https://doi.org/10.15360/1813-9779-2022-1-4-10

Nosocomial Infection in Patients with Severe and Critical COVID-19

Mikhail V. Bychinin[1], Igor O. Antonov[1], Tatiana V. Klypa[1], Irina A. Mandel[1,2]*, Andrey I. Minets[1], Nadezhda A. Kolyshkina[1], Yana B. Golobokova[1]

[1] Federal Scientific and Clinical Center for Specialized Types of Medical Care and Medical Technology, Federal Medical-Biological Agency of Russia, 28 Orekhovy bulvar, 115682 Moscow, Russia
[2] I. M. Sechenov First Moscow State Medical University, Ministry of Health of Russia, 8 Trubetskaya Str., Bldg. 2, 119991 Moscow, Russia

Нозокомиальная инфекция у пациентов с тяжелым и крайне тяжелым течением COVID-19

М. В. Бычинин[1], И. О. Антонов[1], Т. В. Клыпа[1], И. А. Мандель[1,2]*, А. И. Минец[1], Н. А. Колышкина[1], Я. Б. Голобокова[1]

[1] Федеральный научно-клинический центр специализированных видов медицинской помощи и медицинских технологий Федерального медико-биологического агентства России, Россия, 115682, г. Москва, Ореховый бульвар, д. 28
[2] Первый Московский государственный медицинский университет им. И. М. Сеченова Минздрава России, Россия, 119991, г. Москва, ул. Трубецкая, д. 8, стр. 2

For citation: *Mikhail V. Bychinin, Igor O. Antonov, Tatiana V. Klypa, Irina A. Mandel, Andrey I. Minets, Nadezhda A. Kolyshkina, Yana B. Golobokova.* Nosocomial Infection in Patients with Severe and Critical COVID-19. *Obshchaya Reanimatologiya = General Reanimatology.* 2022; 18 (1): 4–10. https://doi.org/10.15360/1813-9779-2022-1-4-10 [In Russ. and Engl.]

Summary

The aim of the study was to determine the etiology and frequency of nosocomial infections in patients with severe and critical COVID-19.

Material and methods. A retrospective, single-center study included 168 patients with COVID-19 admitted to the intensive care unit (ICU). All episodes of infection, clinical and laboratory characteristics, and outcome were documented in patients.

Results. Hospital-acquired infections were detected in 82 (48.8%) of 168 patients, more frequently in men (P=0.028). A total of 232 episodes of nosocomial infections were observed including ventilator-associated pneumonia (48.2%), bloodstream infection (39.2%), nosocomial pneumonia/tracheobronchitis (13.4%), and urinary tract infection (5.2%). The main causative agents of nosocomial infections were resistant strains of Acinetobacter baumannii and Klebsiella pneumoniae. Infections developed on the average on day 6 [3; 9] of ICU stay and were associated with the initial severity of the patients assessed by SOFA (P=0.016), SpO_2 (P=0.005), lymphopenia severity (P=0.003), Neutrophil-Lymphocyte Ratio (P=0.004), C-reactive protein (P=0.01), aspartate aminotransferase (AST) level (P=0.022), or vitamin D (P=0.035) levels. Patients diagnosed with infection were more likely than those without infections to require mechanical ventilation (67.6% vs 32.4%, P<0.001), high-flow oxygen therapy (50.0% vs 31.0%, P=0.020), renal replacement therapy (36.8% vs 9.3%, P=0.003), and had longer ICU length of stay (13 [9; 18] vs 4 [2; 8], P<0.001), hospital length of stay (19 [14; 29] vs 15 [11; 20], P=0.001) and mortality (47 (57.3%) vs 25 (29.0%), P<0.001).

Conclusion. In patients with severe and critical COVID-19 a high incidence of nosocomial infections was found, which negatively affected the outcome. In more than half of the cases, the infection was caused by resistant strains of Gram-negative bacilli. Procalcitonin is a useful biomarker for identifying bacterial infection in patients with COVID-19.

Keywords: COVID-19; SARS-CoV-2; nosocomial infection; intensive care; outcome

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

DOI:10.15360/1813-9779-2022-1-4-10

Correspondence to:

* Irina A. Mandel
E-mail: irina.a.mandel@gmail.com

Адрес для корреспонденции:

* Мандель Ирина Аркадьевна
E-mail: irina.a.mandel@gmail.com

Introduction

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains a major social and financial burden. It posed multiple challenging questions to the medical community in general and intensive care unit (ICU) specialists in particular. One of the major issues associated with SARS-CoV-2 infection is that a significant proportion of coronavirus disease 2019 (COVID-19) patients suffer from respiratory failure requiring intensive care [1, 2].

The development of immune hyperinflammatory response associated with COVID-19 has prompted the widespread use of immunomodulatory drugs [3], which began long before the evidence of their efficacy has been unequivocally established in large clinical trials due to the emergency of the pandemic situation. These drugs included glucocorticosteroids and numerous monoclonal antibodies including tocilizumab and olokizumab.

Despite the improved outcome with the use of above-mentioned drugs, COVID-19 patients have an increased risk of developing a secondary bacterial infection [4, 5]. In patients with moderate disease, superinfection frequency was reported to range from 3.6% to 24% [6, 7], whereas very limited data are currently available for COVID-19 patients admitted to ICU.

This study aimed to determine the etiology and frequency of nosocomial infections in patients with severe and critical COVID-19.

Materials and Methods

This retrospective single-center study included 168 patients with severe and critical COVID-19, who were hospitalized in the ICU of Federal Scientific and Clinical Center of Specialized Types of Medical Care and Medical Technologies of the Federal Medical and Biological Agency of Russia from April 6 to July 1, 2020. During this period, the clinical center served as an infectious disease hospital for patients with COVID-19. The diagnosis of COVID-19, assessment of disease severity, and patient therapy were done according to the temporary guidelines of the Ministry of Health of the Russian Federation on prevention, diagnosis and treatment of novel coronavirus infection (COVID-19) [8]. The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The study protocol was approved by the local ethical committee of the Federal Scientific and Clinical Center (Protocol No. 5, June 3, 2020).

The following information was collected from the study participants: demographics, comorbidities, routine laboratory tests (complete blood count, common urine analysis, blood clinical chemistry, coagulation test), Sequential Organ Failure Assessment (SOFA) score, localization and causative agent of infection, as well as clinical outcome. Only laboratory-confirmed nosocomial infection cases with a positive culture with a titer above the diagnostic cut-off were included in the study. These patients were also required to have a clinical presentation of the infection and/or worsening organ function [9]. Microorganisms were considered multidrug-resistant if they were resistant to more than one antibiotic drug from at least 3 groups of antibacterial drugs [10].

Statistical analysis.

Quantitative data are presented as the median (*Me*) and interquartile range [25%; 75%], category parameters are shown as absolute numbers (n) and percentage (%). Given that most of the quantitative data were not normally distributed, a non-parametric significance test, such as the Mann–Whitney test, was used for the analysis. For categorical parameters, chi-square statistics with Yates correction, and Fisher's exact test were used. The proportion of missing data did not exceed 10% for each parameter. The differences were considered significant if *P*-value was below 0.05. The SPSS 28.0.0.0 (IBM SPSS Statistics, Chicago, IL, USA) software package was used for data processing and statistics.

Results

Nosocomial infection was detected in 82 (48.8%) out of 168 patients. Clinical characteristics of the patients are shown in Table 1 which compares patients who developed a superinfection with those who did not. Groups of COVID-19 patients with or without superinfection were very similar in their age, however, inter-group differences in terms of gender and disease severity (SOFA scores and SpO_2) were notable (Table 1). Respiratory failure was the most common cause of admission to the ICU.

Hypertension, coronary heart disease, and diabetes mellitus were the most frequent comorbidities in the patients of both groups. No significant differences in the incidence of these diseases between the groups were observed. Patients in the superinfection group, in contrast to the control group, needed norepinephrine (76.8% и 31.3%, $P<0.001$), mechanical ventilation (67.6% vs 32.4%, $P<0.001$), high-flow oxygen therapy (50% vs 31%, $P=0.033$) more often. Also, superinfection group patients were more likely to receive renal replacement therapy (36.8% vs 9.3%, $P=0.001$) even though fewer patients had chronic kidney disease in this group (11.6% vs 3.7%, $P=0.053$). Data on antibiotic administration prior to admission to the ICU was available for 128 out of 168 patients. In both groups of patients, frequent prescription of antibacterial drugs was noted (94.5% and 90%).

We found significant intergroup differences in the results of routine laboratory tests such as lymphocyte count ($P=0003$), neutrophil-lymphocyte ratio ($P=0.004$), C-reactive protein ($P=0.01$), aspartate aminotransferase ($P=0.022$), and vitamin D levels ($P=0.035$) (Table 2). Significant differences were revealed between procalcitonin levels on day 5 ($P=0.031$) and day 10 ($P=0.001$).

Nosocomial infections were first detected on the average on day 6 [3–9] after ICU admission. In total, 232 episodes of nosocomial infections were recorded in 82 patients during their stay in the ICU (35 patient had 2 episodes, 12 patients had 3 episodes, 9 subjects had 4 episodes, 9 patients had 5 episodes, and 1 patient had 6 episodes). Sixty-seven cases of positive cultures were excluded from the analysis (12 blood cultures, 33 lower airway sputum cultures), as these were considered contamination. The most frequent complications included ventilator-associated pneumonia (VAP) (98 [48%] episodes) and bloodstream infection (91 [39%] episodes) (Table 3).

Leading causative agents of bloodstream infection included *A. baumannii* (34%) and *K. pneumoniae* (25%). Gram-positive bacteria were detected less frequently (*Coagulase-negative staphylococci* 15%, *E. faecium* 8%, *E. faecalis* 3%), *Candida albicans* was found in 1% of episodes. Gram-negative bacteria were also among the most frequent causes of infections of the respiratory tract, such as VAP and nosocomial pneumonia/tracheobronchitis (*A. baumannii* — 51%, *K. pneumoniae* — 27%, *Pseudomonas aeruginosa* — 12%). *Aspergillus* spp. was found in a single case of VAP. Urinary tract infections were predominantly caused by *E. faecium* (25%) and *E. faecalis* (25%) (Table 3).

All *Acinetobacter baumannii, Klebsiella pneumoniae*, and *Stenotrophomonas maltophilia* strains were multidrug-resistant.

Compared to COVID-19 patients without nosocomial infection, those with a diagnosed superinfection had an overall longer stay in the ICU (13 [9–18] vs 4 [2–8]; $P<0.001$), longer hospital stay (19 [14–29] vs 15 [11–20]; $P=0.001$) and higher mortality (47 (57.3%) vs 25 (29%); $P<0.001$). Septic shock developed in 52 (63%) patients with infection and was the leading cause of death in these patients.

Table 1. Baseline characteristics and clinical outcomes in COVID-19 patients with/without nosocomial infection.

Parameters	Value in groups		*P* value
	Patients with nosocomial infection, *n*=82	Patients without nosocomial infection, *n*=86	
Clinical parameters			
Age, years	64 [57–76]	67 [57–74]	0.763
Male, *n* (%)	46 (56.1%)	35 (39.3%)	0.066
SOFA, score	2 [1; 3]	2 [1; 2]	0.160
SOFA, score (day 5)	5 [3; 7]	3 [2; 4]	0.060
SOFA, score (day 10)	6 [4; 9]	4 [3; 7]	0.136
SpO_2, %	85 [80; 88]	88 [80; 93]	**0.005**
APACHE II	14 [11; 18]	13 [10; 13]	0.179
Comorbidities			
Coronary heart disease, *n* (%)	37 (45)	42 (48,8)	0.569
Hypertension, *n* (%)	59 (72)	60 (70)	0.846
Use of ACE inhibitors, *n* (%)	32 (39.5)	36 (40.9)	0.853
Chronic kidney disease, *n* (%)	3 (3.7)	10 (11.6)	0.053
Liver disease, *n* (%)	3 (3,75)	3 (3,5)	0.953
Diabetes mellitus, *n* (%)	30 (36.6)	26 (30.2)	0.383
Lung disease, *n* (%)	11 (13.4)	6 (7)	0.167
Cerebrovascular disease, *n* (%)	12 (15.0)	20 (23.5)	0.224
Cancer, *n* (%)	5 (6.1)	11 (12.8)	0.140
Organ support and therapy			
Mechanical ventilation, *n* (%)	75 (67.6)	36 (32.4)	**<0.001**
Mechanical ventilation, days	11 [8; 16]	2 [0; 9]	**<0.001**
Prone position	70 (85.9)	45 (52)	**<0.001**
High-flow oxygen therapy, *n* (%)	40 (50)	27 (31)	**0.033**
High-flow oxygen therapy, days	1 [1; 3]	4 [1; 6]	**0.020**
Renal replacement therapy, *n* (%)	30 (36.8)	8 (9.3)	**0.001**
Norepinephrine, *n* (%)	63 (76.8)	27 (31.3)	**<0.001**
Glucocorticosteroids, *n* (%)	25 (30)	19 (22)	0.139
Antibiotic therapy before ICU (*n*=128)	74/70 (94.5)	54/49 (90.7)	0.450
Outcomes			
LOS in ICU, days	13 [9; 18]	4 [2; 8]	**<0.001**
Hospital stay, days	19 [14; 29]	15 [11; 20]	**0.001**
Mortality in ICU, *n* (%)	47 (57.3)	25 (29)	**<0.001**

Note. Data are presented as the median and percentiles [0.25; 0.75], absolute (*n*) and relative (%) values. ACE, angiotensin-converting enzyme; ICU, intensive care unit; LOS, length of stay; SOFA, sequential organ failure assessment. The Mann–Whitney test and chi-square test were used.

Table 2. Laboratory data of COVID-19 patients with/without nosocomial infection

Parameters	Value in groups		*P* value
	Patients with nosocomial infection, *n*=82	Patients without nosocomial infection, *n*=86	
White blood cell count, 10^9/l	8.0 [6.4; 10.9]	8.0 [6.8; 11.8]	0.53
Lymphocytes, 10^9/l	0,69 [0.5; 0.9]	0,88 [0.6; 1.3]	**0.003**
NLR	10.4 [7.2 ; 14.8]	7.6 [4.3; 13.1]	**0.004**
Platelets, 10^9/l	203 [170; 272]	214 [155; 300]	0.856
Ferritin, μg/l	911 [540; 1700]	628 [402; 1159]	0.070
Interleukin 6, pg/ml	183 [66; 321]	139 [50; 636]	0.901
D-dimer, ng/ml	0.9 [0.56; 2.06]	0.8 [0.4; 1.8]	0.318
Fibrinogen, g/l	4.0 [3.2; 4.9]	4.2 [3.3; 5.0]	0.588
Procalcitonin, ng/ml	0.4 [0.18; 0.97]	0.26 [0.13; 0.65]	0.157
Procalcitonin, ng/ml, day 5	1.52 [0.70; 5.59]	0.41 [0.30; 1.83]	**0.031**
Procalcitonin, ng/ml, day 10	1.32 [0.42; 8.99]	0.54 [0.50; 2.2]	**0.001**
CRP, mg/l	152 [98.9; 237.2]	102.3 [46.9; 159.3]	**0.010**
Vitamin D, ng/ml	9.0 [5.3; 11.9]	12.7 [9.1; 19.7]	**0.035**
AST, U/l	48 [33; 64]	39 [28; 52]	**0.022**
ALT, U/l	35 [26; 54]	30 [22; 47]	0.069
Creatinine, μmol/l	71 [63; 91]	76 [61; 106]	0.376
Bilirubin, μmol/l	12 [8; 16]	11 [8; 15]	0.702
Glucose, mmol/l	8 [7; 11]	8 [6; 11]	0.222

Note. Data are presented as the median and percentiles [0.25;0.75]. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio. The Mann–Whitney test was used.

Discussion

We analyzed all the documented episodes of nosocomial infections in severe and critical COVID-19 patients. To the best of our knowledge, this is one of the first studies in the Russia where the incidence and etiology of superinfection in COVID-19 patients admitted to the ICU is explored in the context of the patient's clinical presentation, results of routine laboratory tests, and outcome.

The incidence of nosocomial infections in the study participants was 48.8%, which is slightly higher than reported elsewhere [5, 7, 11, 12]. This may be due to the differences in the cohort selection, as only severe and critical COVID-19 patients were included.

Nosocomial infections included VAP, tracheobronchitis/nosocomial pneumonia, bloodstream infection, and urinary infections, all of which are typical for ICU-admitted patients. The proportion of patients with bloodstream infections was unusually high (39%) of all the infection episodes. This may have been caused by the ICU staff overload during the peak of the COVID-19 pandemic, as the ICU capacity was increased by 250% to accommodate all the patients requiring intensive care. Special attention was given at that time to counteracting the infections transmitted via respiratory droplets, whereas other methods of infection control (central venous catheter /tracheostoma care) were not sufficiently addressed [13].

The most frequent causative agents of nosocomial infections among patients were multidrug-resistant *A. baumannii* and *K. pneumoniae*. Gram-negative bacteria have been previously reported as the most frequent causes of late nosocomial infections in COVID-19 patients in other countries [14, 15], whereas early superinfection was largely represented by gram-positive microorganisms [16]. *Acinetobacter* spp. and *Klebsiella* spp. are known to be widely spread in Russian Federation [17], and inappropriate use of antibacterial drugs, albeit in line with the guidelines, may have contributed to the development of their multiple resistance [8, 18]. In line with the first version of Russian guidelines on diagnosis and treatment of COVID-19 [8], more than 90% of the patients in our study received empirical antibacterial therapy with the generation III cephalosporins and macrolides. However, the co-infection was quite rare among COVID-19 patients in the ICU, which is consistent with other studies [5, 6]. Also, severe COVID-19 may mimic bacterial sepsis [19], which undoubtedly prompted many doctors to administer antibiotics and was later deemed inappropriate.

Unlike Bartolleti et al [20], we did not observe a significant rate of infections caused by *Aspergillus* spp. This discrepancy may have been caused by the lack of systematic screening for this infection in our clinic.

Progression of the nosocomial superinfection associated with COVID-19 severity. Specifically, we noted significant differences in the SOFA score, SpO_2, lymphocyte counts, neutrophil-lymphocyte ratio, aspartate aminotransferase and C-reactive protein levels between the patients with or without superinfection. All of these parameters were previously associated with disease severity and recog-

nized as negative prognostic factors of COVID-19 outcome [7, 12]. Significant differences between groups in the level of procalcitonin were detected on days 5 and 10. The increase in procalcitonin levels in COVID-19 patients reflects the organism's response to bacterial infection and is independent of the hyperimmune inflammatory response. In our opinion, serial measurement of procalcitonin level helps identify patients with secondary bacterial infection and should be used routinely in patients with COVID-19 both for initiation of antibiotic therapy and assessment of its effectiveness.

Secondary bacterial infection was more frequent in male COVID-19 patients. The risks of severe COVID-19 and unfavorable outcomes are known to be higher for men [5]. Dananche et al [21] reported male sex as a risk factor for VAP which could be attributed to the differences in immune response in men due to genetic factors and hormonal status [22]. Significant differences in vitamin D levels in patients with and without superinfection were found, which is consistent with the protective role of vitamin D in bacterial infections and sepsis [23]. Accordingly, vitamin D level below 10 ng/ml is known to be an independent predictor of unfavorable outcome in patients with severe COVID-19 [24].

Of all the immune-modulating drugs, glucocorticosteroids were used most frequently in our patients. According to the RECOVERY trial [25], the use of dexamethasone has led to a reduction of mortality rate (on day 28) among COVID-19 patients who required mechanical ventilation or oxygen support. Unfortunately, no data on the rate of infections associated with the use of dexamethasone are available. Our groups of patients with/without nosocomial superinfections were balanced in terms of the steroid use. According to Bardi et al [26], steroids were the only medications associated with the risk of nosocomial infections (which was below the level of statistical significance in a multifactorial analysis), yet it did not influence the mortality rate.

In our study, nosocomial infection was associated with higher mortality, longer ICU and hospital stay, and longer duration of mechanical ventilation. In the group of patients with infection, 63% developed septic shock. Complications of infections in ICU-admitted patients are well-known and their effects on the patient outcomes have been described [27, 28]. In a recent study [26], nosocomial infection in COVID-19 patients was reported as an independent negative outcome predictor and was one of the causes of death in 1/3 of patients. Another recent study [29] showed that the development of septic shock in patients with COVID-19 increases the chances of death by 58 times (OR (95% CI): 58.1 (5.97–7812.8), $P<0.001$).

Table 3. Microbiological data by type of infection, *n* (%).

Bacterial/fungal superinfection	*n*=232
Bloodstream infection	***n*=91 (39.2%)**
Acinetobacter baumannii	31 (34.0%)
Klebsiella pneumoniae	23 (25.0%)
Coagulase-negative staphylococci (methicillin-resistant)	14 (15.0%)
Stenotrophomonas maltophilia	8 (9.0%)
Enterococcus faecium	8 (9.0%)
Pseudomonas aeruginosa	3 (3.0%)
Enterococcus faecalis	3 (3.0%)
Staphylococcus aureus	1 (1.0%)
Candida albicans	1 (1.0%)
Ventilator-associated pneumonia	*n*=98 (42.2%)
Acinetobacter baumannii	52 (53.0%)
Klebsiella pneumoniae	25 (26.0%)
Pseudomonas aeruginosa	10 (10.0%)
Stenotrophomonas maltophilia	4 (4.0%)
Staphylococcus aureus (methicillin-resistant)	4 (4.0%)
Proteus mirabilis	2 (2.0%)
Aspergillus fumigatus	1 (1.0%)
Nosocomial pneumonia / tracheobronchitis	*n*=31 (13.4%)
Acinetobacter baumannii	14 (45.0%)
Klebsiella pneumoniae	10 (32.0%)
Pseudomonas aeruginosa	5 (16.0%)
Stenotrophomonas maltophilia	2 (6.0%)
Staphylococcus aureus (methicillin-resistant)	1 (3.0%)
Urinary infection	*n*=12 (5.2%)
Enterococcus faecium	3 (25.0%)
Enterococcus faecalis	3 (25.0%)
Klebsiella pneumoniae	2 (16.7%)
Acinetobacter baumannii	2 (16.7%)
Pseudomonas aeruginosa	1 (8.2%)
Candida non-albicans (*C.glabrata. C.tropicalis*)	2 (16.7%)
Candida albicans	2 (16.7%)

Our study has several limitations. Only infections documented by culture were included and, therefore, some episodes could be missing. This study was limited to a single center, with its local pattern of antimicrobial resistance, which may limit the generalizability of the findings. The retrospective design reduces control over multiple confounders and data collection.

Conclusion

In patients with severe and critical COVID-19, a high incidence of nosocomial infections was observed. Nosocomial infection was associated with the initial severity of the disease at presentation as well as with the unfavorable outcome. Most frequently, antibiotic-resistant strains of gram-negative bacteria were the causative infectious agents. Procalcitonin is a useful biomarker for identifying bacterial infection in patients with COVID-19.

References

1. *Zhou F., Yu T., Du R., Fan G., Liu Y., Liu Z., Xiang J., Wang Y., Song B., Gu X., Guan L., Wei Y., Li H., Wu X., Xu J., Tu S., Zhang Y., Chen H., Cao B.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020; 395 (10229): 1054–1062. DOI: 10.1016/S0140-6736 (20)30566-3.
2. *Möhlenkamp S., Thiele H.* Ventilation of COVID-19 patients in intensive care units. *Herz.* 2020; 45 (4): 329–331. DOI: 10.1007/s00059- 020-04923-1
3. *Alijotas-Reig J., Esteve-Valverde E., Belizna C., Selva-O'Callaghan A., Pardos-Gea J., Quintana A., Mekinian A., Anunciacion-Llunell A., Miró-Mur F.* Immunomodulatory therapy for the management of severe COVID-19. Beyond the antiviral therapy: A comprehensive review. *Autoimmun Rev.* 2020; 19 (7): 102569. DOI: 10.1016/j.autrev. 2020.102569.
4. *Cataño-Correa J.C., Cardona-Arias J.A., Porras Mancilla J.P., García M.T.* Bacterial superinfection in adults with COVID-19 hospitalized in two clinics in Medellín-Colombia, 2020. *PLoS One.* 2021; 16 (7): e0254671. DOI: 10.1371/journal.pone.0254671.
5. *Rawson T.M., Moore L.S.P., Zhu N., Ranganathan N., Skolimowska K., Gilchrist M., Satta G., Cooke G., Holmes A.* Bacterial and Fungal Coinfection in Individuals With Coronavirus: A Rapid Review To Support COVID-19 Antimicrobial Prescribing. *Clin Infect Dis.* 2020; 71 (9): 2459–2468. DOI: 10.1093/cid/ciaa530.
6. *Lansbury L., Lim B., Baskaran V., Lim W.S.* Co-infections in people with COVID-19: a systematic review and meta-analysis. *J Infect.* 2020; 81 (2): 266–275. DOI: 10.1016/j.jinf.2020.05.046.
7. *Musuuza J.S., Watson L., Parmasad V., Putman-Buehler N., Christensen L., Safdar N.* Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: A systematic review and meta-analysis. *PLoS One.* 2021; 16 (5): e0251170. DOI: 10.1371/journal.pone.0251170.
8. Interim guidelines. Prevention, diagnosis and treatment of new coronavirus infection (COVID-19). Version 7 from 03.06.2020. Moscow: Ministry of Health of the Russian Federation; 2020. The link is active on 05.09.20 [In Russ.]. https://static-0.rosminzdrav.ru/system/attachments/attaches/000/050/584/original/03062020_%D0%9CR_COVID-19_v7.pdf.
9. *Horan T.C., Andrus M., Dudeck M.A.* CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control.* 2008; 36 (5): 309–332. DOI: 10.1016/j.ajic.2008.03.002.
10. *Magiorakos A.P., Srinivasan A., Carey R.B., Carmeli Y., Falagas M.E., Giske C.G., Giske C.G., Harbarth S., Hindler J.F., Kahlmeter G., Olsson-Liljequist B., Paterson D.L., Rice L.B., Stelling J., Struelens M.J., Vatopoulos A., Weber J.T., Monnet D.L.* Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect.* 2012; 18 (3): 268–281. DOI: 10.1111/j.1469-0691.2011.03570.x.
11. *Grasselli G., Zangrillo A., Zanella A., Antonelli M., Cabrini L., Castelli A., Cereda D., Coluccello A., Foti G., Fumagalli R., Iotti G., Latronico N., Lorini L., Merler S., Natalini G., Piatti A., Ranieri M.V., Scandroglio A.M., Storti E., Cecconi M., Pesenti A.* COVID-19 Lombardy ICU Network. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA.* 2020; 323 (16): 1574–1581. DOI: 10.1001/jama.2020.5394.
12. *Huang C., Wang Y., Li X., Ren L., Zhao J., Hu Y., Zhang L., Fan G., Xu J., Gu X., Cheng Z., Yu T., Xia J., Wei Y., Wu W., Xie X., Yin W., Li H., Liu M., Xiao Y., Gao H., Guo L., Xie J., Wang G., Jiang R., Gao Z., Jin Q., Wang J., Cao B.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020; 395 (10223): 497—506. DOI: 10.1016/S0140-6736 (20)30183-5.
13. *Zhou P., Liu Z., Chen Y., Xiao Y., Huang X., Fan X-G.* Bacterial and fungal infections in COVID-19 patients: A matter of concern. *Infect Control Hosp Epidemiol.* 2020; 41 (9): 1124–1125. DOI: 10.1017/ ICE.2020.156.
14. *Giacobbe D.R., Battaglini D., Ball L., Brunetti I., Bruzzone B., Codda G., Crea F., De Maria A., Dentone Ch., Di Biagio A., Icardi G., Magnasco L., Marchese A., Mikulska M., Orsi A., Patroniti N., Robba Ch., Signori A., Taramasso L., Vena A., Pelosi P., Bassetti M.* Bloodstream infections in critically ill patients with COVID-19. *European journal of clinical investigation.* 2020; 50 (10): e13319. DOI: 10.1111/eci.13319.
15. *Dugnon E.., Caméléna F., Deniau B., Habay A., Coutrot M., Ressaire Q.* Bacterial Pneumonia in COVID-19 Critically Ill Patients: A Case Series. *Clinical Infectious Diseases.* 2021; 72 (5): 905–906. DOI: 10.1093/cid/ciaa762.
16. *Sharifipour E., Shams S., Esmkhani M., Khodadadi J., Fotouhi-Ardakani R., Koohpaei A., Doosti Z., Ej Golzari S.* Evaluation of bacterial co-infections of the respiratory tract in COVID-19 patients admitted to ICU. *BMC Infect Dis.* 2020; 20 (1): 646. DOI: 10.1186/s12879-020-05374-z.
17. *Kutsevalova O.Yu., Pokudina I.O., Rozenko D.A., Martynov D.V., Kaminsky M.Yu.* Modern problems of antibiotic resistance gram-negative nosocomial infections in the Rostov region. *Meditsinskij vestnik Yuga Rossii.* 2019; 10 (3): 91–96. [In Russ.]. DOI: 10.21886/2219-8075-2019-10-3-91-96.
18. *Seligman R., Ramos-Lima L.F., Oliveira Vdo A.,Sanvicente C., Sartori J., Pacheco E.F.* Risk factors for infection with multidrug-resistant bacteria in non-ventilated patients with hospital-acquired pneumonia. *J Bras Pneumol.* 2013; 39 (3): 339–348. DOI: 10.1590/S1806-37132013000300011.
19. *Li H., Liu L., Zhang D., Xu J., Dai H., Tang N., Su X., Cao B.* SARS-CoV-2 and viral sepsis: observations and hypotheses. *Lancet.* 2020; 9; 395 (10235): 1517–1520. DOI: 10.1016/S0140-6736 (20)30920-X.
20. *Bartoletti M., Pascale R., Cricca M., Rinaldi M., Maccaro A., Bussini L., Fornaro G., Tonetti T., Pizzilli G., Francalanci E., Giuntoli L., Rubin A., Moroni A., Ambretti S., Trapani F, Vatamanu O., Ranieri V.M., Castelli A., Baiocchi M., Lewis R., Giannella M., Viale P.; PREDICO study group.* Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. *Clin Infect Dis.* 2020; 28: ciaa1065. DOI: 10.1093/cid/ciaa1065.
21. *Dananché C., Vanhems P., Machut A., Aupée M., Bervas C., L'Hériteau F., Lepape A., Lucet J.C., Stoeckel V., Timsit J.F., Berger-Carbonne A., Savey A., Bénet T.; Healthcare-Associated Infections (HAIs) Surveillance Network of ICUs (Réseau REA-Raisin).* Trends of incidence and risk factors of ventilator-associated pneumonia in elderly patients admitted to French ICUs between 2007 and 2014. *Crit Care Med.* 2018; 46: 869–877. DOI: 10.1097/CCM.0000000000003019.
22. *Lipsky M.S., Hung M.* Men and COVID-19: A Pathophysiologic Review. *Am J Mens Health.* 2020; 14 (5): 1557988320954021. DOI: 10.1177/ 1557988320954021.
23. *Parekh D., Patel J.M., Scott A., Lax S., Dancer R.C., D'Souza V., Greenwood H., Fraser W.D., Gao F., Sapey E., Perkins G.D., Thickett D.R.* Vitamin D Deficiency in Human and Murine Sepsis. *Crit Care Med.* 2017; 45 (2): 282–289. DOI: 10.1097/CCM.0000000000002095.
24. *Bychinin M.V., Klypa T.V., Mandel I.A., Andreichenko S.A., Baklaushev V.P., Yusubalieva G.M., Kolyshkina N.A., Troitsky A.V.* Low Circulating Vitamin D in Intensive Care Unit-Admitted COVID-19 Patients as a Predictor of Negative Outcomes. *J Nutr.* 2021; May12: nxab107. DOI: 10.1093/jn/nxab107
25. *RECOVERY Collaborative Group, Horby P., Lim W.S., Emberson J.R., Mafham M., Bell J.L., Linsell L., Staplin N., Brightling C., Ustianowski A., Elmahi E., Prudon B., Green C., Felton T., Chadwick D., Rege K., Fegan C., Chappell L.C., Faust S.N., Jaki T., Jeffery K., Montgomery A., Rowan K., Juszczak E., Baillie J.K., Haynes R., Landray M.J.* Dexamethasone in Hospitalized Patients with COVID-19. *N Engl J Med.* 2021; 384 (8): 693–704. DOI: 10.1056/NEJMoa2021436.
26. *Bardi T., Pintado V., Gomez-Rojo M., Escudero-Sanchez R., Azzam Lopez A., Diez-Remesal Y., Martinez Castro N., Ruiz-Garbajosa P., Pestaña D.* Nosocomial infections associated to COVID-19 in the intensive care unit: clinical characteristics and outcome. *Eur J Clin Microbiol Infect Dis.* 2021; 40 (3): 495–502. DOI: 10.1007/s10096-020-04142-w.
27. *Despotovic A., Milosevic B., Milosevic I., Mitrovic N., Cirkovic A., Jovanovic S., Stevanovic G.* Hospital-acquired infections in the adult intensive care unit-Epidemiology, antimicrobial resistance patterns, and risk factors for acquisition and mortality. *Am J Infect Control.* 2020; 48 (10): 1211–1215. DOI: 10.1016/j.ajic.2020.01.009.
28. *Signorini L., Moioli G., Calza S., Van Hauwermeiren E., Lorenzotti S., Del Fabro G., Renisi G., Lanza P., Saccani B., Zambolin G., Latronico N., Castelli F., Cattaneo S., Marshall*

J.M., Matteelli A., Piva S. Epidemiological and Clinical Characterization of Superinfections in Critically Ill Coronavirus Disease 2019 Patients. *Critical care explor.* 2021; 3 (6): e0430. DOI: 10.1097/CCE.0000000000000430.

29. *Al Mutair A., Al Mutairi A., Zaidi A.R.Z., Salih S., Alhumaid S., Rabaan A.A., Al-Omari A.* Clinical Predictors of COVID-19 Mortality Among Patients in Intensive Care Units: A Retrospective Study. *Int J Gen Med.* 2021; 14: 3719–3728. DOI: 10.2147/IJGM.S313757.

Received 09.09.2021, online first 17.01.2022