid will be simulated.

No ban, recommendation or administrative regulation can decrease the rate as effective as the cost does. Nowadays, we have come across a paradoxical situation when rarely administered due to high cost ceftazidime/avibactam (III generation inhibitory protective antipseudomonal cephalosporin which is actually an antgramnegative reserve line 1 preparation) is used to inhibit Klebsiella spp. and P. aeruginosa strains with total (!) carbapenem resistence [4,5]. It is successfully used not in casuistic cases, but with certain though small regularity (in cystic fibrosis) when combined with amikacin and sometimes as monotherapy.

The issue of antibiotics distribution is far from being settled today. The management commonly delivers it to the service of clinical pharmacology developed to deal with the issues. Unfortunately, turnover of the drugs at the medical institution can be controlled only manually under the modern conditions of imperfection of the regulatory framework.

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