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STRUCTURE AND RESISTANCE OF MICROORGANISMS TO ANTIMICROBIAL DRUGS WHILE PROVIDING MEDICAL CARE TO PATIENTS WITH COVID-19

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ABSTRACT

The present article aims to study the structure of microorganisms and their resistance to antimicrobial drugs while providing in-hospital medical care to patients with COVID-19. C. Albicans 46.82% (n=375) and C.Glabrata 21.97% (n=176) (prevailed among monotypes of fungal infection. Str. Pneumonia 25.24% (n=617) antimicrobial association of Str. pneumonia + spp. Candida 11.17% (n=273) were the leaders in the frequency of selection among all microorganisms. The prevailing pathogens in deceased patients were: Kl. pneumonia 36.3% (n=159). Candida fungi 21.92% (n=96).The analysis of resistance to antimicrobial drugs showed that Streptococcus pneumonia (n=890) has low level of resistance to benzylpenicillin 4.2% (n=37), levofloxacin 11.5% (n=102), linezolid 0%, and at the same time a high level of resistance to erythromycin 27.4% (n=244), lincomycin 25.2% (n=224), doxycycline 15.5% (n=141).An overwhelming number of isolates of K.pneumoniae (n=326) was resistant to ampicillin 97.9%, cefuroxime 94.2%, cefotaxime 87.7%, ceftazidime 85% and cefepime 73% with rather low resistance to amoxicillin and clavulanic acid 52.1% (n=170) and meropenem 33.4% (n=109). The number of isolates of microorganisms with pan-resistance makes 7.6% (n=125). The maximum proportion among PDR strains of microorganisms comes from K. pneumonia and is amounted to 33.4% (n=109) from all isolates of Klebsiella. C. Albicans and Str. Pneumonia are the most often selected pathogens in patients with COVID-19 who are receiving in-hospital medical care. An increasing frequency of detection of Klebsiella spp. XDR and PDR strains lead to a necessity of a proper choice of drugs for empirical antibacterial therapy.

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Introduction

Since the end of January 2020 new cases of COVID-19 have been registered in many countries around the world. On March 11th2020 WHO declared the beginning of the COVID-19 pandemic [1, 2].

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So far there has been no answer to the question: «Is the lung damage in case of COVID-19 in its classical form similar, for example to a lung damage in case of infection by SARS «SARS-CoV», MERS «MERS-CoV», «H1N1» in the form of pneumonia with typical symptoms of inflammation of bronchopulmonary system which generally has microbial and viral etiology with the further developing in respiratory distress syndrome? Or is it specific damage of lungs, kidneys, heart, brain etc.» [3, 4].

Meanwhile, as the President of Russian Respiratory Society, Academician of RAS A.G.Chuchalin said "Actually, those changes in a lung tissue that we observe in the case of COVID-19 – are not cases of pneumonia but pneumonitis with diffuse damage to alveoli and sedimentation of a large quantity of fibrin. Truly, in these cases, fibrosis of lung tissue can often occur, and it can be identified roentgenologicaly in a month or two or even more after the onset of the disease». A certain role in launching and supporting a pathological process with this pathology may belong to fungal pathogens [5]. The Academic adviser of FSSI RI of Human Morphology, the President of Russian Society of Pathology, Professor Lev V. Kaktursky points out the comprehensive extent of disruption of not only lungs but also other organs and tissues [6]. Certainly, the most common complication of COVID-19 is acute respiratory distress-syndrome. Other registered complications include a septic shock, an acute kidney injury, a myocardial injury, secondary bacterial and fungal infections.

Non-invasive and invasive mechanical lung ventilation is being used for providing medical care for patients with the most frequent types of complications, but it in return increases the risks of ventilator-associated pneumonia and other purulent-septic complications.

On the other hand, pathogenetic therapy is being widely being used for the treatment of COVID-19. It is provided by using glucocorticoid medications (dexamethasone, methylprednisolone), Janus-kinase inhibitors (tofacitinib, baricitinib), IL-17 inhibitor (netakimab), IL-6 inhibitor (olokizumab), IL-6 receptor inhibitors (tocilizumab, sarilumab, levilimab). One of the most frequent complications of all medications listed above is an increased risk of the development of secondary bacterial infections [7]. Thus, the pathogenetic therapy being provided to patients with COVID-19 increases the risk of secondary purulent-septic complications and worsens their course.

Empirical antimicrobial therapy is required for the correction of the latter. It should be based on the microbial landscape of causative agents of secondary purulent-septic complications and knowledge of resistance to AMD.

At the same time, the emergence of secondary bacterial infection in patients with COVID-19 may be considered from the perspective of nosocomial infections (NI), or healthcare-associated infections (HAIs).

Up-to-date HAIs based on current theoretical understandings about regularities of development of an epidemic process at medical organizations (MO). The general criterion for referring infections to HAIs is the direct connection of their emergence with the provision of medical care (diagnosis, treatment, prophylaxis, and rehabilitation). That is why cases of infections not only acceding to the primary disease in hospitalized patients but also connected with providing of any types of medical care are attributed to HAIs (including the cases of infections of medical care producers) (The health and safety rules and standards 2.1 3.2630 10).

In the context of HAIs pathogens dissemination, the problem of their regional and local circulation as well as searching for effective AMDis of great importance. Another serious problem concerns the costs, related to the development of a strategy of infectious security at medical organizations, where medical care to patients with COVID-19 is provided.

Aim of the Study

Research of the structure of microorganisms and their resistance to antimicrobial drugs while providing in-hospital medical care to patients with COVID-19.

Materials and Methods

In the course of the research, we used the data of bacteriological studies of biological materials (sputum, bronchoalveolar lavage, blood, autopsy material) which were taken from patients with COVID-19 who received treatment at an infectious hospital in 2020. A retrospective analysis of 3,599 results of bacteriological studies received from patients and 718 results of bacteriological studies received from the Department of pathological anatomy was conducted.

Bacteria identification was conducted according to normative documents which regulate the work of bacteriological laboratories. Identification of microorganisms' sensibility to antimicrobial drugs was carried out by disk diffusion method, the interpretation of sensibility rates was carried out according to clinical recommendations «Identification of Microorganisms 'Sensibility to Antimicrobial Drugs» (approved on XVIInternational Congress of Antimicrobial Chemotherapy IACMAC/ESCMID, 2014).

Evaluation of extreme resistance (XDR)and pan-resistance (PDR) of pathogens to antimicrobial drugs was conducted according to definitions, accepted in the international clinical practice, considering the species identification of microorganisms.

Statistical processing of results was made by methods of descriptive statistics using the «MS Office EXCEL 2003» program and $\chi 2$ method, a level of P-value was taken at $p<0,05$.

Results and Discussion

Our microbiological monitoring showed that patients with COVID-19 had resolutive bacteriological tests in 67.94% of cases (n=2,445), which indicates a significant role of microorganisms in the course of the disease. Comparable results were obtained during the bacteriological research of deceased patients, where the percentage of resolutive tests was 61.0% (n=438). Thus, 2/3 of patients with COVID-19 have got a secondary infection during their stay at the hospital.
During the in-hospital stay of patients with COVID-19 spp. Candida were selected in 59.75% (n=1,461) of cases. Selection of spp. Candida fungi was only was observed in 32.76% of cases (n=801), and in association with microorganisms, it was observed in 27,00% (n=660). C. Albicans 46.82% (n=375) and C. Glabrata 21.97% (n=176) **(Table 1)** prevailed among monotypes of fungal infection.

Table 1. Structure of results of spp. Candida selection from patients admitted to hospital in terms of work at infectious COVID-19 hospital in 2020

	Mono selection		Mixed infection with bacteria		Total	
	n	**%**	**n**	**%**	**n**	**%**
C. albicans	375	46,82	370	56,06	745	50,99
C. krusei	129	16,10	130	19,70	259	17,73
C. tropicalis	121	15,11	87	13,18	208	14,24
C. glabrata	176	21,97	73	11,06	249	17,04
spp. Candida	801	32,8	660	27,0	1461	59,75

Considering a high selection ratio of spp. Candida fungi genus, we may presume with a high probability that it plays its role at the pathogenesis of ARDS development in patients with COVID-19 in sustaining the inflammatory process. It demands a further examination of pathomorphological changes in this group of patients.
Str. Pneumonia 25.24% (n=617), the microbial association of Str. pneumonia + spp. Candida 11.17% (n=273) and Kl. pneumonia + spp. Candida 8.3% (n=203) **(Figure 1)** are the most frequently selected microorganisms. Thus, pneumococcus accounted for more than 36.4% of resolutive tests. Most frequently, in case of mixed infection of Str. Pneumonia / spp. Candida a combination of pneumococcus with C. Albicans 54.95% (n=150) was selected, non-albicans strains (C. Crusei, C. Glabrata) accounted for 30.4% (n=83). A similar pattern was registered in the case of mixed infection of Kl. pneumonia + spp. Candida, where the combination of Kl. pneumonia / C. Albicans were selected in 58.13% (n=118), and Kl. Pneumonia / C. non-albicans strains were accounted for 28.08% (n=57).

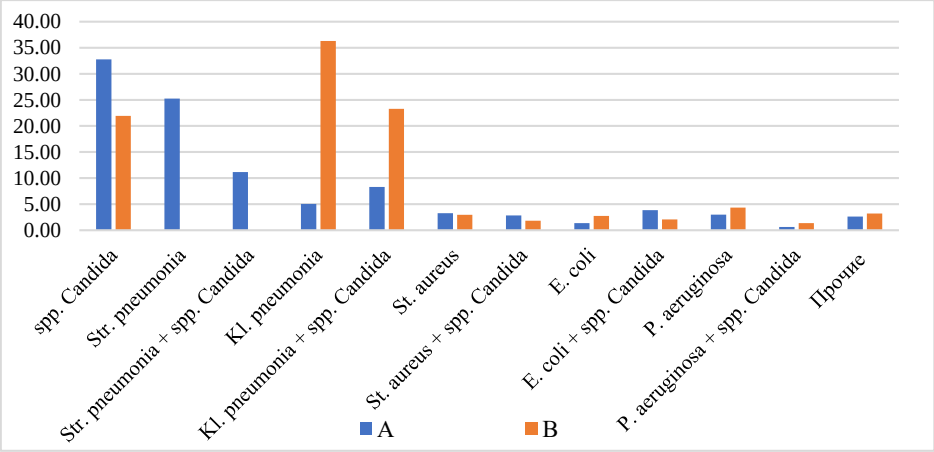

Figure 1. Structure of selected microorganisms received from patients admitted at infectious COVID-19 hospital (n=2445) (letter A) and from Department of Pathological Anatomy (n=438) (letter B) in 2020, %.

At the same time, the prevailing pathogens in deceased patients were Kl. pneumonia 36.3% (n=159), microbial association of Kl. pneumonia + spp. Candida 23.29% (n=102), mono selection of spp. Candida fungi 21.92% (n=96) **(Figure 1)**.
In microbial association of Kl. pneumonia / spp. Candida non-albicans strains of C. Crusei 56.86% (n=58) and C. Glabrata 10.78% (n=11) were selected most often among all Candida species **(Table 2)**. The composition of mono-selected spp. Candida fungi in deceased patients also reliably differed compared to the one in patients receiving in-hospital care ($p<0,05$). C. Crusei 56.25% (n=54) and C. Glabrata 13.54% (n=13) were dominant at this group. In total, all fungal pathogens in deceased patients were identified in 50.46 % (n=221) of cases.

Table 2. Structure of results of spp. Candida selection from bacteriological researches at Department of Pathological Anatomy in terms of work at infectious COVID-19 hospital in 2020, (%)

	Mono selection		Mixed infection with bacteria		Total	
	n	**%**	**n**	**%**	**n**	**%**

C. krusei	54	56,25	68	54,4	122	55,20
C. glabrata	13	13,54	12	9,6	25	11,31
C. albicans	14	14,58	28	22,4	42	19,00
C. tropicalis	15	15,63	17	13,6	32	14,48
spp. Candida	96	21,92	125	28,54	221	50,46

Given the foregoing, there are reliable differences in the microbial landscape in patients receiving in-hospital care and deceased patients. Considering selected microorganisms from deceased patients, which belong to in-hospital pathogens, with a high probability rate we can speak about healthcare-associated infections. Particularly vast contamination of patients with spp. Candida is connected to the ongoing pathogenetic therapy and selection of Kl. Pneumonia is connected to invasive and non-invasive mechanical lung ventilation.

At the same time, invasive candidiasis usually occurs as in-hospital infection in up to 12% and is characterized by high mortality up to 70% [8]. On the other hand, bronchopulmonary candidiasis does not have pathognomonic, clinical, and radiographic findings and can proceed as interstitial lung damage and, consequently, at CT scan it can look like lung damage in patients with COVID-19 [7, 9, 10]. Hence, a further examination of a pathomorphological lung pattern in deceased patients with COVID-19 is required.

The analysis of leading microorganisms' resistance to antimicrobial drugs showed that Streptococcus pneumonia (n=890) has a low level of resistance to benzylpenicillin 4.2% (n=37), levofloxacin 11.5% (n=102), linezolid 0%, and at the same time a high level of resistance to erythromycin 27.4% (n=244), lincomycin 25.2% (n=224), doxycycline 15.5% (n=141).

The proportion of St. aureus (MRSA)oxacillin-resistant strains amounted to 38.9% (n=58). The fact of selection of vancomycin-resistant St. aureus (VRSA)at 8.7% (n=13) should also be taken into account. Meanwhile, not a single linezolid-resistant strain of staphylococcus was detected.

An overwhelming number of isolates of K.pneumoniae (n=326) was resistant to ampicillin 97.9%, cefuroxime 94.2%, cefotaxime 87.7%, ceftazidime 85%, and cefepime 73% with a rather low resistance to amoxicillin and clavulanic acid 52.1% (n=170), which indirectly demonstrates extended spectrum of activity in this particular causative agent of β-lactamase(ESBL).'Real-life' clinical practice and dynamics of patients monitoring allow us to conclude that the resistance of gram-negative bacteria to AMD from carbapenems' group is steadily increasing, although until recently carbapenems were considered to be a reserve group of antibiotics [9]. Thus 33.4% (n=109) of isolates of K. pneumoniae showed the resistance to meropenem that is an alarming predictive indicator. A possible mechanism of resistance to β-lactams in general and carbapenems, in particular, is the production of carbapenemases [11, 12]. The level of resistance to ciprofloxacin and amikacin was comparable and amounted to 45.1% (n=147) и 41.7% (n=136) accordingly.

The number of isolates of microorganisms with pan-resistance makes 7.6% (n=125). The maximal share among PDR strains of microorganisms accounts forK. pneumonia and makes 33.4% (n=109) of all isolates of Klebsiella. At the same time, there is an alarming sign that the appearance of PDR strains of E. Coli 4.7% (n=6) may point to the possible mechanisms of resistance, which can be transmitted by plasmids or transposons. It can lead to fast growth of PDR strains among all agents of Enterobacteriaceae spp. P. aeruginosa showed the resistance to all groups of AMD in 10.23% (n=9) **(Figure 2)**.

The detection of microorganisms with significant drug resistance (XDR – microorganisms are resistant to all AMD but one or two classes) showed similar results. Thus, the rate for K. pneumonia was 41.72% (n=136), for E. Coli made 10.24% (n=13), and for P. Aeruginosa made 18.18% (n=16). Strains possessing significant drug resistance are a reservoir of strains that can potentially become pan-resistant in the future.

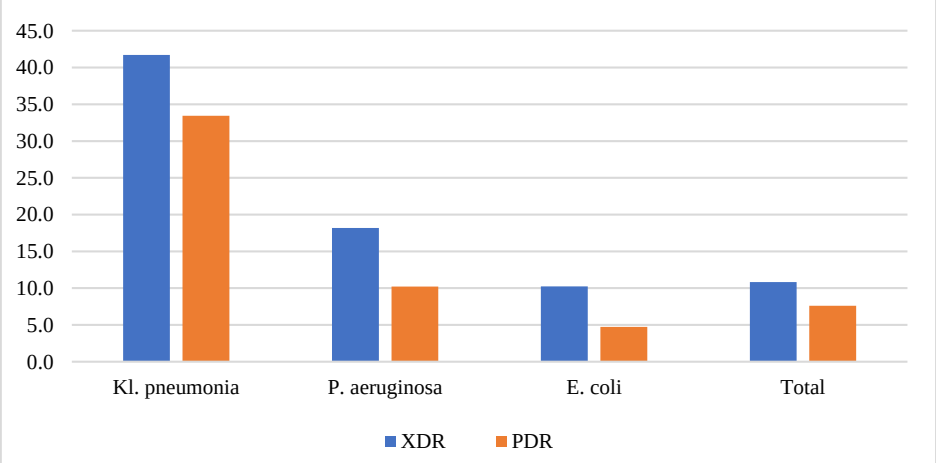

Figure 2. Selection of microorganisms with extensive drug resistance (XDR - microorganisms are resistant to all AMD but one or two classes) and pan-resistant microorganisms (PDR - resistant to all known classes of AMD) from clinical samples in 2020 (%).

Conclusion

The data that we obtained confirm the necessity of AMD (antimicrobial drugs) and antifungal drugs administration to patients with COVID-19 who are receiving hospital care. Considering a high proportion of C. Albicans and Str. Pneumonia amoxicillin and fluconazole may be the drugs of choice.

The leading pathogens of secondary infectious complications in patients with COVID-19 are featuring a high resistance frequency to AMD, including carbapenems.

An increasing frequency of Kl. Pneumonia selection which has an extreme resistance and pan-resistance to antimicrobial drugs demands a proper choice of agents for empirical antibacterial therapy. For a more reasonable choice of drugs, it is necessary to take into account the fact of extensive circulation of hospital strains of Klebsiella spp. as a variant of healthcare-associated infections.

It is possible only under systematic surveillance of the constantly changing microbiological landscape at infectious hospitals based on the data of microbiological monitoring. For containment of microorganisms' resistance growth to AMD, it is necessary to implement a systemic approach to control the adequacy of AMD administration for medical treatment of patients with COVID-19 and also to conduct the monitoring of prevailing pathogens' sensitivity to disinfecting agents.

1. The predictor of an unfavorable prognosis in patients with COVID-19 is the selection of microbial association of strains that have PDR to C. Krusei and C. Glabrata.
2. All patients in ICU with ARDS should receive drugs (as starting antifungal therapy) active to C. Krusei and C. Glabrata, such as voriconazole, caspofungin, micafungin, or anidulafungin.
3. A high proportion of Kl. pneumonia that has extreme resistance and pan-resistance to antimicrobial drugs demands the monitoring of sensitivity of microorganisms circulating in the hospital to certain disinfectants.
4. Taking into account the intensive usage of drugs with immunosuppressive activity for the treatment of patients with COVID-19 as well as the increase in secondary infectious complications it is necessary to monitor the etiological structure of microorganisms and a common level of antibiotic resistance at an infectious hospital.

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Ethics statement: Research work meets the ethical standards developed in accordance with the Helsinki Declaration of the World Medical Association "Ethical principles for conducting scientific medical research with human participation" as amended in 2000. The summary of the conducted study was considered and approved at the meeting of the Ethical Committee of the Far-Eastern State Medical University of June 21, 2019 (Protocol № 5).

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