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POLYPHARMACY IN MANAGMENT OF IN-PATIENTS WITH NOVEL CORONAVIRUS DISEASE (COVID-19)

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The aim. To identify polypharmacy cases and develop the ways to optimize pharmacotherapy of patients with COVID-19 hospitalized in infectious disease facilities.
Materials and methods. ATC/DDD analysis with calculation of DDDs/100 bed days and a sample analysis of 500 patients' prescriptions were performed for presenting drug utilization statistics in the infectious disease facilities of Volgograd region, which had been reassigned to treat patients with COVID-19 in 2020 and 2021.
Results. Five or more drugs were administered simultaneously in 96.8% of patients. Antibacterial drugs were in 74.3% of the analyzed prescriptions in 2020 and in 73.5% in 2021. The total consumption of antibiotics was 102.9 DDDs/100 bed-days in 2020 and 95.7 DDDs/100 bed-days in 2021. The cases of multiple administrations of biological disease modifying antirheumatic drugs and the use of cyclophosphamide have been identified. In 73.6% of prescriptions in 2020 and 85.4% of 2021, omeprazole at the dose of 40 mg per day was used (77.3 and 84.6 DDDs/100 bed-days, respectively). In 2021, there were cases of concomitant intravenous prescribing of acetylcysteine under the trade name of Fluimucil® with tableted forms of ambroxol and acetylcysteine under the name of ACC®. The cumulative consumption of hepatotoxic drugs was 269.2 DDDs/100 bed-days in 2020 and 401.5 DDDs/100 bed-days in 2021.
Conclusion. Lack of drugs with proven effectiveness for treatment of COVID-19, worked-out treatment algorithms, a high mortality of patients in the hospitals led to polypragmasy, excessive prescribing of drugs in the hospitals. The prescription of antibacterial drugs, omeprazole, mucolytics, hepatotoxic drugs, immunosuppressors in infectious hospitals should be monitored by clinical pharmacologist.
Keywords: polypharmacy; COVID-19; ATC/DDD analysis; antibiotics; immunosuppressors; mucolytics; omeprazole; drug-induced liver injury
Abbreviations: INN – international nonproprietary name; GEBP – genetically engineered biological; GCS – glucocorticosteroid; NSAIDs – nonsteroidal anti-inflammatory drugs; PPIs – Proton Pump Inhibitors; ACE – angeotensin converting enzyme; ARDS – acute respiratory distress syndrome; MP(s) – medicinal preparations; RF – Russian Federation; WHO – World Health Organization; SD – standard dose; SCD – standard course dose; DDD – defined daily dose; PDD – prescribed daily dose; NDDDs – Number of Defined Daily Doses; NPDDs – Number of prescribed Daily Doses; CI – confidence interval; ICU – intensive care unit; ADR – adverse drug reactions; DILI- drug-induced liver injury.

ПОЛИПРАГМАЗИЯ ПРИ ЛЕЧЕНИИ СТАЦИОНАРНЫХ БОЛЬНЫХ С НОВОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИЕЙ COVID-19

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RESEARCH ARTICLE

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Цель. Выявить случаи полипрагмазии и разработать пути оптимизации фармакотерапии пациентов с COVID-19, госпитализированных в инфекционные отделения.
Материалы и методы. Для оценки объёма и структуры потребления ЛС в инфекционных отделениях Волгоградской области, перепрофилированных для лечения больных COVID-19 в 2020 и 2021 гг., был проведен ATC/DDD-анализ с расчётом показателей DDD/100 койко-дней и выборочный анализ 500 листов назначений.
Результаты. Одновременно 5 и более ЛС принимали 96,8% пациентов. Антибактериальные ЛС встречались в 74,3% проанализированных врачебных назначений в 2020 г. и в 73,5% в 2021 г., суммарный объём потребления составил 102,9 DDD/100 койко-дней в 2020 г. и 95,7 DDD/100 койко-дней в 2021 г. Были выявлены случаи множественных введений ГИБП и применение циклофосфамида. В 73,6% врачебных назначений 2020 г. и 85,4% в 2021 г. применялся омепразол в дозе 40 мг в сутки (77,3 и 84,6 PDD/100 койко-дней соответственно). В 2021 г. были выявлены случаи одновременного назначения ацетилцистеина под торговым наименованием «Флуимуцил®» внутривенно с таблетированными формами амброксола и ацетилцистеина под наименованием «АЦЦ®». Суммарное потребление гепатотоксичных ЛС составило 269,2 DDD/100 койко-дней в 2020 г. и 401,5DDD/100 койко-дней в 2021 г.
Заключение. Отсутствие препаратов с доказанной эффективностью для лечения COVID-19, отработанных алгоритмов лечения, наличие высокой летальности пациентов в стационаре привели к полипрагмазии, избыточному назначению ЛС в стационаре. Назначение антибактериальных ЛС, омепразола, муколитиков, гепатотоксичных препаратов, иммуносупрессоров в инфекционных стационарах должно быть ограничено и проводиться под контролем клинического фармаколога.
Ключевые слова: полипрагмазия; COVID-19; ATC/DDD анализ; антибиотики; иммуносупрессоры; муколитики; омепразол; лекарственно-индуцированное повреждение печени
Список сокращений: МНН – международное непатентованное название; ГИБП – генно-инженерные биологические препараты; ГКС – глюкокортикостероиды; НПВС – нестероидные противовоспалительные средства; ИПП – ингибиторы протоновой помпы; АПФ2 – ангиотензтин превращающий фермент 2; ОРДС – острый респираторный дистресс синдром; ЛС – лекарственные средства; РФ – Российская Федерация; ВОЗ – Всемирная организация здравоохранения; СД – стандартная доза; СК – стандартная курсовая доза; DDD – средняя поддерживающая суточная доза; PDD – средняя назначенная суточная доза; NDDD – число средних поддерживающих доз; NPDD – число средних назначенных суточных доз; ДИ – доверительный интервал; ПИТ – палата интенсивной терапии; НЛР – нежелательные лекарственные реакции; ЛИПП – лекарственно-индуцированное поражение печени.

INTRODUCTION

In the context of the COVID-19 pandemic, there has been a rapid increase in the use of both new and old "off-label" drugs, the effectiveness and safety of which have not been sufficiently studied. High lethality, deficiency of drugs with proven efficacy, a desire to help patients can lead to the prescription of a great number of medicinal preparations (MPs) – polypharmacy.

The term "polypragmasia" (from the Greek "poly" – a lot, "pragmasia" – an object, thing) or, in non-russian literature, "polypharmacy" (from the Greek poly – a lot and pharmacy – medicine), first appeared in the medical literature more than 150 years ago. It was defined as "mixing together a lot of drugs in one prescription", "the use of a lot of drugs to treat one or more diseases." A consistent consensus in the concept of "polypharmacy" has not been reached [1, 2].

In 2017, Masnoon N. et al. published an analysis of 1156 English-language articles on the problem of defining "polypharmacy/polypragmasia". 138 definitions were identified, 111 of which were only quantitative, 15 took into account the duration of the simultaneous use of drugs and 12 were qualitative definitions. In quantitative definitions, "polypharmacy" was most often understood as the prescription of 5 or more drugs (45.4% of the articles included in the analysis). Some authors distinguished small (simultaneous prescription of 2–4 drugs), large (simultaneous prescription of 5–9 drugs) and excessive (simultaneous prescription of 10 or more drugs) polypharmacy. In a qualitative definition, polypharmacy has been described as "prescription of more drugs to a patient than it is required by a clinical situation"; "a simultaneous prescription of several drugs"; "a simultaneous and prolonged use of different drugs by the same person." At the same time, a number of authors distinguished between appropriate (rational) and inappropriate (unreasonable) kinds of polypharmacy [3].

Currently, in the health care of the Russian Federation (RF), active work is underway to reduce the incidence of polypharmacy in medical practice. In Order of Ministry of Public Health of the Russian Federation No.575n dated November 2, 2012 "On approval of the procedure for the provision of medical care in the profile of "Clinical pharmacology"[1], paragraph 6 states that in the case of a simultaneous prescription to a patient of 5 or more items of drugs or more than 10 items in course treatment (polypharmacy), the patient should be referred for a consultation with a doctor – a clinical pharmacologist.

A reason for a simultaneous prescription of several drugs may be the presence of concomitant diseases (multimorbidity), clinical recommendations, guidelines of professional medical societies and treatment

[1] Order of the Ministry of Health of the Russian Federation No. 575n dated November 2, 2012 "On approval of the Procedure for providing medical care in the profile "clinical pharmacology". Available from: http://www.rosminzdrav.ru/documents/5534-prikaz-minzdrava-rossiiot-2-noyabrya-2012-g-575n.

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standards, containing in some cases recommendations for the use of complex therapy for more than 5 drugs for only one indication, the effectiveness of which corresponds to high levels of evidence [4].

In this regard, when analyzing a patient's therapy, only a quantitative assessment of polypharmacy is insufficient and requires a more complete study of the validity of prescribing drugs, assessing the risk of developing drugs interactions and adverse drug reactions (ADRs).

THE AIM. To identify polypharmacy cases and develop the ways to optimize pharmacotherapy of patients with COVID-19 in infectious disease facilities.

MATERIALS AND METHODS

To assess the volume and structure of drug consumption in infectious disease facilities of Volgograd region, converted for the treatment of patients with COVID-19 in 2020 and 2021, an ATC/DDD analysis was carried out with the calculation of the Defined Daily Doses per 100 bed-days (DDDs/100 bed-days) indicator and a sampling analysis of 500 case histories and prescriptions, including the prescription in intensive care units (ICUs).

The ATC/DDD methodology is recommended by the World Health Organization (WHO) as an international standard for the qualitative characterization of drug prescriptions, the provision of statistical data on drug consumption and comparative analyses at the international level within one framework [5].

It should be notified that the methodology under consideration, in contrast to the ABC and VEN analyses, does not depend on the cost of drugs; the data are easily comparable over time. However, the deficiency of DDD values for a number of drugs, including drugs of the domestic origin, causes some difficulties. The DDD (defined daily dose) is the estimated average maintenance daily dose of a drug used for its main indication in adults. The experts emphasized that this unit of measure does not always coincide with the PDD (a prescribed daily dose – the average prescribed daily dose, derived from a sample of prescriptions for the treatment of a particular disease). However, given the objectives of our study to identify cases of polypharmacy, as criteria for assessing the volume of consumption, in most cases, the DDDs published on the website of the WHO Center for Methodology of Drug Statistics were used[2].

Glucocorticosteroids (GCSs) are the first-choice drugs for the treatment of patients with cytokine storm. According to the Russian Guidelines[3], for the treatment of moderate and severe forms of COVID-19, various schemes for the administration of corticosteroids can be used using doses that are several times higher than the DDDs established by WHO. Thus, the DDD of dexamethasone was 1.5 mg, while most common (32.6% of medical prescriptions in 2020 and 74.3% in 2021), dexamethasone was used at the dose of 20 mg per day for 3 days with a subsequent dose reduction (the average daily dose when using this regimen is 14 mg per 1 patient for 12 bed-days). The maximum dose of dexamethasone in patients admitted to the ICU was 80 mg per day, and dexamethasone was also prescribed at the dose of 24 mg, 32 mg, and 48 mg per day.

Prednisolone (DDD/10 mg) and methylprednisolone (DDD/20 mg) have been rarely used at very high doses (prednisolone – 300–750 mg/day, methylprednisolone – 250–1000 mg/day) in short courses of up to 3 days. Thus, the doses of prednisolone and methylprednisolone used in real clinical practice exceeded the DDD by 12.5–75 times, and when calculating the DDDs/100 bed-days index, high values were obtained that do not reflect the actual consumption of these drugs.

According to the Russian Guidelines[4], the prescription of parenteral anticoagulants, at least in prophylactic doses, is indicated for all hospitalized patients. The WHO DDDs for heparin, enoxaparin, and nadroparin were 10 000 IUs, 2 000 anti-Xa IUs, and 2 850 anti-Xa IUs, respectively, while the median PDD prescriptions were consistent with the so-called median prophylactic doses reported in the guidelines (22 500 IU, 800 anti-Xa IUs and 11 400 anti-Xa IUs, respectively). Omeprazole was used in most cases at the dose of 40 mg per day (73.6% of the prescription lists), while the recommended dose of omeprazole for most indications[5] and the DDD indicated on the WHO website, is 20 mg per day. The dose of levofloxacin in most case histories was 1.0 g per day with a DDD of 0.5 g, and azithromycin was 0.5 g with a DDD of 0.3 g.

Due to the fact that dexamethasone, parenteral anticoagulants, omeprazole, levofloxacin and azithromycin were prescribed in the doses exceeding the DDDs recommended by WHO, PDDs were used to analyze the consumption volume of these drugs.

The number of the established or prescribed daily doses – NDDDs (the number of DDDs) or NPDDs (the number of PDDs) of drugs – was calculated as the ratio of the number of MPs to DDDs or PDDs. The DDDs/100 or PDDs/100 indicator was determined in relation to the consumed NDDDs or NPDDs per year, multiplied by 100, to the total bed-day for the year.

For domestic drugs olokizumab and levilimab that do not have DDDs on the WHO website, or for other

[2] WHO Collaborating Centre for Drug Statistics Methodology. Available from: http://www.whocc.no/atc_ddd_index/.

[3] Prevention, diagnosis and treatment of novel coronavirus infection (COVID-19). Interim guidelines. Version 15 (22.02.2022). Ministry of Health of the Russian Federation.; 2022.

[4] Ibid.

[5] Russian State Register of Medicines. Available from: https://grls.rosminzdrav.ru/Default.aspx.

genetically engineered biological preparations (GEBPs) either, to assess the volume of consumption, a standard dose per 100 treated patients was calculated.

A standard dose (SD) is the dose recommended for the administration in mild and moderate COVID-19. To assess the volume of the drugs consumption used in the facilities in the pulse therapy mode (the administration of high doses for 3 days), a standard course dose (SCD – a median of prescribed course doses) according to the prescription lists and the ratio of the number of SCs per 100 treated patients, was calculated.

RESULTS AND DISCUSSION

A sampling analysis of hospitalized patients with COVID-19 case histories revealed 11 [8; 13] drugs prescriptions per patient during the period of hospitalization while taking 8 [6; 11] MPs. At the same time, 5 or more drugs were taken by 96.8% of patients.

According to the accounting and reporting documentation for the issuance of drugs to facilities for the treatment of 3,750 patients (45 315 bed-days) in 2020 and 5 130 patients (58 439 bed-days) in 2021, 117 international non-proprietary names (INNs) drugs were used in 2020 and 129 INNs drugs in 2021, a third of which did not have DDDs on the WHO website. According to the WHO Center of International Drug Statistics, it was not possible to establish an average daily maintenance dose (DDD) for topical preparations, including intranasal forms of interferon, solutions of crystalloids, colloids, parenteral nutrition, local and general anesthetics, parenteral forms of nitroglycerin and acetylcysteine. Domestic drugs olokizumab and levilimab, hepatoprotectors and metabolic drugs used in the studied facilities were not in the database of the WHO center.

The calculation of DDDs or PDDs/100 bed-days was made for 79 drugs in 2020 and 85 drugs in 2021, among which there were antibacterial drugs; agents affecting hemostasis; GCSs and other immunosuppressants; bronchodilators; mucolytics; surfactant preparations; non-steroidal anti-inflammatory drugs (NSAIDs); antihistamines; the drugs that affect the gastrointestinal tract; insulins; cardiovascular agents; iron preparations and centrally acting preparations (Fig. 1).

A further detailed analysis was made of the drugs that are not the basis of COVID-19 therapy or the drugs that are mandatory for prescribing in all cases of the disease, the volume of consumption of which, however, was high in the studied facilities.

Antibacterial drugs

Like any other disease of viral etiology, COVID-19 is not an indication for the use of antibacterial drugs. Bacterial infections are not often complications of a novel coronavirus infection course [6, 7], so most patients with COVID-19, especially in mild and moderate cases, do not need antibiotic therapy[6]. However, antibiotics were present in 74.3% of prescriptions in 2020 and 73.5% in 2021, and in combined antibiotic therapy in 35.6%. In 2020, in facilities, ceftriaxone as monotherapy and in combination with azithromycin or levofloxacin was most often prescribed as initial therapy, and in 2021 these were levofloxacin or ceftriaxone. In all analyzed lists of intensive care units (ICUs) prescriptions, antibacterial drugs were prescribed, and the most common of them were cefoperazone-sulbactam or meropenem as monotherapy or in combination with vancomycin or linezolid.

The combination of broad-spectrum antibacterial drugs, especially *β*-lactam antibiotics with macrolides and fluoroquinolones, has long been considered irrational, including due to the weakening of an bactericidal antibiotic action while taking it with a bacteriostatic drug[7]. However, even before the COVID-19 pandemic, the growth of antibiotic-resistant strains and changes in the structure of causative agents of community-acquired pneumonia had made adjustments to clinical guidelines. Thus, in 2018, the prescription of ceftriaxone in combination with azithromycin or levofloxacin was recommended to hospitalized patients with severe community-acquired pneumonia of bacterial etiology[8].

The doses of antibacterial drugs used in facilities, in most cases coincided with the DDDs recommended by WHO (with the exception of azithromycin and levofloxacin). However, the total consumption of antibacterial drugs exceeded 100 DDDs/100 bed-days, which was the result of the combination antibiotic therapy.

An earlier ABC analysis of drug consumption in facilities [8] revealed a decrease in the share of the expenditure on antibiotics in 2021 compared to 2020. Thus, the purchase of antibacterial drugs in 2020 accounted for 52% of Segment A costs, and in 2021, it was 13.6%. However, their total consumption in terms of DDDs/100 bed-days in 2020 was only 7% higher than in 2021 (102.9 DDDs/100 bed-days in 2020 and 95.7 DDDs/100 bed-days in 2021). A decrease in the relative share of the expenditure on antibacterial drugs in 2021, based on the ABC analysis, is associa-

[6] Prevention, diagnosis and treatment of novel coronavirus infection (COVID-19). Interim guidelines. Version 15 (22.02.2022). Ministry of Health of the Russian Federation.; 2022.

[7] Strachunsky LS, Belousova YuB, Kozlov SN. Obshchie osobennosti antiinfekcionnyh himiopreparatov [General features of anti-infective chemotherapy drugs]. A practical guide to anti-infective chemotherapy. RC "Pharmedinfo", 2007. – 427 p. Russian

[8] Clinical guidelines. Community-acquired pneumonia. Russian Respiratory Society Interregional Association for Clinical Microbiology and Antimicrobial Chemotherapy. – 2018. – 97 p. Available from: https://minzdrav.midural.ru/uploads/clin_recomend%20РФ.pdf

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ted to a greater extent with an increase in the expenditure on biological disease modifying antirheumatic drugs (GEBPs) and anticoagulants. It is also caused by a restriction in the purchase of expensive antibiotics in favor of the most affordable ones, rather than a decrease in the frequency of prescribing antibacterial drugs. Thus, it was the calculation of the DDDs/100 bed-days indicator, and not the ABC analysis, which made it possible to evaluate and compare the annual consumption of antibacterial drugs, regardless of the dosing regimen, costs, the number of patients treated, and hospital stays (Fig. 2).

The prescription of antibacterial drugs for the COVID-19 treatment is a problem not only for the healthcare of the Russian Federation, but also for the whole world. Langford B.J. et al. [9] analyzed the data from 154 studies on COVID-19 antibiotic therapy (30 623 patients). The frequency of antibiotic therapy prescription was 74.6% (95% CI 68.3–80.0%), which is consistent with the authors' data. However, only 8.6% (95% CI in 4.7–15.2%) of patients in 31 studies had a laboratory-confirmed bacterial co-infection. Thus, more than half of the prescriptions of antibacterial drugs can be characterized as the prescription of more drugs than the clinical situation requires.

One of the most likely reasons for the excessive prescription of antibacterial drugs at the beginning of the COVID-19 pandemic, in the authors' opinion, may be the adherence of practitioners to previously recommended empirical therapy regimens for community-acquired pneumonia of bacterial etiology. It should be notified that in 2021, against the background of the widespread use of immunosuppressants for the treatment of cytokine storm, the risk of infectious complications, the blurring of the clinical picture of a bacterial infection and changes in the general blood test while taking GCSs, a high lethality of patients in hospitals, could serve as a reason for prescribing antibacterial drugs to patients with severe COVID-19 without a proven bacterial infection.

Glucocorticosteroids, GEBPs, janus kinase inhibitors and cytostatics

The discovery of a hyperimmune response role, or cytokine storm as the basis for the pathogenesis of an acute respiratory distress syndrome and a multiorgan dysfunction in COVID-19 prompted the widely used in rheumatology anti-inflammatory drugs.

Dexamethasone was notified in 37.5% of physicians' prescriptions to patients with COVID-19 in 2020 and 91.3% in 2021. Fewer than 5% of prescriptions included prednisolone, methylprednisolone, baricitinib, and cyclophosphamide. GEBPs were prescribed in 3.9% of cases in 2020 (tocilizumab, olokizumab, levilimab) and in 11.6% in 2021 (tocilizumab, olokizumab, levilimab, sarilumab and secukinumab).

Prednisolone, secukinumab, and cyclophosphamide were not included in the standard COVID-19 treatment regimens recommended by the Ministry of Health of the Russian Federation and in force at the time, these drugs were prescribed[9].

According to the recommendations, janus kinase inhibitors (baricitinib) and GEBPs are indicated to patients with COVID-19 in combination with corticosteroids and were used in the studied facilities together with dexamethasone. In most prescription lists, GEBPs were administered to patients with COVID-19 in a single dose, however, in case of insufficient effectiveness, according to the recommendations, it was possible to re-administer the drug after 12–24 hours.

Despite a low frequency of GEBPs use (Table 1), the cases of multiple injections, as well as the introduction of cyclophosphamide in patients hospitalized in the ICUs after GEBPs injections have been identified. In the case history of one patient, 10 injections of 3 GEBPs were recorded. This fact is considered as polypharmacy.

The active tactics of using immunosuppressive drugs to treat patients with COVID-19 is triggered by the paradigm of "cytokine storm", a condition in which an overly strong immune response, mediated by overproduced pro-inflammatory cytokines, causes extensive lungs damage and a state of thrombosis propensity. Accordingly, it is assumed that death occurs primarily due to the inflammatory lungs disease, impaired micro- and macrocirculation and an eventually respiratory failure or vascular coagulopathy [10].

In this regard, in real clinical practice, in patients with a progressive respiratory failure in the absence of the standard therapy effect, multiple administrations of GEBPs, pulse therapy with corticosteroids, and cyclophosphamide were used as a kind of "despair" therapy.

However, there are also conflicting views, associated with a violation of the immunological defense mechanism, leading to an uncontrolled virus spread and organs damage [11]. Despite extensive research around the world, the pathophysiological processes that play a critical role in morbidity and mortality among patients, remain unknown and require further clinical studies, including retrospective ones, to assess the benefit/risk of immunosuppression in patients with COVID-19.

[9] Prevention, diagnosis and treatment of novel coronavirus infection (COVID-19). Interim guidelines. Version 14 (27.12.2021). Ministry of Health of the Russian Federation; 2021.

Omeprazole and antisecretory therapy

According to Rambhade S. et al. [12], one of the common causes of polypharmacy is a cascade of prescriptions (prescribing cascade), when drugs are prescribed for the treatment or prevention of adverse drug reactions (ADRs) caused by other drugs. Omeprazole 40 mg daily was used in 73.6% of prescriptions in 2020 and 85.4% in 2021. A high frequency of prescribing antisecretory therapy for patients with COVID-19 against the background of the widespread use of corticosteroids, anticoagulants, NSAIDs and a high risk of gastrointestinal bleeding was most likely carried out for prophylactic rather than therapeutic purposes.

Even before the COVID-19 pandemic, retrospective cohort studies had identified an increased risk of developing community-acquired and nosocomial kinds of pneumonia with the use of proton pump inhibitors (PPIs) [13–15]. Currently, the PPIs intake is considered by many authors as an independent risk factor for more severe outcomes in patients with COVID-19 [16–22].

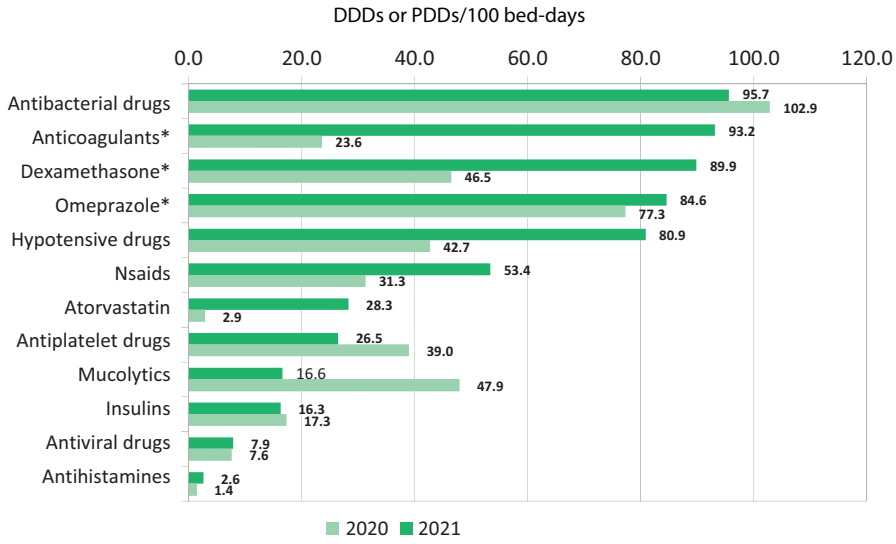

Figure 1 – Structure and volume of consumption of the most commonly used drugs and groups of drugs in patients with COVID-19

Note: * – PDDs were used for calculation

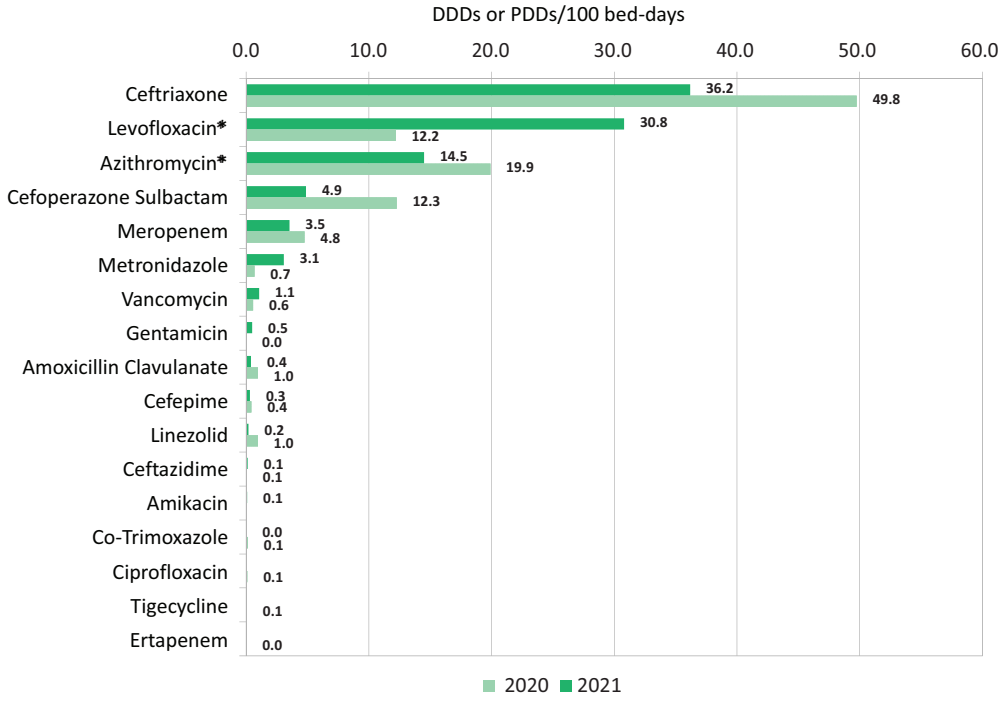

Figure 2 – Structure and volume of antibacterial drugs consumption in patients with COVID-19

Note: * – PDDs were used for calculation.

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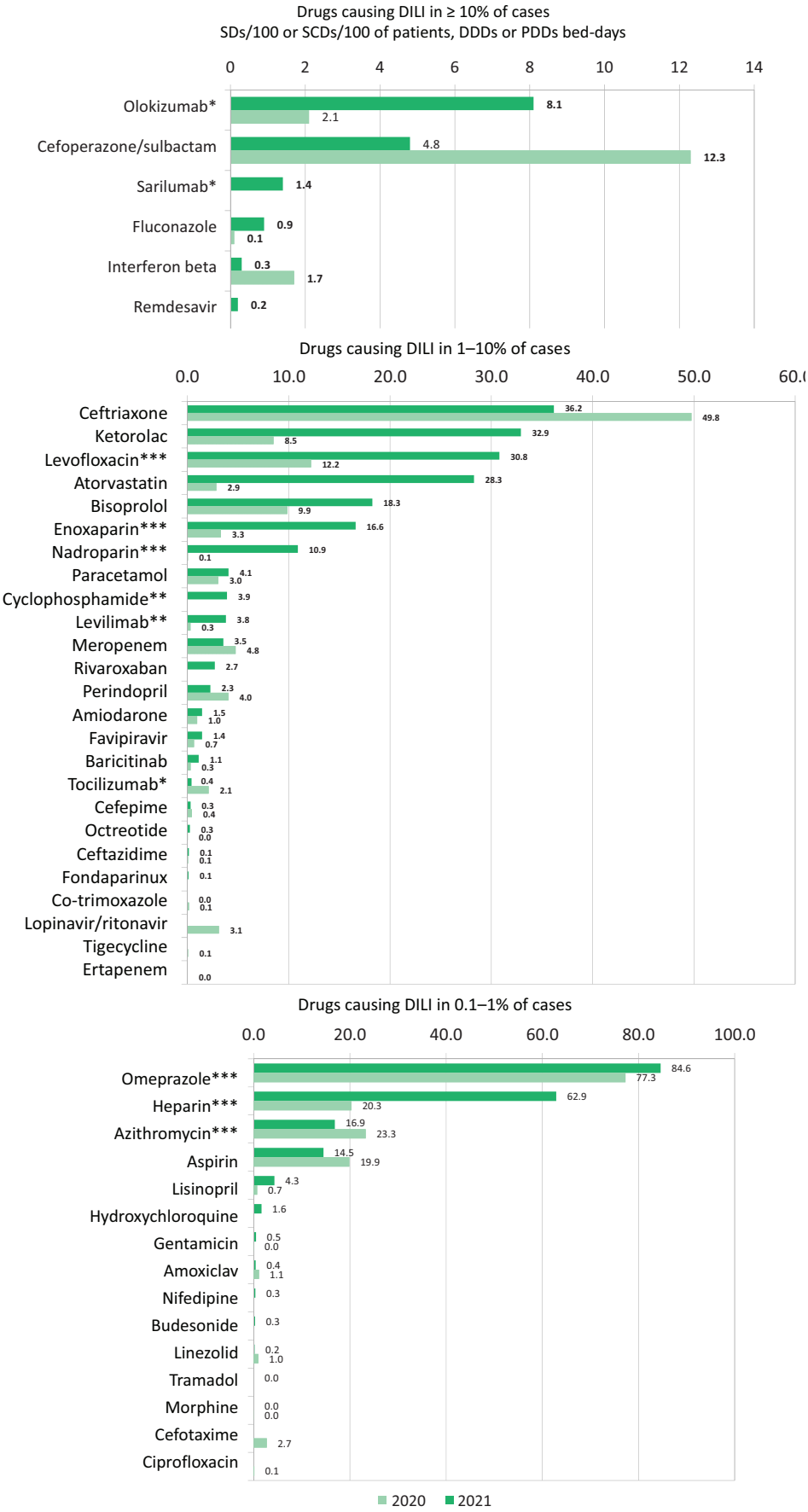

Figure 3 – Structure and volume of hepatotoxic drugs consumption in patients with COVID-19
Note: * – SDs were used for calculation; ** – SCDs were used for calculation; *** – PDDs were used for calculation

Table 1 – Structure and volume of immunosuppressants consumption by patients with COVID-19

INN	Doses used for calculation	Calculated indicator	Volume of consumption	
			2020 3 750 patients (45 315 bed-days)	2021 5 130 patients (58 439 bed-days)
Dexamethasone	14 mg	PDD/100 bed-days	46.5	89.9
Baricitinib	4 mg	DDD/100 bed-days (PDD coincides with DDD)	0.31	1.1
Tocilizumab	320 mg	SD /100 patients	2.1	0.44
	20 mg	**DDD for RA treatment /100 bed-days**	2.8	**0.62**
Olokizumab	64 mg	SD /100 patients	2.1	8.1
Levilimab	324 mg	SD /100 patients	0.3	3.8
Sarilumab	200 mg	SD /100 patients		1.4
	14.3 mg	**DDD for RA treatment /100 bed-days**		**1.7**
Secukinumab	300 mg	SD /100 patients		0.1
	10 mg	**DDD for RA treatment /100 bed-days**		**0.26**
Prednisolone	1800 mg	CK/100 patients	4.4	13.3
Methylprednisolone	2250 mg	CK/100 patients	2.6	2.5
Cyclophosphamide	800 mg	CK/100 patients		3.9

Note: PDD – prescribed daily dose; DDD – defined daily dose; SD – standard dose per 1 injection for mild and moderate COVID-19; SCD — standard course dose per 1 patient; RA – rheumatoid arthritis.

H_2-histamine blockers may be an alternative to omeprazole and other PPIs if antisecretory therapy is required. In small clinical trials early in the pandemic, a famotidine use was associated with improved COVID-19, reduced risks of intubation and death [23–26]. Two in silico studies suggested a direct antiviral effect of famotidine and proposed one of the two SARS-CoV-2 proteases as potential molecular targets [27, 28], but a subsequent in vitro study did not confirm this effect [29], and a meta-analysis did not reveal a significant reduction in mortality from COVID-19 against the background of famotidine use [30]. Despite the fact that famotidine was not purchased in infectious disease facilities under study in 2020 and 2021, the analysis of history cases revealed the experience of prescribing this drug to the patients who had started taking it before the admission to hospital, and a high frequency of recommendations for taking famotidine when the patient was discharged from hospital.

Mucolytics

The Russian Guidelines on the COVID-19 case management in the "symptomatic treatment" section only indicate the possibility of prescribing mucolytics to patients with bronchitis against the background of COVID-19, without listing drugs and algorithms.

In September 2020, Olaleye O.A. et al. described the possibility of using ambroxol, an active metabolite of bromhexedine, as a blocker of the interaction between the spike protein of the SARS-CoV-2 virus and the ACE2 receptor and, thus, disrupt the penetration of the virus into the cell [31], which was subsequently confirmed in in vitro study [32]. The concentrations of ambroxol significantly exceeded the concentrations of drugs in the blood plasma of patients when it was used in standard doses, which does not allow transferring these data to the clinic. The anti-inflammatory and antioxidant activities inherent in the mucolytic acetylcysteine, also made it a good candidate for preventing the development of a cytokine storm in COVID-19 patients [33]. However, the results of a large cohort study published in early 2022, did not prove the ability of acetylcysteine to reduce the risk of developing ARDS and a severe COVID-19 course [34].

In 2020, more than a half of medical prescriptions contained ambroxol, and in 2021, acetylcysteine was added to ambroxol and used in combination with it. Moreover, cases of a simultaneous administration of acetylcysteine under the trade name Fluimucil® (intravenously) with tablet forms of ambroxol and acetylcysteine under the trade name of ACC® have been identified. Currently, there are no data in the literature on the advisability of prescribing combination therapy with mucolytics to bronchitis patients. Moreover, a number of authors believe that this may lead to an excessive sputum production [35]. A simultaneous use of parenteral and oral forms of drugs containing one active substance is also considered irrational [36].

Hepatotoxic drugs

In the published studies, an impaired liver function has been reported in 37.2–76.3% of hospitalized patients with COVID-19. This is a result of many factors, such as a drug-induced liver injury (DILI), an acute inflammatory response, and hypoxia associated with a severe respiratory distress and ARDS, as well as a possible coronavirus liver replication [37–40].

A simultaneous intake of several drugs with a potential hepatotoxicity more often causes a liver damage as a result of a pharmacodynamic interaction. In internation-

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al[10] and Russian databases[11,12] a search was conducted on the incidence of DILI for all the drugs used in infectious in-patient hospitals in 2020 and 2021.

Among the drugs used in 2020, only 4 (cefoperazone/sulbactam, interferon beta, fluconazole, and olokizumab) are the drugs that cause DILI in 10% or more of patients. In 2021, the drugs with a severe hepatotoxicity (DILI ≥ 10%) were also joined by remdesevir and sarilumab. The volume of drugs consumption with a severe hepatotoxicity was relatively small. However, the total consumption of drugs that cause DILI in 1–10% of patients (23 drugs in 2020 and 22 drugs in 2021) and 0.1–10% of patients (12 drugs in 2020, 13 drugs in 2021) were several times higher than 100 DDDs/100 bed-days. That was the result of the combined prescription of 2 or more drugs that can cause a liver dysfunction (Fig. 3). The most commonly prescribed groups of drugs with hepatotoxic effects were PPIs, antibacterials, and anticoagulants. The volume of hepatotoxic antiviral drugs consumption was 3.8 DDDs/100 bed-days (lopinavir/ritonavir and favipiravir) in 2020 and 1.8 DDDs/100 bed-days (favipiravir and remdesavir) in 2021.

CONCLUSION

In 2020, the healthcare system of the Russian Federation and the world faced a pandemic of a new rapidly spreading infection. The deficiency of drugs with proven efficacy, proven treatment algorithms, high mortality of patients in the hospital forced practitioners to use all available means to save patients' lives, which inevitably led to polypharmacy. It should be remembered that the prescription of a great number of drugs can lead not so much to the desired increase in the effectiveness of therapy, as to the development of ADRs and an increase in the economic burden. The prescription of antibacterial drugs, omeprazole, mucolytics, hepatotoxic drugs, immunosuppressants in the infectious disease facilities of hospitals should be limited and carried out under the supervision of a clinical pharmacologist. The Russian Guidelines on the COVID-19 case management in the "symptomatic treatment" section.

The latest versions of the Russian Guidelines of the Ministry of Health of the Russian Federation on the COVID-19 case management contain clear criteria for prescribing antibiotic therapy, compliance with which will reduce the unreasonable prescription of this group of drugs. If antisecretory therapy is needed, considering famotidine, a drug that does not adversely affect the course of COVID-19, unlike omeprazole, and causes DILI with a lower incidence (<0.1%), is recommended. The routine use of mucolytics in patients with COVID-19, especially combined ones, should be used only in case of sputum that is difficult to separate. The prescription of combined immunosuppressive therapy with the use of multiple GEBPs injections, pulse therapy with corticosteroids, cyclophosphamide is currently unreasonable, and further retrospective clinical studies are required.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

VIP – development of research design, editing and final approval of the article;
AYuR – data processing, article writing and final approval of the article; NSP – collection of material, data processing and final approval of the article; DAN – collection of material and final approval of the article.

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