DOI: 10.17816/KMJ2020-403

Multidisciplinary health care monitoring and training program: impact on antibiotic use

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Abstract

Aim. To develop a program for monitoring the use of antibacterial agents and training in their rational use using the information on consumption and expenses in a multidisciplinary healthcare institution.

Methods. From 2011 to 2014, a group of clinical pharmacologists developed and implemented a monitoring program for the use of antibacterial agents using the ATC/DDD and ABC/VEN methodology in SBIH "Penza Regional Clinical Hospital named after N.N. Burdenko". Hospital doctors were trained in the principles of rational use of drugs and antibiotics as part of continuing education in clinical pharmacology using monitoring results — analysis of the costs and consumption of antibacterial agents.

Results. Over the four years of monitoring and three years of educational activities, the most pronounced changes have occurred in the use of fluoroquinolones, aminoglycosides, macrolides and carbapenems. Fluoroquinolones consumption reduced 2 times, and it cost of purchase reduced 6 times (of total). Aminoglycosides consumption increased 3 times, primarily due to amikacin 5 times consumption increase. Macrolides consumption reduced 3 times, primarily due to clarithromycin decrease in consumption. At the same time, the antibacterial agents of the cephalosporin group leading in consumption, with their cost had decreased 2-fold. However, carbapenems consumption increased 3 times, with their costs increase 7 times.

Conclusion. Over the three years of the program, expenses and consumption of antibacterial agents of the fluoroquinolone and macrolide group were reduced, with an increase in the consumption of aminoglycosides and carbapenems without changes in the consumption of cephalosporins; costs of cephalosporins and carbapenems led to an increase in overall antibiotic costs; further efforts and studies are needed to study the use of antibacterial agents.

Keywords: pharmacoepidemiology, drug use, antibiotics.

For citation: Aleksandrova E.G., Abakumova T.R., Evstigneev S.V. et al. Multidisciplinary health care monitoring and training program: impact on antibiotic use. *Kazan Medical Journal.* 2020; 101 (3): 403–411. DOI: 10.17816/KMJ2020-403.

Background

The rise in the consumption of antibacterial agents and the cost thereof are typical for any healthcare institution, be it anywhere around the world [1,2]. This in turn encourages the growing problem of the spread of the resistant strains of microorganisms and hospital infections. Accordingly, the nosocomial, or hospital, strains of microorganisms that are resistant to most antimicrobial agents have particularly become widespread in most parts of the world, including in Russia [3-5]. These infections complicate the course of the underlying disease during the patient's stay at the hospital, which leads to the lengthening of the duration of hospitalization and increasing the cost of treatment. Nosocomial infections can also increase the risk of failure [6–8]. While bacterial resistance typically occurs as a result of an improper use of antibiotics, studies have shown that in about half of the cases, doctors are incompetent to properly prescribe antibiotics to the patients [7,9,10].

However, with an adequate and comprehensive approach to this issue, it is possible to reduce the frequency of nosocomial infections [9]. The introduction of special measures at various levels, such as programs on the monitoring of the use of antimicrobial agents, serves as the main way of the inhibition of the resistance of pathogens, as well as a mean to cut down the financial costs for medicines and healthcare in general [11]. Polyhedral

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interventions, where educational activities are imparted at many levels, have shown successful effects on improving the practice of prescribing antibiotics at the outpatient stage [12].

Moreover, the Cochrane systematic review for improving the prescription of antibiotic by physicians in a hospital environment has shown the effectiveness of two broad categories of interventions: restrictive methods with rules for prescribing antibiotics and methods using educational activities to facilitate prescribing.

The execution of the antibiotic prescribing policies (restrictive measures with specific prescribing rules) resulted in a 1.95-day reduction in the duration of antibiotic treatment [95% confidence interval (CI) from 2.22 to 1.67; 14 randomized controlled studies; 3,318 participants; high-confidence evidence] without increasing the risk of death between the intervention and control studies (11% in both groups). This indicates that the use of antibiotics can be reduced without a negative influence on mortality (CI from −1% to 0%; 28 randomized controlled trials; 15,827 participants; evidence of moderate assurance).

Further, the actions aimed at antibiotic use policies reduced hospital stay by 1.12 days (95% CI from 0.7 to 1.54 days; 15 randomized controlled studies; 3,834 participants; evidence of moderate assurance). Therefore, both the restrictive and educational methods have been successful in reducing the abusive prescription of antibiotics in hospitals, and as a result, the evidence obtained in this systematic Cochrane review justifies the need to make decisions on the implementation of such measures to improve the use of antibacterial agents in hospitals [13].

Besides, educational activities, normalization of the hospital form of antibacterial medicines, rules for prescribing antibiotics, and internal audit and evaluation of the effectiveness of the program (with an analysis of the cost and use of antibiotics and quality control of antibacterial therapy) are few important steps toward the fulfillment of the strategy for controlling antimicrobial therapy [antibiotic stewardship program] in the delivery of hospital medical care [10, 14]. Doctors in many Russian medical institutions do not have proper information about the use of anti-infectives in their healthcare institutions or even within their departments. For this reason, as an important step to improve the strategy for antibiotic use, it is important not only to obtain the indicators of antibiotic use but also to equip the healthcare professionals with this information in a timely and adequate manner [15].

Aim: To develop a program for monitoring the use of antibacterial agents and training healthcare professionals on their rational use with the help of data on the consumption cost of antibacterial agents in a multidisciplinary healthcare institution.

Material and methods

This comprehensive study was conducted by a group of clinical pharmacologists with the support of the administrative staff at the Burdenko regional clinical hospital in Penza from 2011 to 2014. Using the ATC/DDD (Anatomic Therapeutic Chemical classification/Defined Daily Dose) and ABC/VEN methodologies, the drug consumption and cost during the study period were regularly analyzed.

In 2011, the baseline level of antibiotic consumption and expenses in a healthcare institution was first estimated. Based on the data obtained, a program was developed for training doctors on the rational use of drugs and antibiotics, and starting from 2012, a training session was subsequently conducted for hospital doctors as part of their advanced training in clinical pharmacology using the results of monitoring the cost and consumption of antibacterial agents were analyzed both for the hospital as a whole and for each department separately.

The educational module was used twice a year during 2012–2014 with a lecture course and a practical block with the analysis of medicinal prescriptions in a number of departments of the hospital. In 2014, a field training cycle was conducted at the hospital. As part of the monitoring program, the rational use of antibacterial drugs in hospital departments was analyzed as one of the key factors in reducing the spread of the resistant strains of microorganisms.

Moreover, when performing the ABC/VEN analysis, the share of expenses of the drug from the total budget for the purchase of antibacterial drugs was calculated. We used cost shares because we studied a large set of data on the expenses of all hospital departments for four years, so the methods of sample statistics are not acceptable here.

To assess the consumption of antibacterial agents, the ATC/DDD or ATC/USD (anatomic therapeutic chemical classification/established daily dose) methodology was used.

As recommended by the World Health Organization (WHO), to study the use of drugs in hospitals and compare the consumption of drugs in institutions of different capacities and at different time intervals, the drug utilization at the hospital stage was analyzed using the indicator DDD/100 bed days [16]. For this, the data was collected from the institution's pharmacy.

For the expression of the drug utilization used in the hospital in units DDD, the total amount of a drug in milligrams/grams used during the year was divided by the defined daily dose of this antibiotic accepted by the WHO for the given year [17].

Table 1. Utilization of the main groups of antibacterial agents at the Penza regional clinical hospital named after N.N. Burdenko during 2011–2014, the established daily dose/100 bed days

Antibacterial agents (ATC group)	Year			
	2011	2012	2013	2014
Cephalosporins (J01D A)	14.42	18.4	18.07	15.55
Fluoroquinolones (J01M A)	11.43	9.23	7.22	5.62
Aminoglycosides (J01G)	4.18	3.89	17.33	14.09
Penicillin (J01C)	4.09	3.99	3.7	2.9
Macrolides (J01F)	3.5	3.01	2.19	1.2
Carbapenems (J01D H)	0.12	0.42	1.03	0.38
Other	2.28	2.12	2.17	2.91
The antibiotics utilization in general	40.02	39.06	51.71	42.65

When calculating the DDD/100 bed days indicator, the number of bed days was adjusted in accordance with the bed occupancy indicator, which allowed us to compare the drug utilization in medical institutions with different rates, in different hospitals, and in different years. The used indicator of the drug utilization reflects the percentage (%) of hospital patients who received daily therapy with this drug, provided that the prescribed daily dose was equal to one DDD.

In the present work, we studied information pertaining to the use of systemic antibacterial agents [ATC (Anatomical Therapeutic Chemical Classification System)] (J01 group).

Although the results of the consumption of antibacterial agents were partially published in 2017 [18], this article is a comprehensive study of antibiotic consumption and purchasing expenses with a detailed analysis of the use of individual antibiotics, as well as the impact of educational activities on their use.

Results

While the utilization of all antibacterial agents increased from 40.02 DDD/100 bed days in 2011 to 42.65 DDD/100 bed days in 2014 [18], the expenses thereof increased from 13.92% to 22.14% of the total drug expenses, respectively [19]. The antibacterial drugs of the cephalosporin group (Table 1) dominated the structure of utilization.

Overall, the monitoring and training program did make some improvements in the use of fluoroquinolones, aminoglycosides, and macrolides.

Table 2. Utilization of systemic antibacterial agents of the fluoroquinolones group (J01M A), defined daily dose/100 bed days, 2011–2014

Name of the medicinal product (international nonproprietary name)	Year			
	2011	2012	2013	2014
Ciprofloxacin	8.42	7	3.04	2.81
Levofloxacin	1.19	0.44	1.66	1.39
Norfloxacin	1.05	1.11	0.92	0.7
Pefloxacin	0.77	0.68	0.32	0.2
Ofloxacin	—	—	1.09	0.5
Moxifloxacin	—	—	0.19	0.02
Subtotal	11.43	9.23	7.22	5.62

However, in particular, during the four years of monitoring and three years of educational activities, the most prominent changes occurred in the use of fluoroquinolones, aminoglycosides, macrolides, and carbapenems.

While the consumption of fluoroquinolones twice decreased from 11.4 to 5.6 DDD/100 bed days, the cost of fluoroquinolones reduced six times from 22% of the total costs for antibacterial agents in 2011 to 3.5% in 2014. In addition, the volume of ciprofloxacin consumption reduced significantly from 8.4 in 2011 to 2.8 DDD/100 bed days in 2014. Accordingly, its share of expenses from the total costs on all antibacterial products also reduced from 9.1% in 2011 to 1.3% in 2014. However, the study of the use of other representatives of the group of fluoroquinolones showed that the consumption of levofloxacin and norfloxacin practically did not change 1.2 DDD/100 bed days and 1.04 DDD/100 bed days in 2011 and 1.4 USD/100 bed days and 0.92 USD/100 bed days, respectively, in 2014. On the contrary, pefloxacin utilization reduced more than threefold from 0.77 to 0.2 DDD/100 bed days. Besides, moxifloxacin was used only in 2013–2014 with a utilization rate of 0.19 and 0.02 DDD/100 bed days, respectively (Table 2).

The two agents from the group of aminoglycosides–amikacin and gentamicin were used. Aminoglycosides utilization increased threefold from 4.18 to 14.09 DDD/100 bed days. This was mainly due to amikacin, the utilization of which increased five times from 2.4 to 13 DDD/100 bed days while that of gentamicin reduced from 1.8 to 1.0 DDD/100 bed days (Fig. 1). Of note, although the cost of these antibiotics fell from 4.5% to 2.7% of the total antibiotic expenditure, the aforementioned changes in the consumption occurred.

Moreover, a threefold reduction was observed in the macrolide utilization (from 3.5 in 2011 to 1.2

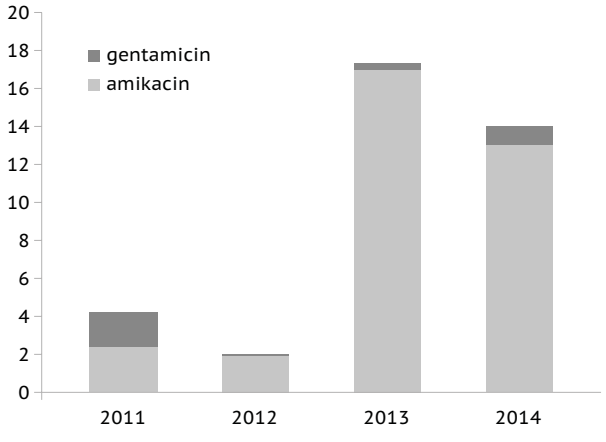

Figure 1. Utilization of systemic antibacterial agents of the aminoglycoside group (J01G), defined daily dose/100 bed days, 2011–2014.

DDD/100 bed days in 2014). The most used antibiotic in this group was clarithromycin. Its utilization reduced 4.5 times from 3.2 to 0.7 DDD/100 bed days. The utilization of azithromycin and erythromycin, however, did not change much. Besides, roxithromycin was used only in 2011 and 2013 (Table 3). Reducing the consumption of macrolides is also a positive factor since they have limited indications for use at the hospital stage.

Interestingly, the antibacterial agents of the cephalosporin group were the most consumed antibacterial agents: 14.4 and 15.6 DDD/100 bed days in 2011 and 2014, respectively. However, there was a twofold reduction in their cost from 51% to 22% of the total spending on antibiotics. However, the utilization of medicines is not always correlated with their cost. A reduction in the cost with an increase in the utilization indicates preferred purchases of generics. In addition, among the cephalosporin, the third-generation agents–ceftriaxone and cefotaxime were used more often. The ratio of utilization of these two agents has changed over the years of implementation of the program: while the utilization of ceftriaxone was 5.6 DDD/100 bed days in 2011 and 8.8 DDD/100 bed days in 2014 and that of cefotaxime was 4 DDD/100 bed days in 2011 and 2.7 DDD/100 bed days in 2014, the cost of both the agents has reduced. We also report a reduction in the expenses of cefepime (a fourth-generation cephalosporin antibiotic) from 16.8% to 4.32% of the total expenses of antibiotics, as well as a reduction in its utilization from 1.1 to 0.3 DDD/100 bed days.

However, despite all the positive aspects of our monitoring and training program, new problems have emerged in the use of antibiotics that require attention: a threefold increase in the carbapenems utilization from 0.12 to 0.38 DDD/100

Table 3. Utilization of systemic antibacterial agents of the macrolide group (J01F), defined daily dose/100 bed days, 2011–2014 of systemic antibacterial agents of the macrolide group (J01F), defined daily dose/100 bed days, 2011–2014

Name of the medicinal product (international non-proprietary name)	Year			
	2011	2012	2013	2014
Clarithromycin	3.23	2.58	1.24	0.75
Azithromycin	0.26	0.43	0.94	0.44
Erythromycin	0.01	0.002	0.007	0.01
Roxithromycin	0.002	—	0.0003	—
Subtotal	3.5	3.01	2.19	1.21

bed days. Particularly in 2013, the rate of utilization of carbapenems went extremely high to 1.03 DDD/100 bed days, primarily due to ertapenem (0.48 DDD/100 bed days). As a result, the cost of carbapenems increased seven times from 6.75% to 47.42% of the total expenses of all antibiotics. Doripenem utilization also increased from 0.01 to 0.19 DDD/100 bed days and its cost from 1.18% to 31.57% of the expenses of all antibiotics. Additionally, ertapenem utilization increased twofold from 0.03 to 0.06 DDD/100 bed days and its cost from 1.2% to 6.69% of all expenses for antibiotics. The imipenem/cilastatin utilization also increased from 0.01 to 0.04 DDD/100 bed days and its cost from 0.87% to 5.4% of all antibiotic expenses. The use of meropenem, however, did not change significantly, its utilization being 0.07 DDD/100 bed days in 2011 and 0.08 DDD/100 bed days in 2014, while the cost increased from 2.5% in 2011 to 3.76% in 2014 (Fig. 2).

Further, an increase in the utilization of the antibacterial agent of the group of glycopeptides vancomycin was observed from 0.05 to 0.08 DDD/100 bed days, with a high level of utilization in 2013–0.8 DDD/100 bed days (Fig. 3). Its cost also increased from 0.52% to 2.18% of the total expenses on antibiotics. In addition, while the linezolid utilization increased six times from 0.009 DDD/100 bed days in 2011 to 0.056 DDD/100 bed days in 2014 (see Fig. 3), its cost increased threefold from 1.38% to 4.1% of the total expenses on antibiotics.

Discussion

The indicators of antibiotic utilization in the hospital are comparable to their utilization in multispecialty hospitals in Russia and Belarus [1,20,21]. The third-generation cephalosporins without antisynegic activity (ceftriaxone, cefotaxime) remain the most to be prescribed in the vast majority of hospitals in the Russian Federation. A portion of

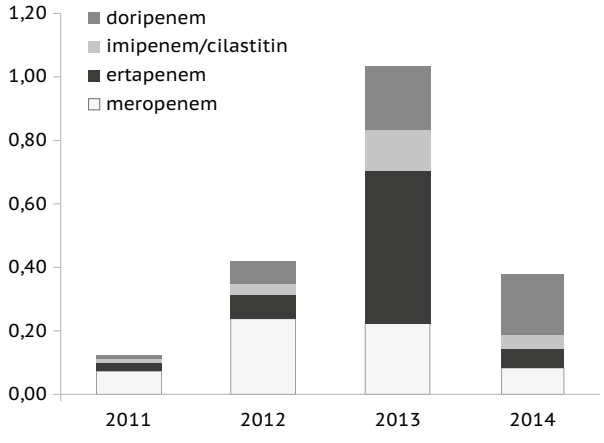

Figure 2. Utilization of systemic antibacterial agents of the carbapenem group (J01D H), defined daily dose/100 bed days, 2011–2014.

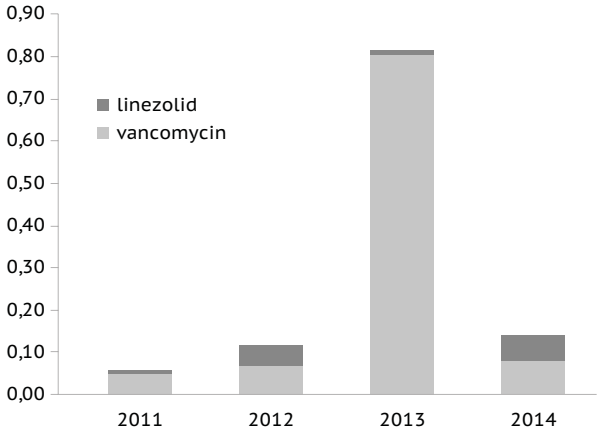

Figure 3. Utilization of vancomycin (J01XA01) and linezolid (J01XX08), defined daily dose/100 bed days, 2011–2014.

their prescriptions in individual hospitals reached from 28% to 60% of all prescriptions of antibacterial agents [7, 15, 20]. However, an abuse of cephalosporins is dangerous because of the possible development of the so-called "parallel damage" which leads to the selection of polyresistant microorganisms [15]. For instance, in case control studies, the use of cephalosporins has been identified as the only independent risk factor (odds ratio 13.8; 95% CI 2.5–76.3; p = 0.01) for colonization of vancomycin-resistant enterococci [22].

We consider it a definite achievement to reduce the use of fluoroquinolones in the hospital. In 2011, the utilization of fluoroquinolones in the hospital was higher than in a number of other hospitals in the Russian Federation; for example, in the Khabarovsk surgical hospital in 2011, the utilization of fluoroquinolones was 7.66 DDD/100 bed days [20]. Therefore, the reduction of fluoroquinolones utilization twice from 11.4 to 5.6 DDD/100 bed days is noteworthy, since fluoroquinolones should be considered as a means for the treatment of nosocomial infections of various localities caused by resistant microorganisms and community-acquired complicated infections [14]. Generally, fluoroquinolones are used at a high frequency in Russian hospitals; in particular, the ERGINIStudy revealed a frequency of 21% of their prescriptions. Ciprofloxacin is the most commonly used (12% of all prescriptions for nosocomial infections) [7].

Additionally, new studies have shown that the use of fluoroquinolones can lead to a risk (odds ratio of 3.5) of subsequent infections caused by metal-β-lactamase producing strains of *Pseudomonas aeruginosa*, and, accordingly, to a resistance to carbapenems [14, 23]. A study conducted in India has shown the possible role of prior ciprofloxacin therapy as a risk factor for infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA) [14,24].

Besides, in 2010, the utilization of macrolides in Russian hospitals averaged 1.9 DDD/100 bed days, which is less than in our hospital in 2011 (3.5 DDD/100 bed days) [1]. In 2011, the macrolide utilization was also low in the multispecialty surgical hospital in Khabarovsk 0.96 DDD/100 bed days [20]. By 2014, we had reduced macrolide utilization, mainly due to clarithromycin, and in 2014, macrolide utilization was 1.2 DDD/100 bed days and clarithromycin utilization was 0.7 DDD/100 bed days. In hospital settings, macrolides are recommended for a combined therapy of severe community-acquired pneumonia and a combined therapy of pelvic infections and treatment of chlamydia and mycoplasma infections. There are no significant differences in the natural antimicrobial activity of macrolides, so the presence of one parenteral and two enteral macrolides is sufficient in the hospital [14].

A threefold increase in the utilization of aminoglycosides from 4.18 to 14.09 DDD/100 bed days provides for additional study of the practice of their use. The aminoglycosides utilization in hospitals in the Russian Federation in 2010 averaged 2.5 DDD/100 bed days, in intensive care units 13.2 DDD/100 bed days, with the highest level of utilization in the medical center of Yaroslavl (5 and 36.6 DDD/100 bed days, respectively), with the predominant use of amikacin [1,25]. Increased utilization of amikacin could be associated with changes in the treatment of a number of infections or the spectrum of resistance of a number of pathogens. Amikacin is usually recommended for nosocomial infections for a combined therapy of infections caused by *P. aeruginosa* [14]. When using aminoglycosides, possible adverse reactions should not be

overlooked: diuresis, creatinine, and hearing acuity should be monitored, and the duration of therapy should not exceed seven days.

Besides, the increase in the use of carbapenems is typical of many medical institutions in the Russian Federation [1, 20, 21, 25]. In our institution, their utilization increased threefold from 0.12 to 0.38 DDD/100 bed days. The long-term widespread use of the third-generation cephalosporins in the hospital may have contributed to an increase in the need for carbapenems. It has been shown that cephalosporin therapy in the previous 30 days is an independent risk factor (odds ratio of 10.8) for infection with stably derepressed β-lactamase producers of the AmpC class (*Klebsiella pneumoniae* and *Escherichia coli*), which was confirmed in a case control study conducted at a multidisciplinary hospital [26]. Experts note a sharp increase in the proportion of carbapenem-resistant isolates of nosocomial strains of microorganisms, including strains that produce carbapenemases. In this situation, it is more urgent than ever to restrict their unjustified use [3].

Moreover, the level of vancomycin utilization in 2011 and 2014 is comparable to its utilization in other hospitals in the Russian Federation [20, 21]. An increased use of vancomycin and linezolid in the hospital may be associated with changes in the spectrum of resistance of *S. aureus*. Experts have identified an increase in the resistance of this pathogen to antimicrobial agents over time [4], and this resistance can be correlated with the increase in the utilization of agents. In addition, previous use of antibiotics (95% CI = 1.7–1.9; $p < 0.001$) increases the risk of MRSA infection 1.8 times [27]. While vancomycin is recommended as an agent for the treatment of infections caused by MRSA of various localization and antibiotic-associated diarrhea caused by *Clostridioides difficile*, linezolid is recommended for the treatment of infections caused by MRSA of various localization (except angiogenic and urinary), including in the case of strains with reduced sensitivity to vancomycin, as well as in combination therapy of pneumonia associated with artificial ventilation [14].

Conclusions

1. From 2011 to 2014, a group of clinical pharmacologists with the support of the hospital administration developed, and implemented a program for monitoring the use of antibacterial drugs and training doctors on the rational use of drugs in a multidisciplinary healthcare facility.

2. For the duration of the program, significant reductions were seen in the utilization and costs of antibiotics of the fluoroquinolone and macrolides, with increased utilization of aminoglycosides and carbapenems without a change in the cephalosporins utilization.

3. Expenses on cephalosporins and carbapenems has led to the increase in total expenses on antibiotics.

4. Further efforts and research are needed to investigate the use of antibacterial agents. When choosing a program to improve the strategy for the use of drugs and antibiotics, among other things, feedback from healthcare professionals is important as well as a multidisciplinary approach that takes into account the needs and characteristics of a particular healthcare institution.

Contribution of authors. A.G.A.—systematization and evaluation of the results of analysis; writing the text of the article; TR.A.—collecting and analysis of the results; S.V.E.—collecting and analysis of the results; A.F.T.—collecting and analysis of the results; V.N.H.—collecting and analysis of the results; L.E.Z.—a general manager, editing, and generalization of results.

Funding. The authors received honoraria from Burdenko regional clinical hospital in Penza for hospital administration visit. There was no other funding.

Conflict of interest. The authors declare no conflict of interest.

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